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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 PRELIMINARY 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 that was taught in the prior art. Genentech's scientists—including the chemical engineers who pioneered the creation of anti-HER2 antibodies—tried for years to create such a composition using known methods, but were unable to do so until they developed a novel "reverse wash" purification method that removed 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 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.

Pfizer challenges claims 1 and 5-7 of the '218 patent on three separate grounds, but fails to demonstrate a reasonable likelihood of success for any of them.

First, each prior art reference fails to disclose several claim limitations, most notably a composition containing "one or more acidic variants … wherein the amount of acidic variant(s) is less than about 25%." Though Pfizer attempts to recast these failings as instances of "inherent" disclosure, Pfizer fails to apply the proper legal standard for establishing inherency, *i.e.*, that the prior art's teachings "necessarily" and "inevitably" result in the claimed invention. Instead, Pfizer tries to circumvent this exacting standard, for example by arguing that a missing element could be found in an entirely separate prior art embodiment—contrary to black letter law that inherent anticipation requires every element to be present in a single embodiment. Similarly, Pfizer argues that a missing element could be derived by performing various calculations on a drawing in a reference even though the drawing lacks quantified points of measurement—contrary to established precedent that such a drawing cannot be used to determine whether an element is present. Pfizer's flawed legal theories cannot support institution of an *inter partes* review ("IPR").

Second, Pfizer's fallback argument—that the various claim limitations missing from the prior art would have been obvious—is equally deficient. Pfizer

identifies no evidence that a person of ordinary skill in the art 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—precisely the type of inchoate assertions that the Board has repeatedly found are insufficient as a matter of law.

Third, Pfizer also fails to present a *prima facie* case that any of the prior art references is enabling. Indeed, Pfizer omits two references—Waterside and Harris—from its enablement argument entirely. But there can be little doubt that none of the references teaches how to make the claimed antibody composition. Pfizer's own expert attempted to make the composition based on the prior art teachings, yet he was ultimately forced to rely on outside teachings and post-dating technology—including Genentech's commercial embodiment of its FDA-approved anti-HER2 drug composition, Herceptin®. Tellingly, the same failure arose in proceedings before the European Patent Office regarding a European counterpart to the '218 patent. The opponent's expert attempted to demonstrate that the prior art was enabling, yet the expert could not create the claimed composition by following the prior art teachings and thus inadvertently proved the opposite. The

European Patent Office ruled that the counterpart patent was valid over the same three prior art references that Pfizer now asserts.

Finally, Pfizer's petition also should be rejected under Section 325(d). All three prior art references were considered during prosecution, and the Examiner correctly concluded that the challenged claims should issue over them. There is no need for the Board to revisit that issue.

The Board should deny institution.

II. TECHNOLOGY BACKGROUND

A. HER2-Positive Breast Cancer

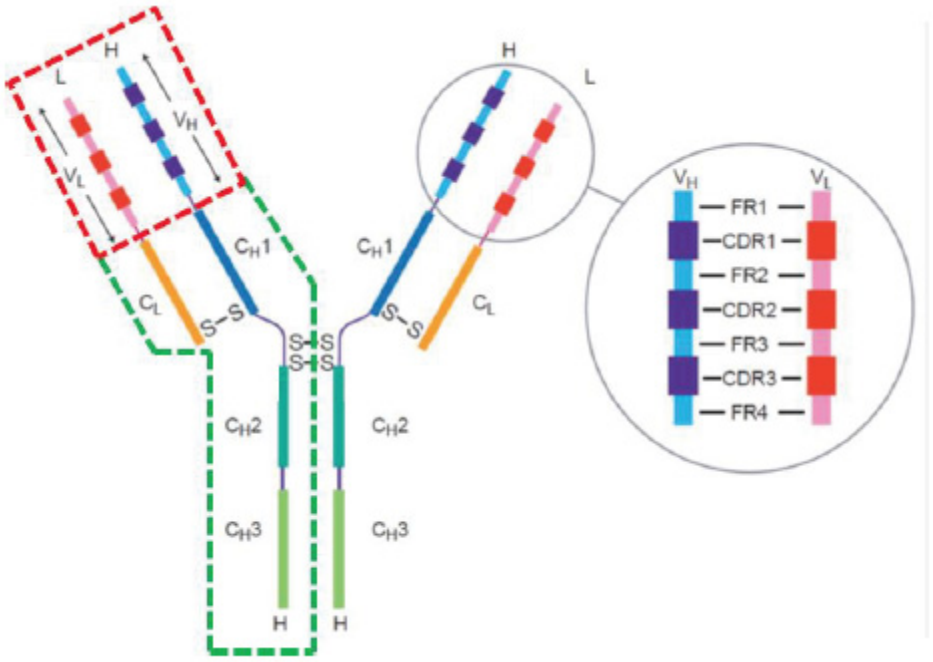
Cancer is a disease involving an abnormal growth of cells (*i.e.*, a tumor) that divides uncontrollably and invades the surrounding tissue. One particularly aggressive form of cancer is known as HER2-positive breast cancer, which is characterized by the overexpression of human epidermal growth factor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

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.) "Monoclonal" antibodies are directed against a single antigenic site. (*Id.*, 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.)

In the 1990s, 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*.)

C. Protein Degradation And Acidic Variants

Pharmaceutical antibodies, 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.) 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. (*Id.*, 1:34-38.)

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.) Variants that are more acidic than the original protein are referred to as "acidic variants," 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; *see also* Paper 1, 13-14.) One type of acidic variant is a "deamidated variant," in which an amide functional group is removed from the protein to form a free carboxylic acid (*e.g.*, deamidation at asparagine). (Ex. 1017, 5.) 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 intermediate. (*Id*., 6-7.) This process, referred to as "succinimide formation," produces basic variants. (*Id.*; Ex. 1004, 21, 28.)

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

III. THE '218 PATENT

A. The Invention

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. (*See, e.g.*, Ex. 1019; Ex. 1043.) But in the course of developing a commercial treatment (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 obtain the improved composition claimed in the '218 patent.

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 maintained its potency and efficacy. (Ex. 1001, 2:27-49.) As the name implies, "reverse wash" purification involves a step that, contrary to standard purification practices, reverses one or more attributes of the purifying buffer (for example, conductivity, pH, or both) previously used in the purification process. (*Id.*, 2:32-39.) As a result, Dr. Blank and Ms. Basey were

able to obtain 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.) This is especially important when developing therapeutic antibodies at manufacturing scale (as opposed to laboratory scale) because it achieves a consistently high rate of recovery of the desired antibody across batches, ensuring that the resulting cancer treatment drug is consistently pure and effective. (*Id.*, 2:45-49.)

B. Prosecution History

The '218 Patent issued from Application No. 13/313,931 filed on December 7, 2011 as a continuation of 12/418,905, and claims priority to Application No. 60/084,459 filed on May 6, 1998. (Ex. 1001 cover page.)[1]

The Examiner considered numerous prior art references during the prosecution of the '218 patent, including all three references that Pfizer asserts in its petition—Andya, Waterside, and Harris. (Ex. 1002, 121-122, 302.) The Examiner also considered the briefs, declarations, and decisions in the European Patent Office and United Kingdom proceedings (discussed in Section III(C) below)

[1] Pfizer has challenged a related patent, U.S. Patent No. 6,339,142, in a separate petition (IPR2017-02019).

that addressed validity challenges to a European counterpart to the '218 patent based on Andya, Waterside, and Harris. (*Id.*, 301-312.)

On September 18, 2015, the Examiner allowed the claims. (Ex. 1002, 289.) The patent issued on February 2, 2016. Due to a terminal disclaimer, it will expire on May 3, 2019. (*Id.*, 294.)

C. Foreign Proceedings

European Patent No. EP 1 308 455 ("the EP '455 patent," Ex. 1021) is a European counterpart to the '218 patent. Like the challenged claims here, the claims of the EP '455 patent require a composition that contains "one or more acidic variants … wherein the amount of acidic variant(s) is less than about 25%." (Ex. 1021, 17.) The EP '455 patent has been the subject of a number of proceedings in which its validity has been challenged.

In the United Kingdom ("UK"), Pfizer subsidiary Hospira asserted that the EP '455 patent was invalid in light of Andya and Waterside. The UK Court determined that Waterside did not disclose the claimed composition, but found under the applicable European standards it would not have been sufficiently inventive to modify Waterside to obtain the composition as claimed. (Ex. 1024 ¶242.) The UK court also ruled that Andya taught the claimed composition. (*See* Ex. 1024 ¶217.) The UK court, however, was applying a very different standard than is applicable in the United States. (*See* Ex. 1024 ¶217.) In particular, the UK

court ***agreed*** with Genentech that Andya did not disclose the particular contents of the allegedly anticipatory composition (the "Example 1" composition), but found that a composition made in accordance with the teachings of Andya was "likely" to include at least one acidic variant and was "more likely than not" to contain the particular acidic variants required by certain dependent claims. (*Id.* ¶¶202, 208.) In the United States, by contrast, such a determination falls well below the standard for inherent disclosure, and therefore is insufficient to support a finding of anticipation. *Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295 (Fed. Cir. 2002) ("Inherent anticipation requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present, in the prior art."). Genentech chose not to appeal this decision, which was limited solely to the UK.

The European Patent Office ("EPO"), in a separate ruling issued after the UK decision, rejected the arguments that had been raised in the UK and found that the EP '455 patent was ***not*** invalid in light of Andya, Waterside, or Harris. The EPO Board of Appeal found that Andya failed to disclose the form of the non-native protein in the Example 1 composition, and therefore failed to teach a composition with "one or more acidic variants" as required by the claims. (Ex. 1023, 17-18.) The Board of Appeal further found that Waterside and Harris failed to invalidate the claims, based in part on the fact that the opponent's own expert (Dr. Wang) had tried and failed to create the claimed composition following the

teachings in Waterside and Harris. (*Id.*, 23-25.) The Board of Appeal found that Dr. Wang's inability to create the claimed composition based on Waterside and Harris demonstrated that those references were not enabling. (*Id.*)

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 a method of lyophilizing (*i.e.*, freeze-drying) and reconstituting antibody formulations. (Ex. 1004, 3.) Andya further describes a series of experiments demonstrating that its process produces a stable formulation. In "Example 1," Andya indicates that an anti-HER2 antibody composition was 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 certain figures (Figures 5-8), which show that the reconstituted formulation 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 (explaining that in the figures, the percentage of "native protein was defined as the peak area of the native (not degraded) protein relative to the total peak area"); *see also id.*, 28, 39-40.)

Andya also describes "early screening studies" in which a different "liquid state" anti-HER2 antibody composition was tested. (Ex. 1004, 21, 25-26.) Andya states that when the screening-study composition degraded, it produced at least one acidic variant (deamidated at asparagine). (*Id.* at 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-lyophilization composition used for Example 1, nor does it describe how to create the liquid state composition used for the early screening studies. (*See* Ex. 1004, 20-29.) Andya also does not indicate (contrary to Pfizer's suggestion (Paper 1, 23-24, 39)) that the two compositions are the same or otherwise degrade in the same manner. (*See* Ex. 1004, 20-29.)

In the course of the European proceedings regarding the EP '455 patent, Genentech discovered internal documents demonstrating that Andya's Example 1 starting composition (*i.e.*, pre-lyophilization) was a humMAb4D5-8 antibody composition made in accordance with the "reverse wash" method taught in the

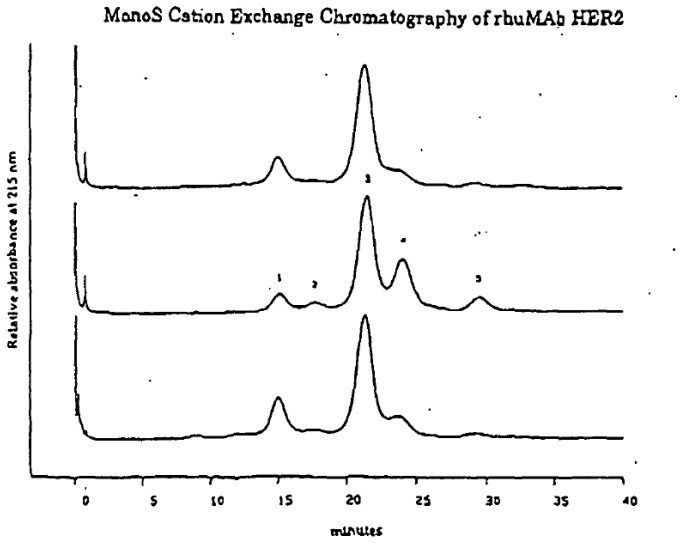
'218 patent. (Ex. 2006 (Basey) ¶¶3-6; Ex. 2008 (Simpson) ¶¶2-7; Ex. 2009 (Storto) ¶¶8-10; Ex. 2011 (Yang) ¶¶4-26.) The reverse wash method was not publicly known at the time, and Andya itself provides no indication that the Example 1 starting composition had been prepared using that method. (Ex. 1004, 12-18; Ex. 2007 (Blank) ¶¶39-47.)

B. Waterside

Waterside (Ex. 1006) is a slide presentation 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 live 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 certain techniques for evaluating the characteristics of anti-HER2 antibodies referred to as "rhuMAb HER2." (Ex. 1006, 3.) It depicts the use of "Mono-S" cation exchange chromatography to characterize several rhuMAb HER2 compositions. (*Id.*, 4.) Waterside shows that such compositions may contain both acidic and basic variants, and teaches that Dr. Harris "[d]ecided not to remove the deamidated material [*i.e.*, acidic variants]." (*Id*.) Waterside does not quantify the amount or relative percentage of each type of protein within

the compositions. (*Id.*, 5-7.) For example, Waterside presents the following chromatograms of three different compositions:



(*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 there no demarcations along the x-axis to indicate the points at which the line transitions from representing one type of protein to another.

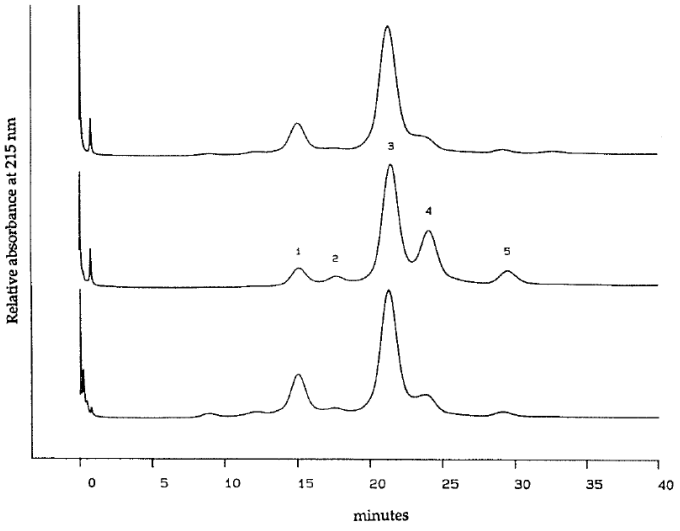
Waterside also does not disclose how to create the starting composition that resulted in the rhuMAb HER2 compositions being tested. (*See id.*, 3-7.)

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 the prosecution of the '218 patent. (Ex. 1002, 122.) According to Pfizer, Harris discloses essentially the same information (including "nearly (if not) identical chromatograms") as Waterside. (Paper 1, 18-22.)

Harris depicts the use of Mono-S cation exchange chromatography to characterize several rhuMAb HER2 compositions (and, unlike Waterside, identifies specific chromatography conditions). (Ex. 1005, 4-5.) Harris includes chromatograms that indicate that the rhuMAb HER2 compositions may contain acidic and basic variants:



(*Id.*, 7.) As with Waterside, 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.

Harris also does not disclose how to create the starting composition that resulted in the rhuMAb HER2 compositions being tested. (*See id.*, 4-9.)

V. PERSON OF ORDINARY SKILL

A person of ordinary skill in the art of the '218 patent would have a Ph.D. in chemistry, biochemistry, chemical engineering, or a closely-related field, and experience with protein chemistry, or the equivalent knowledge gained through an M.S. in chemistry, biochemistry, chemical engineering or a closely-related field, and three-to-five years of relevant protein chemistry work experience.

Pfizer's proposed definition is similar (Paper 1, 9), and to the extent there is any substantive difference, the Board should deny institution under either party's proposed definition for the reasons set forth below.

VI. CLAIM CONSTRUCTION

A. "Therapeutic Composition"

For purposes of this proceeding, the only term requiring construction is "therapeutic composition" (the preamble to all challenged claims), which should be construed to mean "a composition containing a therapeutically effective amount of a polypeptide." 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 or other pathogen-neutralizing polypeptide to have medicinal or healing properties. (*See, e.g.*, Ex. 2015 (Taber's

Cyclopedic Medical Dictionary), 1934 (defining "therapeutic" as "[h]aving medicinal or healing properties").) This construction is 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.").)[2]

Pfizer, by contrast, argues that the word "therapeutic" should be read out of the claims entirely. (Paper 1, 32-34.) Pfizer contends that the term should be given no construction on the ground that the preamble is not limiting. (*Id.*, 32-33.) Pfizer also argues, in the alternative, that it should be construed to mean "an anti-HER2 antibody with the claimed degree of purity." (*Id.*, 33.) Pfizer concedes that this construction is indistinguishable from reading out the term because the claims "already require an anti-HER2 antibody having a specified amount of acidic variants." (*Id*., 34.)

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

Pfizer's attempt to excise the term "therapeutic" from the claims is improper. 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. Thus, the "therapeutic composition" preamble "breathes life and meaning into the claims and, hence, is a necessary limitation to them." *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 866 (Fed. Cir. 1985), *overruled on other grounds*, *Nobelpharma AB v. Implant Innovations, Inc.*, 141 F.3d 1059 (Fed. Cir. 1998); *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)).

B. "Pharmaceutically Acceptable Carrier"

Pfizer proposes construing "pharmaceutically acceptable carrier" to mean "a non-toxic carrier to recipients at the dosages and concentrations employed." (Paper 1, 35.) No construction of this term is necessary at this time, but Genentech

does not contest Pfizer's proposed construction for purposes of this preliminary response.

VII. ARGUMENT

The Board should deny institution. Pfizer's petition is facially flawed for at least four reasons.

First, each of the asserted references fails to expressly disclose certain claim limitations. Pfizer is, in effect, asserting that these limitations are disclosed only under principles of inherency. But there is a high standard for demonstrating that an element is inherently taught in the prior art, and Pfizer fails to show that it has met its burden for satisfying that standard.

Second, Pfizer has failed to provide a legally sufficient basis for finding that any of the missing claim limitations would have been obvious. At no point does Pfizer present evidence of a motivation to modify the asserted references or evidence of a reasonable expectation of success. Instead, Pfizer's arguments generally consist of a single, conclusory sentence, which is insufficient as a matter of law.

Third, Pfizer has failed to present a *prima facie* case that any of the prior art references is enabling. Indeed, Pfizer does not even attempt to argue that two of the references, Waterside and Harris, are enabling. But even if any of Pfizer's references were to disclose the composition as claimed (though they do not), none

of them teaches how to make it. Tellingly, multiple experts—including Pfizer's own expert in this case—have attempted to obtain the claimed composition based on the teachings of the prior art in order to demonstrate that the prior art is enabling, but none has been able to do so. In every case, the expert ultimately turned to teachings outside the prior art and relied on post-dating technology, confirming that the prior art alone does not enable the '218 invention.

Fourth, Pfizer's petition is based on references that were overcome during prosecution. For that reason, Pfizer's petition also should be rejected under Section 325(d).

Alternatively, at a minimum, Pfizer's asserted prior art references are redundant, and Pfizer treats them as providing the same disclosure for purposes of its petition. Therefore, to the extent the Board institutes IPR on any ground, it should reject all other grounds as redundant.

A. Andya (Ground 1): Pfizer Has Not Demonstrated A Reasonable Likelihood Of Success With Respect To Any Challenged Claim.

1. Pfizer Fails To Demonstrate That Andya Discloses Or Renders Obvious A Composition Containing The "Acidic Variants" Required By All Challenged Claims.

Pfizer fails to show that Andya teaches a composition with the acidic variants required by the challenged claims. All of the challenged claims require "a mixture of anti-HER2 antibody and one or more acidic variants" with certain

characteristics. Pfizer asserts that the challenged claims are anticipated by a particular antibody composition described in Andya: the "Example 1" composition (also referred to as the "reconstituted formulation") that is analyzed in Andya Figures 5-8. (Paper 1, 38-39.) Yet Pfizer identifies nothing in Andya that indicates that the Example 1 composition contains any acidic variants, let alone acidic variants with the particular characteristics required by the claims. Instead, Pfizer attempts to fill the gap by relying on Andya's disclosures regarding a ***different*** embodiment (the so-called "screening-study" composition). Such mixing-and-matching from different embodiments cannot support an assertion of anticipation as a matter of law. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008) (a prior art reference is not anticipatory if it merely "includes multiple, distinct teachings that [an ordinary] artisan might somehow combine to achieve the claimed invention."). Pfizer also fails to assert a cognizable claim of obviousness; rather, Pfizer's entire obviousness argument consists of a single, conclusory sentence, which is insufficient as a matter of law. *Veeam Software Corp. v. Symantec Corp.*, IPR2013-00151, Paper 7, *12 (P.T.A.B. Aug. 7, 2013).

a. Andya does not disclose that the Example 1 composition contains the "acidic variants" required by all challenged claims.

Andya does not disclose that the composition depicted in Example 1 contains "one or more acidic variants," let alone the particular acidic variants required by the challenged claims.[3] As Pfizer concedes, Andya does not describe the complete contents of the Example 1 composition, but merely indicates that it contains 78-82% "native (not degraded) protein." (Ex. 1004, 6, 39-40 (Figs. 5-8); Paper 1, 39.) Although Pfizer appears to characterize this as an express disclosure of the required "one or more acidic variants" (Paper 1, 39), Pfizer is actually making an inherency argument, *i.e.*, that a composition containing 78-82% native protein necessarily contains "one or more acidic variants" in the remaining 18-22%.

Regardless of whether Pfizer alleges an express or inherent disclosure, however, Pfizer's argument is plainly incorrect. A composition that contains 78-

[3] All challenged claims further recite a composition "wherein the acidic variant(s) are predominantly deamidated variants wherein one or more asparagine residues of the anti-HER2 antibody have been deamidated" and "wherein the deamidated variants have Asn30 in CDR1 of either or both V_L regions of humMAb4D5-8 converted to aspartate."

82% "native (not degraded) protein" contains 18-22% non-native (degraded) protein, but there are many types of non-native protein, including acidic variants, neutral variants, and basic variants. (Ex. 1017, 5-6; *see also* Paper 1, 13-14.) Andya does not identify the type of non-native protein in the Example 1 composition, which could consist entirely of non-acidic variants. (*See* Ex. 1004, 28.) Thus, Andya neither expressly nor inherently discloses that the Example 1 composition contains "one or more acidic variants" as required by the claims.

The European Patent Office has already rejected the argument that Pfizer advances here. In the proceedings regarding the European counterpart to the '218 patent, the EPO Board of Appeal held that Andya's mere disclosure that Example 1 contains 78-82% native protein provided no information regarding the contents of the remaining 18-22%, and that "[n]o conclusion can thus be drawn about the nature of any particular variant which might be present." (Ex. 1023, 17-18.)

Pfizer asserts (incorrectly) that its position is supported by decisions in the prosecution of certain applications related to the '218 patent. (Paper 1, 40 n.12.) In those prosecutions, claims requiring "one or more acidic variants … wherein the amount of the acidic variant(s) is less than about 25%" were rejected over Andya. (Ex. 1008, 112, 226; Ex. 1009, 51, 91; Ex. 1010, 128, 373.) Critically, however, there was no assertion by the Examiner that Andya disclosed that the Example 1 composition necessarily contained an acidic variant. To the contrary, the Examiner

agreed that Andya "discloses nothing" about the degraded proteins in the Example 1 composition, and that it therefore might not contain ***any*** acidic variants. (Ex. 1008, 226.) The Examiner simply believed—erroneously—that this lack of disclosure was irrelevant to whether Andya disclosed the claim element:

> The deam[i]dated variants may include some amount of acidic variants; these at most would be at a level of about 18-19% …. At the other extreme, ***there might be no acidic variants at all*** (e.g. the de[ami]dated variants might all be basic variants). At either extreme, and for all cases in between, the amount of acidic variants would necessarily be present in an amount "less than about 25%" of the composition. The limitations of the rejected claims are thus met.

(Ex. 1008, 226.) As seen above, the Examiner focused solely on the claim requirement that the total amount of acidic variants be less than 25% of the composition, and rejected the claims based on the mistaken belief that a composition with "no acidic variants at all" could satisfy the claims. (*Id.*; *see also* Ex. 1009, 91; Ex. 1010, 373.) A composition with no acidic variants plainly does not satisfy the separate requirement of a composition that contains "one or more acidic variants."

b. Pfizer's anticipation theory improperly relies on a combination of two separate embodiments within Andya.

Pfizer improperly relies on a combination of two separate embodiments within Andya for its theory that Andya anticipates the challenged claims. Such mixing-and-matching from different embodiments is not permitted for purposes of anticipation.[4] As the Federal Circuit has explained, "it is not enough that the prior art reference … includes multiple, distinct teachings that [an ordinary] artisan might somehow combine to achieve the claimed invention." *Net MoneyIN, Inc.*, 545 F.3d at 1371. Rather, the reference must "clearly and unequivocally disclose the claimed [invention] or direct those skilled in the art to the [invention] without ***any*** need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference." *Id*. (emphasis in original, internal quotation marks omitted).

Pfizer purports to rely on the Example 1 composition for its anticipation theory. But as discussed above, Andya merely discloses that the Example 1 composition consists of 78-82% native protein, which does not indicate whether the remaining 18-22% contains any acidic variants. (*See* Ex. 1004, 28.) Given this

[4] Pfizer also fails to assert a legally sufficient claim of obviousness, as set forth in Section VII(A)(1)(c) below.

deficiency, Pfizer argues that Andya discloses "one or more acidic variants" (and the particular deamidated variants required by the claims) based on its description of a different embodiment with different characteristics—the "liquid state" screening-study composition. (Paper 1, 39.)

Andya describes "early screening studies" that were designed to test the stability of various anti-HER2 antibody formulations. (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)." (*Id.*) Thus, the ***screening-study*** composition included at least one acidic variant, *i.e.*, deamidated at asparagine.

Andya does not make any such disclosure regarding the Example 1 composition. Since the purpose of "Example 1" is to demonstrate the stability of the Andya composition, 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. (*Id.*, 6, 39-40.) But the precise form of the non-native protein (*e.g.*, acidic, neutral, basic) is irrelevant and thus not discussed. 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 composition (which is an aqueous solution) 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. And one of those potential degradation paths—succinimide formation—results in only basic variants. (Ex. 1017, 6-7.) Thus, Andya does not indicate whether the Example 1 composition contains any acidic variants.

Tellingly, Pfizer juxtaposes the description of the screening-study composition (Ex. 1004, 21) with the description of the Example 1 composition (*id.*, 28), and suggests that both statements are describing the same composition (*see* Paper 1, 39). They are not. (Ex. 1004, 21, 28.) Nor are there any relevant similarities identified that would indicate that the two different compositions necessarily would degrade in the same way. Indeed, the only similarity that Andya discloses is that both the screening-study composition and the Example 1 composition contained rhuMAb HER2 antibodies. (*Id.*) But that is not determinative. Even if the amino acid sequence of two antibodies is the same, they will not necessarily degrade in the same manner and to the same degree in different compositions.

For example, Andya explains that the Example 1 composition is formed by lyophilizing and then reconstituting a rhuMAb HER2 antibody in an aqueous solution. (Ex. 1004, 28.) It is well-established that lyophilizing and reconstituting

an antibody may change the manner in which the protein degrades. (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 (for example, its temperature and pH level). (Ex. 1034, 6, 8-9, 15.) Because Andya is silent as to all of these factors, there is no basis to find that the Example 1 composition would degrade in the same manner as the screening-study composition. Indeed, the EPO Board of Appeal considered the identical issue, and likewise concluded that Andya "is silent about the nature of the degraded antibody present in these reconstituted formulations of rhuMAb HER2 [*i.e.*, Example 1]" and "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.)[5]

[5] Pfizer presumably does not rely on the Andya screening-study composition for purposes of its anticipation challenge because the screening-study composition lacks various other claim elements, such as "less than about 25%" acidic variants. (*See* Ex. 1004, 21.)

c. Pfizer fails to advance a cognizable obviousness theory.

Pfizer fails to advance a legally cognizable obviousness theory with respect to the "one or more acidic variants" claim limitation as well as the additional limitations requiring particular deamidated variants. Pfizer argues that if the Board finds that these limitations are not disclosed by Andya, the Board should nevertheless find them to be obvious in light of Andya. (Paper 1, 40, 43, 45.) Pfizer's challenge, however, fails to articulate a proper basis for finding these elements obvious, and therefore is insufficient as a matter of law.

Pfizer's entire obviousness argument for each element consists 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." (Paper 1, 40.) Pfizer includes similar conclusory sentences regarding the claim elements requiring particular deamidated variants. (*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 reason or explanation how a person of ordinary skill in the art would modify Andya to achieve the claimed invention. Nor does Pfizer even attempt to show that a person of ordinary skill would have been motivated to make such modifications or have a reasonable expectation of success in doing so. That failure of proof is fatal. *See, e.g.*, *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). Thus, Pfizer fails to present a cognizable argument that the challenged claims are rendered obvious by Andya.

2. Pfizer Fails To Demonstrate That Andya Is Enabling.

Pfizer also fails to demonstrate that Andya enables one of ordinary skill in the art to make the claimed composition. For that additional reason, Pfizer's petition should be denied. *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)); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 501 F.3d 1263, 1268 (Fed. Cir. 2007) (finding prior art reference disclosing the claimed composition not anticipatory because "it does not tell [a person of ordinary skill in the art] how to obtain it"); *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. (*See* Paper 1, 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).[6] Genentech respectfully submits, however, that the question of whether a prior art publication is enabling is a proposition of unpatentability for which the petitioner bears the burden of proof, and thus 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., Ltd. 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.*

[6] 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.

Diesel Brake Co., 829 F. Supp. 2d 11, 33 (D. Conn. 2011), *aff'd*, 494 F. App'x 96 (Fed. Cir. 2013) (same).[7]

b. Pfizer fails to present a *prima facie* case that Andya is enabling.

Pfizer fails to present a *prima facie* case that Andya is enabling. "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); *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"). Pfizer identifies nothing in Andya that would teach a person of ordinary skill to make a composition having the amount and identity of

[7] Pfizer suggests that since Andya shares a specification with a (non-prior art) patent, it also should be entitled to the presumption of enablement that applies to prior art patents. (Paper 1, 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).

acidic variants in the challenged claims, let alone how to do so without undue experimentation.

Andya discloses a method for lyophilizing and reconstituting 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.*) Thus, even if Andya disclosed that the final output of its formulation experiments was a composition that necessarily falls within the scope of the challenged claims (though 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 person of ordinary skill in the art to create a composition as claimed.[8]

Pfizer, in an attempt to show that Andya is enabling, improperly relies on certain experiments performed by its declarant Dr. Buick. (Paper 1, 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

[8] 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.

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. Nor did he rely on an established prior art method for creating and purifying an antibody. 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 derived from numerous different sources, including modern-day purification techniques and technology. Such experiments plainly fail to show that Andya is enabling.

As an initial matter, Dr. Buick ***calibrated his protocols using Herceptin®—Genentech's own anti-HER2 drug composition***. (Ex. 1042 ¶19.) That alone renders his experiments meaningless, as Herceptin® was not approved and available for sale until September 1998—post-dating Andya and the priority date of the '218 patent. (Ex. 1004, 1; Ex. 1014, 2.) Thus, a person of ordinary skill attempting to follow Andya's teachings would not have had Genentech's inventive composition as a reference to guide their work.

Beyond that, Dr. Buick made numerous other departures from Andya and from the prior art teachings for purposes of his experiments. For example, Andya teaches that the Example 1 composition featured the anti-HER2 antibody described in a prior Genentech patent application—International PCT Application No. WO 92/22653 ("Carter," Ex. 1043). (Ex. 1004, 21.) Given that disclosure in Andya, Dr. Buick purported to rely on Carter to derive the antibody for his experiments.

(Ex. 1042 ¶10.) Yet Dr. Buick did not follow all of Carter's teachings regarding the antibody—whereas Carter teaches that its antibody was produced using a human embryonic kidney cell line (Ex. 1043, 68-69), Dr. Buick chose to use a Chinese hamster ovary cell line (Ex. 1042 ¶8). The use of different cell lines impacts the post-translational modification and the chemical degradation of a protein, and thus the formation of acidic variants. (Ex. 2004, 701-704; Ex. 2005, 122.)

Dr. Buick similarly cherry-picked from a large number of different references (rather than relying on Andya, or any single prior art reference) in order to select the process and inputs for each separate step in his experiments. For example, Dr. Buick:

(1) selected a particular mammalian expression vector ("pcDNA3.1") for expressing the antibody (Ex. 1042 ¶11);

(2) back-translated the amino acid sequence of the antibody and optimized the sequence for transcription (using methods that Dr. Buick ***did not disclose***) (*id.* ¶12);

(3) cloned the DNA sequence into the expression vector using a particular technique described in a textbook ("Ausubel," Ex. 1047) (*id.* ¶13);

(4) performed transient transfection using a particular technique described in a different reference ("Jordan," Ex. 1044) (*id.* ¶14); and

(5) purified the antibody according to a particular protocol developed in ***2011*** (*id.* ¶16).

None of the foregoing steps were described or suggested in Andya, and Dr. Buick does not assert otherwise. (*See* Ex. 1042 ¶¶10-16.) At each point, Dr. Buick had numerous choices: which cell line to use, which cell culture media and conditions to select, which expression vector to use, how to optimize the DNA sequence, how to initiate DNA cloning, how to perform transfection, and how to perform purification. As before, each of these choices affects the 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. 2004, 701-704; Ex. 2005, 122.)[9]

Several of Dr. Buick's choices are particularly telling. For example, Dr. Buick chose to follow the cloning technique taught in Ausubel, yet instead of also following Ausubel's transfection technique, he instead chose to use a different

[9] 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. *See, e.g.*, 42 U.S.C. § 262(l)(2); 21 C.F.R. § 601.2(a).

transfection technique taught in Jordan. (Ex. 1042 ¶¶11, 14; *see also* Ex. 1047, 24.) Similarly, Dr. Buick states that he chose to use a particular type of purification (protein-A Sepharose purification) because it is mentioned in Andya. (Ex. 1042 ¶16; *see also* Ex. 1004, 13.) Yet Dr. Buick chose to use the protein-A Sepharose protocol released ***in 2011*** rather than the earlier version of the protocol that was available at the time of Andya. (Ex. 1042 ¶16.)

The fact that Dr. Buick failed to follow established prior art protocols is not surprising. Indeed, as the Genentech inventors explained in the European proceedings, they were not able to obtain a purified form of the anti-HER2 antibody with less than 25% acidic variants using conventional methods, and thus had to develop the novel "reverse wash" method in order to do so. (Ex. 2007 (Blank) ¶¶39-46; *see also* 2006 (Basey) ¶¶3-6.)

Dr. Buick's experiments further demonstrate that Andya does not enable a person of ordinary skill to create a "therapeutic composition" as required by all challenged claims. 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). Dr. Buick's experiments, however, involved a final composition of only 24 ***micrograms***—such a small amount that all of the peaks could not even be measured. (Ex. 1042 ¶¶19,

21.) A sample of that size does not contain enough antibody to be therapeutically effective. (Ex. 1014 (FDA-approved dosage is 440 ***milligrams***).)

Critically, Pfizer's petition is silent as to the amount of experimentation that would be required for a person of ordinary skill to devise Dr. Buick's multi-step method for creating and purifying a rhuMAb HER2 antibody in order to form (allegedly) a composition as set forth in the challenged claims. (*See* Paper 1, 50-51.) This too is fatal, as the ultimate question of enablement is whether a prior art reference teaches a person of ordinary skill to make the invention "without undue experimentation." *In re Morsa*, 803 F.3d at 1377. Yet Pfizer does not even mention the concept of "undue experimentation" or attempt to address the *Wands* factors for assessing whether the requisite amount of experimentation is undue. *See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Given this failure, Pfizer's petition plainly does not present a *prima facie* case that Andya is enabling.

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

Pfizer also argues that Genentech previously conceded that Andya enables the claimed compositions. (Paper 1, 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 lyophilizing and reconstituting an anti-HER2 composition, *i.e.*, a method for ***formulating*** an already-existing composition.

For example, in the '218 patent, Genentech simply 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 the claimed composition in accordance with the teachings of the '218 patent, that composition could be formulated by lyophilizing and reconstituting it via the method taught in Andya. At no point did Genentech suggest that Andya would enable one to create the claimed composition itself. (*See id.*)

Similarly, during the prosecution of the U.S. Patent No. 6,267,958 ("the '958 patent"), which is a U.S. counterpart to Andya and contains a similar disclosure, 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 (*i.e.*, lyophilizing and reconstituting a pre-existing starting 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.

B. Waterside (Ground 2): Pfizer Has Not Demonstrated A Reasonable Likelihood Of Success With Respect To Any Challenged Claim.

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 document is publicly accessible—and qualifies as a printed publication—only if it "has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it and recognize and comprehend therefrom the essentials of the claimed invention without need of further research or experimentation." *Cordis Corp. v. Boston Sci. Corp.*, 561 F.3d 1319, 1333 (Fed. Cir. 2009) (internal citation and quotation marks omitted). 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 has not demonstrated that Waterside was made available to ***any*** members of the public prior to the critical date. Pfizer alleges that Waterside was distributed to certain attendees of the 1996 Waterside Monoclonal Conference (Paper 1, 7), but Pfizer's evidence does not corroborate that assertion. Pfizer relies on the declaration of Keith Carson, who served as the executive director of the organization that hosted the Waterside conference ("WilBio"). (Ex. 1041 ¶1.) But Mr. Carson merely purports to describe the process by which presentations generally were distributed to certain conference attendees. (*Id.* ¶3.) Even if Mr. Carson's description were accurate, it would fail to authenticate the Waterside document itself or demonstrate that it was in fact distributed.

"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"). 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 Mr. Carson provide any basis to conclude that he could identify an authentic copy if he were presented with one. For example, Mr. Carson does not assert that

Waterside came from WilBio's business records or from his own personal records. Nor does Mr. Carson identify any record-keeping system anywhere in the world from which one could confirm that the version of Waterside that Pfizer relies on matches a document distributed at the Waterside conference.

Instead, Mr. Carson simply states that a document purportedly attached as Exhibit B to his declaration "appears to be in the same format WilBio would have used to print presentations included in binders distributed at conferences run by WilBio during that time frame, including the 1996 Waterside Monoclonal Conference." (Ex. 1041 ¶6.) In fact, Mr. Carson failed to include ***any*** exhibits to his declaration (*see* Ex. 1041), but even if he had, he does not identify any markings or indicators on the missing document that would identify it as being the same as a document that was distributed at the Waterside conference.[10] Thus, Mr. Carson's declaration fails to demonstrate that the version of the slide presentation that Pfizer relies on—or any version at all—was actually distributed at the

[10] The version that Pfizer submitted separately (Ex. 1006) appears to be a generic print-out of a slide presentation in a standard printing format, not any special format that would be unique to WilBio. It is attached to two pages from the 1996 Waterside conference program, with annotations on the cover (such as "EPO-DG 1, 20 12 2006") related to the 2006 EPO proceedings. (Ex. 1006, 1.)

conference. *See, e.g.*, *Celltrion, LLC v. Biogen, Inc.*, IPR2017-01230, Paper 10, *15 (P.T.A.B. Oct. 12, 2017) (finding petitioner failed to meet its burden because "it is unclear from Dr. Andreeff's testimony what version of the newsletter purportedly would have been discussed with and disseminated to referring physicians").

Pfizer also suggests that Genentech "confirmed" in two prior proceedings that Waterside was distributed at the Waterside conference. (Paper 1, 7-8.) Not so. For example, Genentech submitted a version of Waterside in its IDS in the prosecution of the '218 patent and indicated (in the document title) that the slides were "presented" at the Waterside conference—not distributed in paper form. (Ex. 1002, 81.) And the mere fact that a document is cited in an IDS "is insufficient to demonstrate that a document is a printed publication." *LG Elecs., Inc. v. Advanced Micro Devices, Inc.*, IPR2015-00329, Paper 13, *12 (P.T.A.B. July 10, 2015); *see also Microsoft Corp. v. Biscotti Inc.*, IPR2014-01457, Paper 9, *25-28 (P.T.A.B. Mar. 19, 2015) (same).

Similarly, in the UK proceedings Genentech elected not to dispute that Waterside was publicly available before the priority date of the European counterpart patent. (Ex. 1027, 1.) At no point did Genentech assert or concede that Waterside satisfied the higher threshold required for a "printed publication." And even if Genentech had done so (though it did not), the Board has recognized

that such 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." *See, e.g.*, *Argentum Pharm. LLC v. Research Corp. Techs., Inc.*, IPR2016-00204, Paper 19, *10-11 (P.T.A.B. May 23, 2016) (denying institution despite Patent Owner's stipulation in separate proceeding that prior art reference constituted a "printed publication" because "Patent Owner may have agreed to stipulate to certain facts to streamline matters at trial there, for example, or had other reasons to stipulate on the issue in a case involving different parties in a different forum, regardless of whether the [prior art reference] was, in fact, publicly accessible or not"); *Teva Pharm. USA, Inc. v. Indivior UK Ltd.*, IPR2016-00280, Paper 23 at 10-11 (P.T.A.B. June 10, 2016) (same).

In sum, nothing in Pfizer's petition satisfies Pfizer's burden of demonstrating that the particular version of the Waterside slides that it relies on was in fact distributed at the 1996 Waterside conference.

Second, even if Pfizer had shown that its particular version of Waterside had been distributed at the 1996 Waterside conference (though it has not), Pfizer also failed to show that the alleged distribution made the reference "sufficiently accessible to the public interested in the art." *In re Cronyn*, 890 F.2d at 1160. Pfizer relies entirely on its speculation that the reference would have been included in the conference binder that Mr. Carson stated was distributed to approximately

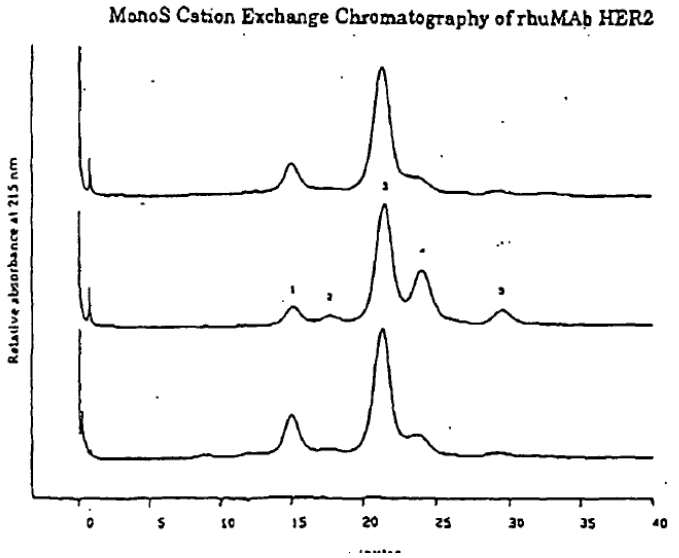
200 (but not all) attendees. (Paper 1, 7.) Even if true, Pfizer does not identify any way in which the interested public could have known that Waterside would be included in binders distributed to certain attendees at the conference, nor any way in which the interested public could have located the reference 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). Without any evidence that Waterside was indexed or otherwise identifiable to those seeking it, Pfizer failed to meet its burden of demonstrating that "persons interested and ordinarily skilled in the subject matter or art[,] exercising reasonable diligence, can locate it." *In re Lister*, 583 F.3d 1307, 1311 (Fed. Cir. 2009).

2. Pfizer Fails To Demonstrate That Waterside Renders Obvious The Challenged Claims.

Pfizer's petition is facially deficient because it fails to demonstrate that Waterside discloses or renders obvious three separate claim elements.

a. Pfizer fails to demonstrate that Waterside discloses or renders obvious a composition that contains "less than about 25%" acidic variants.

Pfizer fails to demonstrate that Waterside discloses 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 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 an alleged visual inspection of the drawing) or inherently (based on Dr. Scandella's alleged calculation of the area under each curve using computer software). (Paper 1, 55-56.) Neither theory is supportable. Pfizer's visual inspection is wholly speculative, while Dr. Scandella's 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).

Most notably, Waterside does not provide quantified reference points in the above figure. 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. 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. 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. 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., Inc.*, 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. Without a reference baseline (y-axis), it is impossible to determine the height of

any point along the curve.[11] Likewise, without horizontal dividing lines (x-axis), one must simply speculate where to demarcate the portions of the curve that correspond to native proteins or variants. Given the lack of clearly-defined reference points, the Waterside drawing provides no basis to conclude that the required amount of acidic variants is "necessarily present" in the Waterside composition. *Trintec Indus., Inc.*, 295 F.3d at 1295.

Moreover, Dr. Scandella's own calculations demonstrate the unreliability of measurements derived from drawings that are not produced according to a precise scale. Pfizer asserts that the Waterside drawing "appear[s] to be the same" as the chromatogram in Harris. (Paper 1, 19.) Yet when Dr. Scandella purportedly performed the same calculations on each diagram, 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 variants is necessarily and inevitably present in the Waterside composition.

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[11] Tellingly, Dr. Scandella states that he performed "baseline corrections" in order to generate a reference baseline (Ex. 1003 ¶ 59), but he provides no explanation for how he did so, nor does he purport to identify anything in Waterside that identifies a specific height value for any point along the curve.

Pfizer argues, in the alternative, that even if Waterside does not inherently disclose a composition "wherein the amount of acidic variant(s) is less than about 25%," this element would have been obvious. (Paper 1, 56.) But Pfizer's ***only*** evidence of a motivation to modify Waterside in this manner 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 of acidic variants).) And in fact, Waterside ***teaches away*** from removing acidic variants, with the author explaining that he "[d]ecided ***not to remove*** the deamidated material." (Ex. 1006, 7.) This is not surprising, as removing acidic variants involves considerable work and results in loss of yield (Ex. 1034, 5-6), 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* Paper 1, 56). 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."). The fact that Pfizer selectively ignores those teachings leading away from the challenged claims confirms its reliance on hindsight. In sum, Pfizer has failed to show that a person of ordinary skill in the art would have been motivated to modify

Waterside to create the claimed composition with less than about 25% acidic variants.

b. Pfizer fails to demonstrate that Waterside discloses or renders obvious the antibody humMAb4D5-8.

Pfizer fails to demonstrate that Waterside discloses the antibody humMAb4D5-8, as required by all challenged claims. Pfizer concedes that Waterside does not expressly refer to humMAb4D5-8, but asserts that the composition characterized in Waterside is "inherently" humMAb4D5-8. (Paper 1, 57.) Pfizer, however, does not raise a proper inherency argument. Instead, Pfizer simply lists the various descriptions in Waterside of the characterized antibody (for example, that it was being considered in Phase III clinical trials) and asserts that, at that time, humMAb4D5-8 was the only antibody that fit those descriptions. (*Id.*) That is not the standard for inherency. Inherency requires that a missing claim element "must inevitably result" from a reference's disclosure. *In re Montgomery*, 677 F.3d at 1380. Pfizer has not asserted that creating a composition with the features described in Waterside would "inevitably result" in the claimed composition, and therefore it has failed to raise a cognizable argument that Waterside inherently discloses humMAb4D5-8.

Pfizer argues, in the alternative, that the humMAb4D5-8 limitation would have been obvious to a person of ordinary skill in the art. But—as with many of

Pfizer's obviousness arguments—Pfizer includes only a single, conclusory sentence. (Paper 1, 57.) As discussed above, such a cursory assertion is insufficient as a matter of law. *See* Section VII(A)(1)(c).

c. Pfizer fails to demonstrate that Waterside discloses or renders obvious a composition "wherein the acidic variant(s) are predominantly deamidated variants."

Pfizer fails to demonstrate that Waterside discloses a composition "wherein the acidic variant(s) are predominantly deamidated variants wherein one or more asparagine residues of the anti-HER2 antibody have been deamidated," as required by all challenged claims. In particular, Pfizer fails to show that the acidic variants are "***predominantly*** deamidated variants." According to Pfizer, all of the acidic variants in Waterside are represented by "peak 1" and "peak 2" in the drawing on page 4. (Paper 1, 56-57.) Pfizer further asserts that ***all*** of the variants in peak 1 and peak 2 are deamidated, and therefore that the Waterside acidic variants are "predominantly deamidated." (*Id.*) Yet Pfizer has no evidence regarding the type of variants in peak 2. Pfizer concedes that Waterside is silent as to the contents of peak 2, but asserts that the variants are "inherently" deamidated because ***Harris*** appears to describe a similar composition and teaches that the ***Harris "peak 2"*** variants are deamidated. (Paper 1, 19-20, 57.) Once again, that is not inherency—inherency requires that a missing claim element "must inevitably result" from a reference's disclosure. *In re Montgomery*, 677 F.3d at 1380. Pfizer identifies

nothing in ***Waterside's*** disclosure that requires "peak 2" to necessarily contain deamidated variants, and thus Pfizer fails to show that Waterside inherently discloses that its acidic variants are "predominantly deamidated variants" as claimed.

Pfizer argues, in the alternative, that this limitation would have been obvious to a person of ordinary skill—once again raising its argument in a single, conclusory sentence. (Paper 1, 64.) As discussed above, that is insufficient to support institution of an IPR as a matter of law. *See* Section VII(A)(1)(c).

3. Pfizer Fails To Demonstrate That Waterside Is Enabling.

Pfizer fails to present a *prima facie* case that Waterside is an enabling prior art reference. Unlike with Andya (*see* Paper 1, 48-51), Pfizer does not even attempt to argue that Waterside is enabling (*see id.*, 51-61).[12] Instead, Pfizer

[12] Pfizer asserts, in its discussion of Andya, that prior art publications should be presumed to be enabling (Paper 1, 48), but Pfizer never asserts that Waterside provides an enabling disclosure. As discussed in Section VII(A)(2)(a), Genentech maintains that whether a prior art publication is enabling is a proposition of unpatentability for which the petitioner bears the burden of proof, and thus there should be no presumption of enablement. *See* 35 U.S.C. § 316(e); *Aqua Prods.*, 872 F.3d at 1306.

improperly attempts to include such arguments in the declaration of Dr. Buick without addressing those arguments in its petition. (*See, e.g.*, Ex. 1042 ¶¶6-7, 25-29.) The Board has repeatedly denied petitions that rely on arguments raised only in an accompanying declaration. *See, 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); *Fidelity Nat'l Info. Servs., Inc. v. DataTreasury Corp.*, IPR2014-00489, Paper 9, *10-11 (P.T.A.B. Aug. 13, 2014). But even if the Board were to consider the question of whether Waterside is enabling, the only evidence properly in the record demonstrates that it is not. For that additional reason, Pfizer's petition should be denied.

Waterside is a series of slides directed to the chromatographic characterization of rhuMAb HER2 antibodies. (Ex. 1006, 3.) As discussed above, Pfizer's petition is premised on the theory that the composition characterized in certain Waterside slides discloses or renders obvious all of the elements of the challenged claims. But even if that were true (though it is not), Pfizer identifies nothing in Waterside that would teach a person of ordinary skill how to make the composition, let alone how to do so without undue experimentation. In other words, Waterside depicts the ***results*** of a chromatographic analysis of a rhuMAb

HER2 antibody, but it provides no disclosure as to how to ***create*** the antibody in the first place. (*See* Ex. 1006, 3-7.)

Dr. Buick attempts to show that Waterside is enabling based on certain experiments. As noted above, Pfizer did not raise this argument in its petition and thus the Board should not consider it. But in any event, Dr. Buick's plainly fail to show that Waterside is enabling.

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.) Dr. Buick merely tested that same composition using a different technique: "Mono-S." (*Id.* ¶27.) But Mono-S is not even taught in Waterside—it is taught in ***Harris***. (*Id.*) Dr. Buick, by his own admission, considered the teachings of Waterside and Harris collectively in a single analysis—he did not consider whether each reference was independently enabling. (*Id.* ¶¶25-29.) Pfizer's petition, however, relies on each reference in separate grounds 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.

Dr. Buick's experiments, moreover, do not show that Waterside and Harris are enabling, even in combination. None of the techniques that Dr. Buick relied on

to create his composition (as detailed in Section VII(A)(2)(b) above) were disclosed in or derived from Waterside or Harris. Further, although Dr. Buick purported to use the Harris "Mono-S" technique to test the composition, he indisputably 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.) 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.) Likewise, Waterside teaches that its antibody composition was manufactured at 12,000-liter scale (Ex. 1006, 4),[13] yet Dr. Buick instead chose to perform his experiments only on a small "analytical scale." (Ex. 1003 ¶112.) Such differences in scale impact both the process and the final product. (Ex. 2012, 258-261.) And just as with Andya, Dr. Buick once again calibrated his cation-exchange protocols using commercial Herceptin® itself. (Ex. 1042 ¶27.) This evidence leads to only one conclusion—that a person of ordinary skill could ***not*** obtain the claimed composition based solely on the teachings of the prior art.

The EPO Board of Appeal similarly concluded that Waterside is not enabling. In the EP '455 patent opposition, the opponent conceded that Waterside

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

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 create a composition that matched 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 create such a composition 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 composition that purportedly matched the chromatogram in the 1995 Harris reference. (*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.)

Pfizer and its declarant Dr. Scandella were plainly aware of Dr. Wang's declaration and the EPO's decision based on it (Dr. Scandella included both on his list of materials considered (Ex. 1003, 87-88)), yet neither Pfizer nor Dr. Scandella addressed the EPO's finding that Dr. Wang's failed experiments demonstrated that Waterside and Harris are not enabling. In any event, Dr. Wang's inability to create a composition with less than 25% acidic variants without relying on the 2001 Harris reference—like Dr. Buick's own reliance on post-dating teachings and technology—confirms that Waterside (and Harris) do not enable the claimed invention.

C. Harris (Ground 3): Pfizer Has Not Demonstrated A Reasonable Likelihood Of Success With Respect To Any Challenged Claim.

1. Pfizer Fails To Demonstrate That Harris Renders Obvious The Challenged Claims.

Pfizer's petition is facially deficient because it fails to demonstrate that Harris discloses or renders obvious several different claim limitations. Because Pfizer treats Harris and Waterside as providing essentially the same teaching and raises essentially the same arguments with respect to each, Genentech's responses likewise follow along similar lines. Genentech reserves the right to draw further distinctions between Harris and Waterside in the event that the Board institutes IPR.

a. Pfizer fails to demonstrate that Harris discloses or renders obvious a composition that contains "less than about 25%" acidic variants.

Pfizer fails to demonstrate that Harris teaches 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. (Paper 1, 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.) 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. *See* Section VII(B)(2)(a).

Pfizer's alternative theory of obviousness is likewise deficient. Pfizer does not articulate a separate argument but simply asserts that this limitation would be obvious in light of Harris for the same reason it would be obvious in light of Waterside. (Paper 1, 64.) But 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. (*Id*., 56.) Thus, for the same reasons discussed in Section VII(B)(2)(a) above, the Board should find that Pfizer failed to meet its burden that Harris discloses or renders obvious a composition that contains "less than about 25%" acidic variants.

b. Pfizer fails to demonstrate that Harris discloses or renders obvious the antibody humMAb4D5-8.

Pfizer also fails to demonstrate that Harris discloses the antibody humMAb4D5-8, as required by all challenged claims. Pfizer concedes that Harris does not expressly disclose humMAb4D5-8, but asserts that "it would have been

obvious to a POSITA that the rhuMAb HER2 of Harris was [] humMAb4D5-8." (Paper 1, 64-65.) Pfizer thus argues that Harris ***inherently*** discloses that the characterized antibody is humMAb4D5-8.[14] But as with its similar argument with respect to Waterside, Pfizer does not apply the proper standard for inherency. Pfizer simply identifies certain attributes of the rhuMAb HER2 antibody that Harris mentions (for example, that three "lots" of the antibody had been produced), and asserts that humMAb4D5-8 was the only antibody that fit those descriptions at that time. (*Id.*, 65.) That is not the standard for inherency. *See In re Montgomery*, 677 F.3d at 1380 (inherency requires that a missing claim element "must inevitably result" from a reference's disclosure). Pfizer has not asserted that creating a composition with the features described in Harris "inevitably result[s]" in the claimed composition, and therefore Pfizer has failed to raise a legally sufficient argument that Harris inherently discloses humMAb4D5-8.

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[14] While Pfizer uses the word "obvious," Pfizer's assertion that it would have been obvious that the antibody "was" humMAb4D5-8 demonstrates that Pfizer is raising an inherency argument and not an obviousness argument. (*See* Paper 1, 64-65.) In any event, Pfizer does not assert that one of ordinary skill in the art would have been motivated to modify Harris and would have had a reasonable expectation of success. (*See id*.)

2. Pfizer Fails To Demonstrate That Harris Is Enabling.

As with Waterside, Pfizer fails to present a *prima facie* case that Harris is an enabling prior art reference, and the Board should not consider Pfizer's improper attempt to incorporate an enablement argument via the declaration of Dr. Buick. Moreover, as Pfizer treats Harris and Waterside as providing the same teachings, the Board should find that Harris is not an enabling prior art reference for the reasons set forth in Section VII(B)(3) above.

D. The Petition Should Be Denied Under Section 325(d) Because The Same References Were Overcome During Prosecution.

The Board should deny institution for the additional reason that the same references that Pfizer asserts in its petition were overcome during prosecution. *See* 35 U.S.C. § 325(d) (petition may be rejected because "the same or substantially the same prior art or arguments previously were presented to the Office"); *Cultec, Inc. v. Stormtech LLC*, IPR2017-00777, Paper 7, *8 (P.T.A.B. Aug. 22, 2017) (informative) (denying institution because "[i]t is beyond reasonable dispute that [the two asserted prior art references] were presented to, and considered by, the Office").

Here, there is no reasonable dispute that the Examiner considered all three asserted references during the prosecution of the '218 patent. Genentech's information disclosure statements included Andya, Waterside, and Harris. (Ex.

1002, 121-122, 302.) The Examiner indicated that he considered these three references by recording on the information disclosure statements that he examined "all references" other than those specifically marked otherwise (and no references were so marked). (*Id.*) This standard practice is sufficient to satisfy Section 325(d) and demonstrate that the references were considered. *See, e.g.*, *Cultec*, Paper 7, *10.

Moreover, the Examiner also considered the briefs, declarations, and decisions in the European proceedings that addressed whether the EP '455 patent (the European counterpart patent) was invalid in light of Andya, Waterside, and Harris. (Ex. 1002, 301-311; *see also* Ex. 1023 (EPO Decision), 14-25; Ex. 1024 (UK Decision), 36-44.) Thus, the Examiner considered essentially the same arguments that Pfizer asserts here, and determined that the '218 patent claims should issue over those references.

Therefore, in addition to the numerous deficiencies detailed above, Pfizer's petition should also be denied pursuant to Section 325(d).[15]

E. The Petition Presents Redundant Grounds.

Pfizer's petition provides no meaningful distinction among Andya, Waterside, and Harris, but simply asserts that each reference independently renders the challenged claims unpatentable. Pfizer's proposed grounds thus should be rejected as redundant.

"[M]ultiple grounds, which are presented in a redundant manner by a petitioner who makes no meaningful distinction between them, are contrary to the regulatory and statutory mandates, and therefore are not all entitled to consideration." *Liberty Mut. Ins. Co. v. Progressive Cas. Ins. Co.*, CBM2012-

[15] Contrary to Pfizer's suggestion (Paper 1, 28-32), the prosecutions of patents related to the '218 patent in which a claim was rejected over Andya are entitled to no weight. As discussed above, in those proceedings the Examiner concluded (correctly) that Andya did not disclose whether its Example 1 composition contained ***any*** acidic variants, but nevertheless rejected the proposed claims based on the mistaken belief that a composition with no acidic variants could fall within the scope of a claim that requires "one or more acidic variants." *See* Section VII(A)(1)(a).

00003, Paper 7, *2 (P.T.A.B. Oct. 25, 2012); *see also* 35 U.S.C. § 316(b); 37 C.F.R. § 42.1(b). The Board has consistently declined to consider prior art when the petitioner offers no meaningful distinction between the references. *See, e.g.*, *Riverbed Tech., Inc. v. Parallel Networks, LLC*, IPR2014-01398, Paper 11, *16-17 (P.T.A.B. Feb. 27, 2015) (declining to institute on a particular ground when it was "provided without explanation as to why it is better than or different from the [other] asserted grounds"); *Conopco, Inc. v. Procter & Gamble Co.*, IPR2013-00505, Paper 9, *17 (P.T.A.B. Feb. 12, 2014) (similar); *Berk-Tek LLC v. Belden Techs. Inc.*, IPR2013-00057, Paper 21, *5 (P.T.A.B. May 14, 2013) (similar).

Here, Pfizer fails to set forth any rationale for its multiple, redundant grounds. Pfizer presents essentially the same arguments with respect to each prior art reference, and does not purport to identify a "meaningful distinction" with respect to any claimed ground of unpatentability. Indeed, Pfizer argues that each reference independently teaches the same claim elements, and affirmatively asserts that the information disclosed in Waterside and Harris is virtually identical (Paper 1, 19-23). Accordingly, the Board should find that Pfizer's asserted grounds are redundant and, if institution is granted on any one ground, deny the rest.

F. *Inter Partes* Review Proceedings Violate The Constitution.

The Board should deny institution because this proceeding would violate Genentech's constitutional rights. Adversarial challenges to an issued patent—like

IPRs—are "Suits at common law" for which the Seventh Amendment guarantees a jury trial. U.S. Const. amend. VII; *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 376-377 (1996). Moreover, because patents are private property rights, disputes concerning their validity must be litigated in an Article III court, not before an executive branch agency. *McCormick Harvesting Mach. Co. v. C. Aultman & Co.*, 169 U.S. 606, 609 (1898). The Supreme Court has granted certiorari in *Oil States Energy Services, LLC v. Greene's Energy Group, LLC*, No. 16-712, to consider the constitutionality of IPRs. Genentech presents this challenge now to preserve the issue pending the Supreme Court's decision.

VIII. CONCLUSION

The Board should deny institution.

Respectfully submitted,

Date: December 14, 2017

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CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Patent Owner's Preliminary Response, contains 13,973 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: December 14, 2017

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CERTIFICATE OF SERVICE

I hereby certify that, on December 14, 2017, I caused a true and correct copy of the following materials:

- Patent Owner's Preliminary Response
- Certificate of Compliance
- Patent Owner's Exhibit List
- Exhibits 2001-2015

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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 MED. 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 REVIEWS IN 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) (June 2013)
2007	Declaration of Gregory Blank (submitted in European Patent Office, Case No. T 2522/10-3304) (Jan. 15, 2008)
2008	Declaration of John Simpson (submitted in European Patent Office, Case No. T 2522/10-3304) (June 24, 2013)
2009	Declaration of Laura Storto (submitted in European Patent Office, Case No. T 2522/10-3304) (July 15, 2013)
2010	Declaration of Dongyuan Wang (submitted in European Patent Office, Case No. T 2522/10-3304) (June 29, 2011)
2011	Declaration of Janet Yang (submitted in European Patent Office, Case No. T 2522/10-3304) (June 6, 2013)
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)