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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 IPR2017-01489
Patent 6,407,213

PATENT OWNER'S PRELIMINARY RESPONSE

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I. INTRODUCTION

In the early 1990s, the field of therapeutic antibodies was still in its infancy. Although scientists had known since the 1970s how to obtain antibodies from animals (*e.g.*, mice) that would bind to specific targets, those antibodies generally could not be used in humans because over time the body's own immune system would attack and inactivate them (known as an "immunogenic" response). Beginning in the late 1980s, a few scientists had attempted to create "humanized" antibodies that incorporated the binding site from a non-human antibody into a human antibody framework—which they hoped might address the immunogenicity problem by reducing the amount of non-human amino acid sequences in the antibody. But those early humanized antibodies suffered from reduced binding affinity or still produced an immunogenic response. Given those challenges, which continued throughout the late 1980s, there were no humanized antibodies on the market, and some doubted it would ever be possible to develop one that could be used therapeutically.

In the late 1980s, Genentech scientists began developing a new humanization approach that solved those problems. Rather than starting from an actual human antibody sequence, they created an artificial "consensus" sequence—consisting of the most frequently occurring amino acids at each location in all human antibodies of the same subclass or subunit structure. That novel consensus

sequence approach—which minimized the prior art immunogenicity problem and provided a broadly-applicable platform for humanizing antibodies—is protected by U.S. Patent No. 6,407,213 ("the '213 patent"). The inventors initially applied their consensus sequence approach to humanize the murine 4D5 antibody and create the drug Herceptin®—a lifesaving therapy for an aggressive form of breast cancer. Their invention was later used to develop numerous other highly successful therapeutic antibodies for a wide range of diseases.

Pfizer's petition challenges certain claims of the '213 patent on seven different obviousness grounds, but fails to demonstrate a reasonable likelihood of success for any of them.

As an initial matter, the references underlying Grounds 2, 3, 4, and 7—Queen 1990 (Ex. 1550) and Tramontano (Ex. 1551)—are not prior art. The '213 inventors reduced their invention to practice before the publication of Queen 1990 and Tramontano by creating and testing humanized antibodies that embody the challenged claims. That actual reduction to practice is corroborated by extensive contemporaneous records from the inventors and several non-inventors.

Even if Pfizer could rely on Queen 1990 or Tramontano, Pfizer has failed to demonstrate a reasonable likelihood of success for any challenged claim.

First, Pfizer argues for each ground that a skilled artisan would have arrived at the challenged claims by combining Queen 1989 (Ex. 1534) or Queen 1990 with

nine different published antibody structures. But the Queen references emphasize the importance of using a "best-fit" approach starting from the ***single*** human antibody sequence most homologous to the original non-human antibody. A skilled artisan would not have taken the opposite approach by combining the Queen references with nine different antibodies—without regard to whether those antibodies are similar to the original non-human antibody.

Second, Pfizer has not demonstrated that certain claim limitations would have been obvious, including (i) "lacks immunogenicity" in claim 63 (Grounds 1-2); (ii) "up to 3-fold more" binding affinity in claim 65 (Grounds 1-4); and (iii) "consensus" sequence in claims 4, 33, 62, 64, and 69 (Grounds 1-2, 5, and 7). Pfizer's arguments for these claims rest on speculation and are not supported by the asserted references.

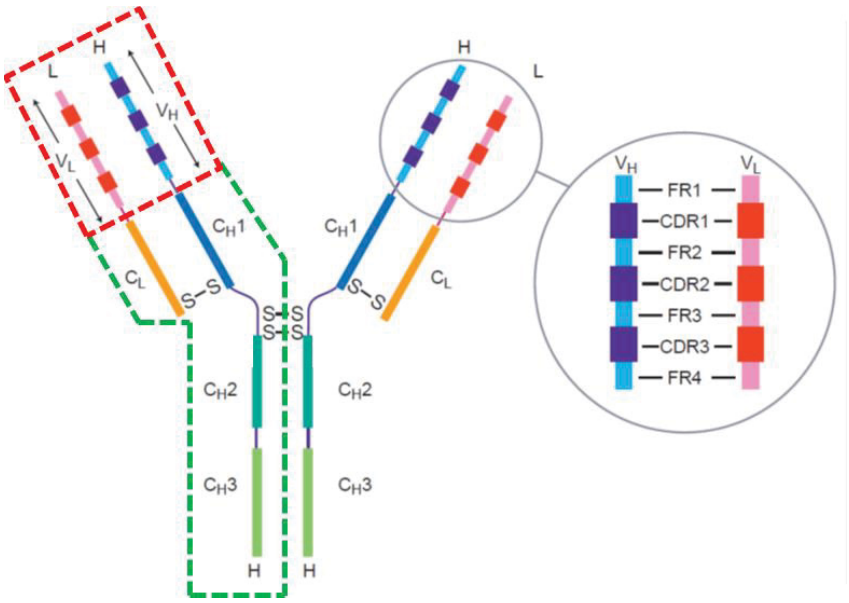
Finally, even under Pfizer's theory, the proposed obviousness combinations for each ground would have resulted in numerous possible amino acid substitutions—including many outside the scope of the challenged claims. Pfizer has not met its burden to explain why the claimed substitutions would have been chosen out of the numerous other possibilities that Pfizer admits a skilled artisan would have had to confront.

The Board should deny institution.

II. TECHNOLOGY BACKGROUND

A. Antibody "Variable" And "Constant" Domains

The immune system defends against foreign substances, known as "antigens" (*e.g.*, viruses or bacteria), by producing antibodies. Antibodies are proteins that recognize and bind to antigens, which facilitates their removal from the body. (Ex. 1582 at 1.) A typical antibody (sometimes called an "immunoglobulin") consists of four amino acid chains: two identical heavy chains and two identical light chains, which join to form a "Y" shape, as shown below:



(Ex. 2023 at 10 (annotated); Ex. 1501, 1:17-20.) Each chain contains a "variable" domain at one end (red box above) and "constant" domains at the other (green box above). (Ex. 1501, 1:20-27.) The variable domains for the heavy chain (V_H) and light chain (V_L) are illustrated above in blue and pink, respectively.

Variable domains directly bind to the antigen. (*Id.*, 1:35-37.) Each variable domain contains three "complementarity determining regions," or "CDRs," (*id.*, 1:35-50), shown as CDR1, CDR2, and CDR3 in the enlarged portion above. Variable domains also contain four "framework regions," or "FRs"—one on either side of each CDR—shown as FR1, FR2, FR3, and FR4 in the same enlarged portion. The framework regions form an immunoglobulin core structure from which the CDRs extend and form a binding site for interaction with the antigen. (*Id.*, 1:47-50.) In contrast to the CDRs, which generally contain unique amino acids (or "residues") for a particular antigen, the framework regions may have more amino acid sequences in common (*i.e.*, the same amino acids at the same positions) across other antibodies. (*Id.*, 1:37-44.)

The constant domains are not directly involved in antigen binding and typically have similar amino acid sequences across all antibodies within a subclass. (Ex. 2016, Presta Decl. ¶ 15.)

B. "Humanized" Antibodies

Before the '213 patent, antibodies targeting a specific antigen could be obtained from animals, such as mice. (Ex. 1501, 1:52-58.) Although those non-human antibodies could bind to a desired target, they had limited use therapeutically because the human immune system would over time identify them as antigens and attack them—known as an "antigenic" or "immunogenic"

response. (*Id.*, 1:55-58.) An immunogenic response had adverse clinical consequences because it inactivated the antibody and resulted in its premature removal from the body. (*E.g.*, Ex. 1528 at 3 (noting "large fall in circulating mouse immunoglobulin" due to immunogenic response and accompanying "adverse clinical reaction").)

Scientists developed several techniques trying to address that issue. One approach used "chimeric" antibodies that combined a non-human variable domain (*e.g.*, the entire variable domain from a mouse antibody) with a human constant domain. (*Id.*, 1:59-2:19.) However, because chimeric antibodies retained a significant portion of the non-human antibody sequence, immunogenicity could still result. (*Id.*, 2:12-19; Ex. 2022 at 2156.)

Attempting to reduce immunogenicity, scientists created "humanized" antibodies that included a human variable domain substituted with the amino acid sequence of the non-human CDRs. (Ex. 1501, 2:20-52.) But that approach could reduce the antibody's ability to bind to specific antigens. (Ex. 1534 at 5 ("Unfortunately, in some cases the humanized antibody had significantly less binding affinity for antigen than did the original mouse antibody.").)[1]

[1] In this proceeding, Patent Owner uses "chimeric" and "humanized" as defined in the '213 patent. (Ex. 1501, 1:59-62 ("chimeric" antibodies have "an

In attempting to address these various shortcomings, scientists pursued techniques seeking to make humanized antibodies that balanced strong binding with low immunogenicity. For example, Queen 1989 (Ex. 1534) selected a human variable domain by comparing a mouse antibody against known human antibody sequences, and choosing a human framework that was "as homologous as possible to the original mouse antibody to reduce any deformation of the mouse CDRs." (Ex. 1534 at 5.) The humanized sequence was then further refined using computer modeling "to identify several framework amino acids in the mouse antibody that might interact with the CDRs or directly with antigen, and these amino acids were transferred to the human framework along with the CDRs." (*Id.*) That technique became known as the "best-fit" approach because it started from a human sequence with the closest match to the non-human antibody. (Ex. 2024 at 4184.)

Even using the best-fit approach, however, it still was difficult to produce an antibody with both strong binding and low immunogenicity. (Ex. 1501, 3:50-52.)

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animal antigen-binding variable domain [that] is coupled to a human constant domain"); *id.*, 8:11-17 ("humanized" antibodies contain a framework region "having substantially the same amino acid sequence of a human immunoglobulin and a CDR having substantially the amino acid sequence of a non-human immunoglobulin").)

The best-fit approach also was inefficient because it required a new human antibody sequence as the starting point for each different humanized antibody.

III. THE '213 PATENT

A. The Invention

Beginning in the late 1980s, Drs. Paul Carter and Leonard Presta at Genentech developed a new approach to humanizing antibodies that solved the prior art binding and immunogenicity problems. Rather than starting from the most homologous human sequence, Drs. Carter and Presta developed a "consensus human sequence"—*i.e.*, "an amino acid sequence which comprises the most frequently occurring amino acid residues at each location in all human immunoglobulins of any particular subclass or subunit structure." (*Id.*, 11:32-38.) That "consensus" sequence provided a single human amino acid sequence that would be the starting point for ***any*** humanized antibody of a particular subclass or subunit structure (*e.g.*, light chain κ1). (*Id.*, 54:66-56:57.)

The '213 inventors developed a multi-step process for their approach. First, they added the non-human CDRs to the human consensus sequence. (*Id.*, 20:12-31.) Next, they evaluated the differences between the framework regions of the non-human antibody and the human consensus sequence to determine whether further modifications to the consensus sequence were needed. (*Id.*, 20:32-40.)

For framework positions where the non-human antibody sequence differed from the human consensus sequence, Drs. Carter and Presta used computer modeling to identify whether the different non-human amino acid (i) "non-covalently binds antigen directly"; (ii) "interacts with a CDR"; (iii) "participates in the V_L-V_H interface," *i.e.*, the interface between variable domains of the heavy and light chains, or (iv) is a glycosylation site outside the CDRs that is likely to affect "antigen binding and/or biological activity." (*Id.*, 20:32-21:36, 54:64-56:57.) They believed that those positions were important to maintaining binding affinity because they could influence the three-dimensional shape of the CDRs. (*Id.*, 20:32-35.) If any of those four requirements was met, the amino acid at that position in the consensus sequence could be substituted with the amino acid that appears at the same position in the non-human antibody. Otherwise, the amino acid sequence of the human consensus sequence was retained. (*Id.*, 20:66-21:8.)

The '213 challenged claims reflect the inventors' novel consensus sequence approach. Each challenged claim requires a "humanized" antibody or variable domain that contains non-human CDRs and one or more specified framework amino acid substitutions. As explained below, the claimed framework substitutions are the amino acid positions that the inventors determined were important to antibody binding.

B. Advantages Of The '213 Invention

The '213 patent's consensus sequence approach was a significant advance over the prior art.

First, using a consensus sequence minimized the immunogenicity problems that plagued other humanization techniques. (Ex. 1502 at 3439-41, ¶¶ 2-9.) At the same time, humanized antibodies made according to the '213 invention retain strong binding for the targeted antigen, or even have improved binding over the original non-human antibody. (Ex. 1501, 4:24-28, 51:50-53.)

Second, under the best-fit approach, the most homologous human sequence itself may be a rare antibody sequence that would trigger an immunogenic response—for example, due to unique variations in individual patients. (Ex. 2020, Presta Decl. ¶ 24.) The '213 patent avoids that problem by starting from a consensus sequence comprising only the most frequently occurring amino acids at each position. (Ex. 1501, 11:32-38.)

Third, unlike the prior art best-fit approach—that required identifying the most homologous human antibody sequence for each antibody to be humanized—the '213 patent provided a single human antibody sequence as a starting point that could be applied to a wide variety of antibodies. (Ex. 1502 at 3439-41, ¶¶ 2-9.) Genentech has used the '213 invention to develop numerous drugs for a wide variety of diseases, such as Herceptin® (breast and gastric cancer), Perjeta® (breast

cancer), Avastin® (colon, lung, ovarian, cervical, kidney, and brain cancer), Lucentis® (macular degeneration), and Xolair® (asthma). (Ex. 2017, Carter Decl. ¶ 4; Ex. 2016, Presta Decl. ¶ 5.)

C. Prosecution History

The '213 patent is a continuation-in-part of an application filed on June 14, 1991. (Ex. 1501, coversheet.) The challenged claims issued over hundreds of references considered during prosecution, including every reference underlying Pfizer's proposed grounds. (Ex. 1501 at 1-6.) Pfizer asserts that the PDB database was not considered during prosecution. (Paper 1 at 14.) But that is incorrect. Indeed, the '213 specification itself repeatedly cites the PDB database. (Ex. 1501, 16:31-34, 19:35-41, 48:13-17.)

During prosecution, the applicants submitted a joint affidavit from Drs. Carter and Presta to antedate U.S. Patent No. 5,693,762, which had a filing date of September 28, 1990. (Ex. 1502 at 4432-33.) The examiner allowed the claims after accepting that antedation evidence. (*Id.* at 4443.) As detailed below, the record in this proceeding further confirms that the '213 invention was also conceived and reduced to practice before the publication of either Queen 1990 (July 26, 1990) or Tramontano (September 5, 1990).

IV. PFIZER'S ASSERTED REFERENCES

A. Queen 1989

Queen 1989 describes the humanization of a murine anti-TAC antibody. (Ex. 1534 at 1 (abstract).) Unlike the '213 patent, Queen 1989 does not disclose the use of a generalized "consensus" sequence. Instead, as discussed above, Queen 1989 used a best-fit approach, which involved (i) searching a database of antibody sequences to identify a human framework "as homologous as possible to the original mouse antibody to reduce any deformation of the mouse CDRs" (*id.* at 5); and (ii) incorporating the murine CDRs into that human sequence (*id.* at 3).

Queen 1989 then identified additional locations in the human framework to substitute with murine residues. If the human framework contained "atypical" residues, Queen 1989 substituted them with more commonly-occurring amino acids from the murine antibody. (*Id.* at 4.) Queen 1989 also used a computer model of the murine antibody "to identify several amino acids which, while outside the CDRs, are likely to interact with the CDRs or antigen." (*Id.* at 1 (abstract).) Using those techniques, Queen 1989 identified nine substitutions. (*Id.* at 3.) None of those substitutions, however, fall within the scope of the challenged claims.

B. Queen 1990

Queen 1990 is a PCT application published July 26, 1990. It is not prior art. (*See infra* pp. 19-41.)

Like Queen 1989, Queen 1990 used a best-fit approach to produce a humanized antibody by starting from a human sequence most homologous to the mouse antibody. (Ex. 1550, 26:5-33:25.) Queen also identified four general criteria for designing humanized antibodies.

Criterion I: As a starting point, Queen 1990 emphasized the importance of choosing the human sequence most similar to the non-human antibody to reduce the possibility of distorting the binding site formed by the CDRs. (*Id.*, 12:17-35.) Queen 1990 mentioned "a consensus framework" (*id.*, 12:19-20), but included no details of what that "consensus framework" might be or how it might be used to make a humanized antibody.

Criterion II: After selecting a best-fit human framework sequence, Queen 1990 provided that "unusual" or "rare" amino acids could be replaced with more common amino acids from the non-human sequence. (*Id.*, 13:22-32.) This step was intended to eliminate residues from the selected human framework that may "disrupt the antibody structure" by replacing them with non-human residues commonly found in other human antibody sequences. (*Id.*, 13:32-37.)

Criterion III: Queen 1990 disclosed that non-human residues may be used immediately adjacent to CDRs because "[t]hese amino acids are particularly likely to interact with the amino acids in the CDR's [sic]" or "interact directly with the

antigen." (*Id.*, 14:1-12.) Accordingly, Queen 1990 hypothesized that using non-human residues at those positions may help maintain strong binding. (*Id.*)

Criterion IV: Queen 1990 used computer modeling, "typically of the original donor antibody," to identify other residues that "have a good probability of interacting with amino acids in the CDR's [sic] by hydrogen bonding, Van der Waals forces, hydrophobic interactions, etc." (*Id.*, 14:14-19.) Non-human residues may be substituted at those positions that may interact with CDRs. (*Id.*, 14:19-21.) Amino acids satisfying this criterion "generally have a side chain atom within about 3 angstrom units of some site in the CDR's [sic]." (*Id.*, 14:22-25.)

Queen 1990 disclosed the sequence of an anti-TAC antibody produced using its humanization technique. (*Id.*, Fig. 2.) However, Pfizer does not contend that any antibody sequence disclosed in Queen 1990 anticipates or renders obvious the challenged '213 claims. Instead, Pfizer argues that Queen 1990's four general criteria would have led a skilled artisan to the specific residue substitutions identified in the challenged claims. (Paper 1 at 36-38.)

C. PDB Database

The Protein Data Bank ("PDB") "was established in 1971 as a computer-based archival file for macromolecular structures" that could "collect, standardize, and distribute atomic co-ordinates and other data from crystallographic studies." (Ex. 1580 at 535.)

Pfizer cites data from nine antibody crystal structures available in the PDB database prior to August 1989. (Ex. 1503C, Foote Exs. F-N.) As discussed below, Pfizer contends that those crystal structures would have supposedly led to numerous possible framework substitutions—only a fraction of which correspond with the challenged claims.

D. Tramontano

Tramontano (Ex. 1551) was published on September 5, 1990. (Ex. 2027 (showing date).) Tramontano therefore is not prior art. (*See infra* pp. 19-41.)

Tramontano analyzed several antibody structures and found that "the major determinant" of the position of one of the CDRs "is the size of the residue at [heavy chain] site 71." (Ex. 1551 at 1 (abstract).) Tramontano discussed potential "applications to antibody engineering" of its discovery concerning the role of position 71H (*id.* at 7), but did not indicate that substitutions at 71H were desirable. Rather, Tramontano highlighted the unpredictability of substituting 71H.[2]

[2] This shorthand follows the convention of Kabat 1987 (Ex. 1552), which assigns standardized numbers to the amino acid positions in antibody heavy ("H") and light ("L") chains. (Ex. 1501, 10:46-57.) For example, "71H" refers to the 71st amino acid position in the heavy chain.

For example, Tramontano noted that Verhoeyen (Ex. 1568) substituted 71H, which reduced binding affinity by "approximately tenfold," while Riechmann (Ex. 1569) substituted 71H in a different antibody, which had "an affinity close to that of the rat original." (Ex. 1551 at 7.) Tramontano had no explanation for those divergent results. (*Id.*)

E. Kabat 1987

Kabat 1987 (Ex. 1552) is a reference book of antibody sequences that includes statistics on the most common amino acids for a given type of immunoglobulin (*e.g.*, human κ light chain subgroup 1). (*Id.* at 8.)

Kabat 1987 does not describe antibody humanization or discuss substitutions beneficial when humanizing an antibody. Rather, Kabat 1987's tabulation of the "most common" amino acids was intended to help scientists evaluate whether their sequence for a given antibody was likely to be correct. (Ex. 2026 at 3 ("It is also possible, by examining the numbers of sequences at the end of each table and the summary tables, to evaluate the probability that a given amino acid at a given position may not be correct.").)

F. Hudziak

Hudziak (Ex. 1521) is a March 1989 publication that studied human breast cancer cells overexpressing the cellular receptor known as "p185^{HER2}." Hudziak

does not describe antibody humanization or discuss substitutions that may be beneficial to antibody humanization.

Hudziak prepared a murine monoclonal antibody (called "4D5") that binds to the extracellular domain of $p185^{HER2}$ and found that it "inhibit[ed] in vitro proliferation of human breast tumor cells overexpressing $p185^{HER2}$." (Ex. 1521 at 1.)

V. PERSON OF ORDINARY SKILL

A person of ordinary skill for the '213 patent would have had a Ph.D. or equivalent in chemistry, biochemistry, structural biology, or a closely related field, and experience with antibody structural characterization, engineering, and/or biological testing, or an M.D. with practical academic or industrial experience in antibody development.

Pfizer's proposed definition is similar (Paper 1 at 16), and to the extent there is any substantive difference the Board should deny institution under either party's proposed definition for the reasons below.

VI. CLAIM CONSTRUCTION

For purposes of this proceeding, the only term requiring construction is "consensus human variable domain" (claims 4, 33, 62, and 69), which should be construed to mean "a human variable domain which comprises the most frequently occurring amino acid residues at each location in all human immunoglobulins of

any particular subclass or subunit structure." That construction comes directly from the definition provided in the '213 patent: "A 'consensus' sequence, structure, or antibody … refer[s] to an amino acid sequence which comprises the most frequently occurring amino acid residues at each location in all human immunoglobulins of any particular subclass or subunit structure." (Ex. 1501, 11:32-38.) Under principles of lexicography, that express definition controls. *Sinorgchem Co. v. Int'l Trade Comm'n*, 511 F.3d 1132, 1136 (Fed. Cir. 2007) ("[T]he inventor's lexicography governs.").

Pfizer has proposed constructions of: (i) "humanized" (claims 1, 30, 62-64, 66, 79, 80); (ii) "and further comprising a framework region (FR) amino acid substitution at a site selected from the group consisting of" (claims 1, 30, 62, 63, 66, 79, and 80); (iii) "numbering system set forth in Kabat" (claims 1, 30, 62, 63, 66, 79, and 80); and (iv) "up to 3-fold more" (claim 65). (Paper 1 at 17-19.) No construction of those terms is necessary, but Patent Owner does not dispute Pfizer's proposed constructions for purposes of this proceeding.

However, because the challenged claims were invented before July 26, 1990 (as detailed below), the "numbering system set forth in Kabat" should be construed to refer to Kabat 1987, and not Kabat 1991—which did not exist at the time. Indeed, the '213 patent's priority application relies only on Kabat 1987.

VII. ARGUMENT

A. The Board Should Deny Grounds 2, 3, 4, And 7 Because Neither Queen 1990 Nor Tramontano Is Prior Art.

Grounds 2, 3, 4, and 7 rely upon Queen 1990 and/or Tramontano. Yet neither Queen 1990 (published July 26, 1990) nor Tramontano (published September 5, 1990) is prior art.

1. The inventors produced and tested humanized 4D5 antibodies using the '213 invention before July 26, 1990.

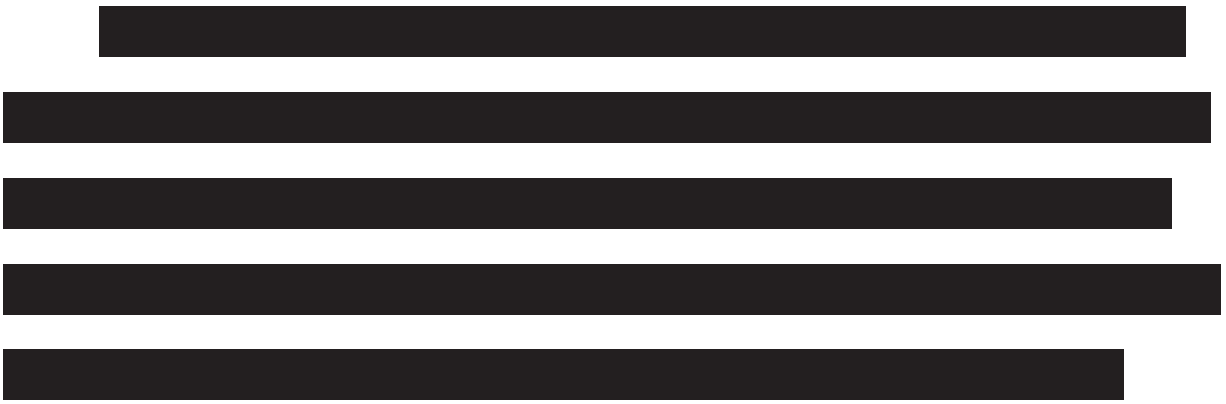
a) Consensus sequence

In 1989, Dr. Paul Carter started his own laboratory at Genentech. (Ex. 2017, Carter Decl. ¶ 3.) As one of his early research projects, Dr. Carter approached Dr. Leonard Presta—a molecular modeler in Genentech's protein engineering department—about pursuing a new technique for humanizing antibodies. (*Id.* ¶ 4; Ex. 2016, Presta Decl. ¶¶ 5, 22-23.) At that time, no one had successfully developed a therapeutic humanized antibody. In fact, many scientists were skeptical of using antibodies therapeutically because foreign antibodies (*i.e.*, those not produced by the body's own immune system) could provoke an immunogenic response. (Ex. 2017, Carter Decl. ¶ 19; Ex. 2016, Presta Decl. ¶¶ 16-21.)

Drs. Carter and Presta, however, conceived of a novel strategy for minimizing immunogenicity. Rather than starting from a published human antibody sequence, as done in the prior art best-fit approach, they sought to

develop a single human "consensus" sequence consisting of the most frequently occurring amino acid residues at each location in all human immunoglobulins of any particular subclass or subunit structure. (Ex. 2017, Carter Decl. ¶¶ 19-20; Ex. 2016, Presta Decl. ¶¶ 23-24.) They believed that this approach would reduce immunogenicity by avoiding reliance on published antibody sequences, which are obtained from a single person and thus contain unique variations specific to that individual. (Ex. 2017, Carter Decl. ¶ 19; Ex. 2016, Presta Decl. ¶ 24.) They also hoped to provide a more efficient platform by using a single sequence as the starting point for antibody humanization. (Ex. 2017, Carter Decl. ¶ 19; Ex. 2016, Presta Decl. ¶ 24.)

Their first application of this platform was to humanize a murine antibody called "4D5," which binds to a cellular receptor ($p185^{HER2}$) associated with an aggressive form of breast cancer. (Ex. 2017, Carter Decl. ¶ 21.) Genentech scientists had previously studied the murine 4D5 antibody and demonstrated that it could inhibit the growth of tumors overexpressing $p185^{HER2}$. (Ex. 1521 at 1.)



[redacted]

b) Humanized 4D5 antibody sequences

[redacted]

[3] The declaration of Irene Loeffler, the custodian of records for Genentech's laboratory notebooks, establishes the authenticity and admissibility of the notebooks discussed herein as business records. (Ex. 2019, Loeffler Decl. ¶¶ 3-7.)

[redacted]

[redacted]

[redacted]

c) Production and testing of humanized 4D5 antibodies

[redacted]

[redacted]

[redacted]

(i) First humanized 4D5 variable domain fragment

[redacted]

[redacted]

[redacted]

[redacted]

(ii) First humanized 4D5 full-length antibody

[redacted]

[redacted]

(iii) Other humanized 4D5 variants

The '213 inventors made five other humanized 4D5 antibodies with different substitutions from HuMAb4D5-5.[4] [redacted]

[4] Those other variants are called HuMAb4D5-3, HuMAb4D5-4, HuMAb4D5-6, HuMAb4D5-7, and HuMAb4D5-8 in the '213 patent. (Ex. 2017, Carter Decl. ¶¶ 67, 76; Ex. 2016, Presta Decl. ¶ 50.)

[redacted]

***

The inventors' success in humanizing the murine 4D5 antibody was directly attributable to their novel consensus sequence approach, which allowed them to quickly identify the key substitutions for a humanized 4D5 antibody and prepare several variants in parallel. [redacted]

[redacted]

2. The challenged claims were reduced to practice before July 26, 1990.

"To demonstrate an actual reduction to practice, the applicant must have: (1) constructed an embodiment or performed a process that met all the limitations of the claim and (2) determined that the invention would work for its intended purpose." *In re Steed*, 802 F.3d 1311, 1318 (Fed. Cir. 2015). An inventor's testimony establishing prior invention must be corroborated. *In re NTP, Inc.*, 654 F.3d 1279, 1291 (Fed. Cir. 2011). As detailed below, the inventors' well-documented and corroborated work preparing and testing humanized 4D5 antibodies demonstrates actual reduction to practice of the challenged claims before July 26, 1990. (*See* Ex. 2017, Carter Decl. ¶ 79; Ex. 2016, Presta Decl. ¶ 53.)

a) HuMAb4D5-5 and HuMAb4D5-8 embody the challenged claims.

(i) Common limitations

Challenged claims 1-2, 4, 12, 25, 29-31, 33, 42, 60, 62-67, 69, and 71-81 require at least three elements: (i) a "humanized" antibody or variable domain; (ii) "non-human" CDRs; and (iii) one or more specified framework substitutions.

HuMAb4D5-5 and HuMAb4D5-8 embody those limitations common to all challenged claims, as shown below for representative claim 1.[5]

Claim Language	HuMAb4D5-5	HuMAb4D5-8
1. A humanized antibody variable domain	HuMAb4D5-5 is a humanized antibody containing humanized HuMAb4D5a heavy and light chain variable domains. (Ex. 2016, Presta Decl. ¶¶ 45, 47; Ex. 2017, Carter Decl. ¶¶ 31, 76; Ex. 2018, Brady Decl. ¶ 15.)	HuMAb4D5-8 is a humanized antibody containing humanized HuMAb4D5c heavy and light chain variable domains. (Ex. 2016, Presta Decl., ¶¶ 45, 47; Ex. 2017, Carter Decl., ¶ 76; Ex. 2018, Brady Decl. ¶ 15.)
comprising non-human Complementarity Determining Region (CDR) amino acid residues which bind an antigen incorporated into a human antibody variable domain,	HuMAb4D5-5 contains the non-human CDRs from the murine 4D5 antibody, which bind to the antigen $p185^{HER2}$. (Ex. 2016, Presta Decl. ¶¶ 40, 45-47; Ex. 2017, Carter Decl. ¶¶ 21, 25, 29, 50-55, 66, 75-76.)	HuMAb4D5-8 contains the non-human CDRs from the murine 4D5 antibody, which bind to the antigen $p185^{HER2}$. (Ex. 2016, Presta Decl. ¶¶ 40, 45-47; Ex. 2017, Carter Decl. ¶¶ 25, 29, 50-55, 75-76.)
and further comprising a Framework Region (FR) amino acid substitution at a site selected from the group consisting of:	HuMAb4D5-5 contains substitutions at 66L, 71H, 73H, 78H, and 93H. (Ex. 2016, Presta Decl. ¶¶ 45, 47; Ex. 2002 at 34-36.)	HuMAb4D5-8 contains substitutions at 55L, 66L, 71H, 73H, 78H, 93H, and 102H. (Ex. 2016, Presta Decl. ¶¶ 45, 47; Ex. 2002 at 34-36.)

[5] Other humanized 4D5 antibodies prepared and tested before July 26, 1990 also meet these limitations. For simplicity, Patent Owner focuses on two variants: HuMAb4D5-5 (the first humanized 4D5 antibody) and HuMAb4D5-8 (Herceptin®).

Claim Language	HuMAb4D5-5	HuMAb4D5-8
4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, and 92H, utilizing the numbering system set forth in Kabat.		

Certain claims present additional considerations for the claimed framework substitutions.

For example, claim 64 defines the claimed substitutions functionally—*e.g.*, at a position that "(a) noncovalently binds antigen directly; (b) interacts with a CDR; (c) introduces a glycosylation site which affects the antigen binding or affinity of the antibody; or (d) participates in the V_L-V_H interface by affecting the proximity or orientation of the V_L and V_H regions with respect to one another." The substitutions contained in HuMAb4D5-5 and HuMAb4D5-8 meet those functional limitations. [redacted]

[redacted]

Claims 1, 30, 62, 63, 66, and 80 recite *Markush* groups of framework substitutions, including positions not substituted in HuMAb4D5-5 or HuMAb4D5-8. However, as discussed above (p. 22), the inventors developed several rules for identifying framework substitutions—*i.e.*, at positions that (1) non-covalently bind to the antigen directly; (2) interact with a CDR; (3) introduce a glycosylation site which affects the antigen binding or affinity of the antibody; or (4) participate in the interface between the variable domains of the heavy and light chains. (Ex. 2016, Presta Decl. ¶ 31; Ex. 2002 at 28-29.) [redacted] And they applied the same rules to identify the specific substitutions in HuMAb4D5-5 and HuMAb4D5-8, which fall within the claimed *Markush* groups. (Ex. 2016, Presta Decl. ¶¶ 45, 47; Ex. 2017, Carter Decl. ¶ 76; Ex. 2002 at 34-36.)

Because the framework substitutions in HuMAb4D5-5 and HuMAb4D5-8 were based on the same rules defining the claimed *Markush* groups, the reduction to practice of those species demonstrates the invention of the full scope of the

claim. *Mikus v. Wachtel*, 504 F.2d 1150, 1151 (C.C.P.A. 1974) ("A prior reduction to practice of the species precludes another party from claiming that he is the first inventor of the genus containing the species."); *In re Taub*, 348 F.2d 556, 562 (C.C.P.A. 1965) ("[O]ne may establish priority for a generic claim on the basis of a showing that he was prior as to a single species.").

Finally, claims 25 (69H) and 72 (76H) recite substitutions not contained in HuMAb4D5-5 or HuMAb4D5-8 because the murine 4D5 antibody and human consensus sequences are the same at those positions. (Ex. 2016, Presta Decl. ¶¶ 34-35, 39-40; Ex. 2001 at 41; Ex. 2002 at 34-36.) However, 69H and 76H are substitutions that the inventors recognized may be important to other antibodies by applying the same rules that they used to make humanized 4D5 antibodies.[6]

[redacted]

[6] The inventors subsequently used their consensus sequence approach to make a humanized anti-VEGF antibody, which includes framework substitutions at 69H and 76H. (Ex. 2016, Presta Decl. ¶ 52; Ex. 2021.)

[redacted] The reduction to practice of humanized 4D5 antibodies containing framework substitutions derived from the same rules applied to identify 69H and 76H demonstrates the prior invention of those claims as well. *See, e.g.*, *In re Schaub*, 537 F.2d 509, 512-13 (C.C.P.A. 1976) (holding that reduction to practice of one embodiment establishes prior invention of obvious variants); *In re Spiller*, 500 F.2d 1170, 1177-78 (C.C.P.A. 1974) (same).

(ii) Additional limitations for certain claims

Several challenged claims contain additional limitations beyond the three just discussed. HuMAb4D5-5 and/or HuMAb4D5-8 embody those additional limitations, as detailed below.

Claims 2, 67, and 81. These claims require that "the substituted residue is the residue found at the corresponding location of the non-human antibody." The substitutions in HuMAb4D5-5 and HuMAb4D5-8 correspond with the amino acids at the same position in the murine 4D5 antibody, as required by claims 2, 67, and 81. (Ex. 2016, Presta Decl. ¶¶ 45, 47; Ex. 2002 at 34-36.)

Claims 4, 33, 62, 64, and 69. HuMAb4D5-5 and HuMAb4D5-8 satisfy the "consensus" sequence limitations of claims 4, 33, 62, 64, and 69. As discussed above (pp. 21-25), the inventors created HuMAb4D5-5 and HuMAb4D5-8 using the humkapI and humiii consensus sequences, which were based upon the most

frequently occurring amino acid residues at each location in all human immunoglobulins in their respective subclasses.

Claims 30-31, 33, 42, and 60. As discussed above (pp. 23-24, 28-29), HuMAb4D5-5 and HuMAb4D5-8 bind $p185^{HER2}$ and contain the non-human CDR residues that bind $p185^{HER2}$, as required by claims 30-31, 33, 42, and 60.

Claims 63 and 65. HuMAb4D5-8 embodies claim 63, which requires that the humanized antibody "lacks immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient in order to treat a chronic disease in that patient." Only 1 out of 885 patients experienced an immunogenic response after repeated administration of HuMAb4D5-8 to treat metastatic breast cancer, which was a substantial improvement over the murine 4D5 antibody. (Ex. 1502 at 3439-40, ¶¶ 2-4; Ex. 2028 at 197 (murine 4D5 provoked immunogenic response).)

HuMAb4D5-8 also embodies claim 65, which requires that the humanized antibody "binds the antigen up to 3-fold more in the binding affinity than the parent antibody binds antigen." (Ex. 1501, 51:48-53 ("[HuMAb4D5-8] binds the $p185^{HER2}$ ECD 3-fold more tightly than does muMAb4D5 itself.").)[7]

[7] Neither Queen 1990 nor Tramontano contains data showing that any disclosed antibody lacks immunogenicity or has up to 3-fold more binding affinity.

b) The inventors determined that HuMAb4D5-5 and HuMAb4D5-8 would work for the intended purpose of the challenged claims before July 26, 1990.

The inventors had sufficiently characterized HuMAb4D5-5 and HuMAb4D5-8 before July 26, 1990 to know they would work for the intended purpose of the challenged claims. By then, they had already confirmed that the expression vectors contained the correct DNA sequence to produce their humanized 4D5 antibodies. (Ex. 2017, Carter Decl. ¶¶ 62-63, 75; Ex. 2018, Brady Decl. ¶ 22; Ex. 2003 at 69-71, 78-81, 95-97; Ex. 2004 at 41, 43, 44, 46; Ex. 2006 at 83, 85; Ex. 2009 at 5, 7-8.) And they had already performed experiments to confirm that they had produced humanized antibodies with the expected size and sequence. (Ex. 2017, Carter Decl. ¶¶ 63-65, 75; Ex. 2018, Brady Decl. ¶¶ 13, 16-24; Ex. 2003 at 97; Ex. 2004 at 44-46; Ex. 2005 at 73; Ex. 2006 at 47, 51, 83, 85; Ex. 2008 at 6, 44-45; Ex. 2009 at 5, 7-8.) In addition, as discussed above (pp. 26-

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Because antedation only requires "priority with respect to so much of the claimed invention as the reference happens to show," *In re Clarke*, 356 F.2d 987, 991 (C.C.P.A. 1966), it is not necessary to show that the studies confirming that HuMAb4D5-8 lacks immunogenicity and has 3-fold more binding affinity were completed before the publication of Queen 1990 and/or Tramontano.

29), the inventors established before July 26, 1990 that HuMAb4D5-5 and HuMAb4D5-8 bind to p185^{HER2}, as required by claims 30-31, 33, 42, and 60.

c) Contemporaneous records from non-inventors corroborate the invention of the challenged claims.

The inventors carefully documented their progress developing HuMAb4D5-5 and HuMAb4D5-8, and contemporaneous records from several non-inventors, including John Brady, Ann Rowland, Tim Hotaling, and Monique Carver, confirm all critical aspects of the invention before July 26, 1990, including the expression, purification, and characterization of HER2 binding affinity for HuMAb4D5-5 and HuMAb4D5-8. (*See supra* pp. 26-29.) That is more than sufficient corroboration. *See Cooper v. Goldfarb*, 154 F.3d 1321, 1330 (Fed. Cir. 1998) (finding sufficient corroboration where the evidence of reduction to practice did not "depend solely on statements or writings by the inventor himself").

3. Queen 1990 and Tramontano are not prior art.

Queen 1990 (published July 26, 1990) and Tramontano (published September 5, 1990) are not prior art under 35 U.S.C. § 102(a) because, as detailed above, the challenged claims were invented before the publication of those references.

Queen 1990 and Tramontano are also not prior art under 35 U.S.C. § 102(b) because the challenged claims properly claim priority to U.S. Patent Application

No. 07/715,272 ("the '272 application"), filed on June 14, 1991—*i.e.*, within one year of the references. As a continuation-in-part of the '272 application, the '213 claims have priority to that earlier application if it provides written description and enablement support for the claims. 35 U.S.C. § 120. As described below, the '272 application describes all limitations of the challenged claims, provides step-by-step instructions to prepare humanized antibodies using a consensus sequence, and discloses data characterizing humanized antibodies that embody the challenged claims.

a) Limitations common to all claims

"Humanized" antibody or variable domain. The '272 application describes humanized antibodies and variable domains. (Ex. 2032, 3:21-23, 29:11-30:6, claims 1, 9.) It also describes step-by-step how the inventors humanized the murine 4D5 antibody (Example 1) and provides a generalized scheme for humanizing any non-human antibody (Example 2). (*Id.*, 75:31-93:1-19.)

"Non-human" CDRs. The humanized antibodies described in the '272 application include non-human CDRs, which bind to the antigen. (*Id.*, 9:12-19, 90:1-18, Figs. 1A-1B.)

Framework substitutions. The '272 application identifies all framework substitutions recited in the challenged claims, including those in the inventors' humanized 4D5 antibodies. (*Id.*, 9:12-26, 82:17-20, Table 1, claim 9.) It also

specifies the factors for identifying framework substitutions, as recited in claim 64 of the '213 patent. (*Id.*, 4:24-27, 14:17-15:11, claims 1, 3.)

b) Additional limitations for certain claims

Claims 2, 67, and 81. The '272 application describes humanized antibodies wherein "the substituted residue is the residue found at the corresponding location of the non-human antibody," as required by claims 2, 67, and 81. (*Id.*, 90:4-20, Table 1, claim 10.)

Claims 4, 33, 62, and 64. The '272 application describes using a human consensus variable domain sequence to humanize an antibody and includes the consensus sequences disclosed in the '213 patent. (*Id.*, 10:29-11:13, 72:16-17, 78:2-7, Figs. 1A-B, Seq. ID Nos. 3-4, claims 12-13.)

Claims 30-31, 33, 42, and 60. The '272 application describes humanized antibodies that bind $p185^{HER2}$ and discloses HER2 affinity data for the humanized 4D5 antibodies that the inventors prepared. (*Id.*, 7:4-5, 18:4-7, 19:3-4, 81:11-12, 82:25-27, Table 1.)

Claim 63. The '272 application explains that the purpose of humanizing antibodies using its consensus sequence approach is to reduce immunogenicity versus the non-human parent antibody. (*Id.*, 6:24-30, 84:24-30.)

Claim 65. The '272 application describes HuMAb4D5-8, which it explains is a humanized antibody that binds the target antigen 3-fold more tightly than the parent murine antibody. (*Id.*, 82:31-83:3, 85:24-27, 85:29-32, Table 1.)

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Because Queen 1990 and Tramontano are not prior art, they cannot render the challenged claim invalid. The Board should thus deny Grounds 2, 3, 4, and 7.

B. Pfizer's Proposed Grounds Fail On The Merits.

As noted at the outset, there are several additional reasons why Pfizer has not demonstrated a reasonable likelihood of success for any challenged claim.

First, Pfizer's proposed grounds rely upon Queen 1989 or Queen 1990 combined with nine antibody structures from the PDB database. The Queen references, however, rely on a best-fit approach, which starts from the ***single*** most homologous human antibody sequence. Pfizer's obviousness theory that a skilled artisan would select ***multiple*** antibodies from the PDB database without regard to whether they are similar to the original non-human antibody conflicts with Queen's core teachings.

Second, regardless of whether a skilled artisan would have combined the Queen references with multiple PDB structures as Pfizer contends, Pfizer has not shown that following limitations would have been obvious: (i) "lacks immunogenicity" in claim 63 (Grounds 1-2); (ii) "up to 3-fold more" binding

affinity in claim 65 (Grounds 1-4); and (iii) "consensus" sequence in claims 4, 33, 62, 64, and 69 (Grounds 2, 5, 7).

Third, all challenged claims require specific framework substitutions that Pfizer has not shown would have been obvious. Pfizer's own arguments confirm that its asserted references encompass numerous possible substitutions, and Pfizer has not explained why a skilled artisan would have been led to the substitutions required by the challenged claims.

1. Grounds 1, 3, 5, and 6: Queen 1989 in view of the PDB database does not render the challenged claims obvious.

For Grounds 1, 3, 5, and 6, Pfizer contends that the challenged claims would have been obvious based upon Queen 1989 combined with the PDB database. However, Pfizer's obviousness theory cannot be reconciled with what Queen 1989 teaches—every step in Pfizer's analysis is either contradicted by Queen 1989, or rests on parameters disclosed only in later references. Moreover, even under Pfizer's theory, combining Queen 1989 with the PDB database would have led to numerous possible framework substitutions. Pfizer has not explained why a skilled artisan would have selected the specific substitutions required by the challenged claims. Accordingly, the Board should deny Grounds 1, 3, 5, and 6.

a) Queen 1989 contradicts Pfizer's obviousness theory.

Pfizer does not rely on any framework substitution disclosed in Queen 1989—because ***none*** of the nine disclosed substitutions correspond with the challenged claims. (Ex. 1534 at 3.) Pfizer nevertheless argues that a skilled artisan would have arrived at the '213 patent's claimed substitutions by the "roadmap" outlined by Queen 1989. (Paper 1 at 34.) But Pfizer's obviousness theory follows the opposite approach of Queen 1989.

Queen 1989 teaches a best-fit approach in which the human framework sequence should be "as homologous as possible to the original mouse antibody" so as "to reduce any deformation of the mouse CDRs." (Ex. 1534 at 5.) Yet, Pfizer's obviousness analysis does not apply that best-fit approach; Pfizer even fails to identify a non-human antibody to be humanized (which is necessary to apply Queen 1989's approach). Instead, Pfizer selected nine different antibodies from the PDB database as the starting point for its analysis, without considering how similar those sequences are to an original non-human antibody—contrary to Queen 1989's teachings. (Paper 1 at 33.)

Because Pfizer presents no reason why a skilled artisan would have dismissed Queen 1989's teaching to select the most homologous human sequence, which Queen 1989 touts as one of its key ideas of "wider applicability" (Ex. 1534 at 5), the Board should deny Grounds 1, 3, 5, and 6.

b) Queen 1989 does not disclose or suggest substituting residues within about 3 angstroms of a CDR.

Pfizer identified framework substitutions by searching for residues in nine structures from the PDB database within "about 3 Å" of the CDRs. (Ex. 1503 ¶ 255 & n.17.) But Queen 1989 does not provide ***any*** parameters for identifying residues that interact with the CDRs, let alone a 3 angstrom cutoff. (Ex. 1534 at 5.) Rather, the only support for Pfizer's "about 3 Å" cutoff appears to be Queen 1990—not Queen 1989. (Ex. 1503 ¶ 263 & n.16 (citing Queen 1990).)

Because Queen 1990 is not offered for Grounds 1, 3, 5, and 6, and is not prior art (as discussed above), Pfizer cannot rely on it to provide parameters for selecting substitutions absent from Queen 1989. This too requires denial of Grounds 1, 3, 5, and 6.

c) Pfizer's proposed combination of Queen 1989 with the PDB database results in a broad genus that would not have led to the claimed substitutions.

Pfizer's obviousness theory also fails because Pfizer has identified no reason why a skilled artisan would have selected the claimed substitutions from among the numerous possibilities that could have been identified from the structures in the PDB database.

In particular, Pfizer has identified a total of 20 possible framework substitutions for Grounds 1, 3, 5, and 6. (Paper 1 at 34; Ex. 1503 ¶ 263.) Less than

half of those substitutions correspond with challenged claims. (*Id.* ¶ 266.) Given the large number of possible substitutions that Pfizer contends a person of ordinary skill would have identified from the asserted references, Pfizer was required to show some reason why a skilled artisan would have been drawn to the specific substitutions recited in the challenged claims. *See, e.g.*, *Insite Vision, Inc. v. Sandoz, Inc.*, 783 F.3d 853, 863 (Fed. Cir. 2015) (rejecting obviousness argument where the prior art disclosed a "laundry list" of possibilities and no guidance leading to the claimed invention). Yet Pfizer has offered no explanation why a skilled artisan would have selected ***any*** of the claimed substitutions—other than by using hindsight.

Lacking any reason why a skilled artisan would have chosen the claimed substitutions, Pfizer argues that a skilled artisan would have selected all 20 substitutions supposedly disclosed under its obviousness theory because "'all the framework residues, that could influence the structure of its combining site, must be retained.'" (Paper 1 at 33.) Despite using quotation marks and apparently citing to Dr. Foote's declaration, Dr. Foote's declaration does not include this statement. The Board should reject Pfizer's unsupported argument.

Pfizer's theory also conflicts with its other cited references, such as the warning in Kurrle (Ex. 1571) that "extreme caution must be exercised to limit the number of changes" to the human antibody sequence. (Ex. 1571, 8:42-43.) Pfizer

cannot contend that a skilled artisan would have adopted ***all*** potential substitutions when its cited references teach the opposite.

Accordingly, the Board should deny Grounds 1, 3, 5, and 6—which depend upon Pfizer's flawed analysis of Queen 1989 in view of the PDB database.

2. Grounds 2, 4, and 7: Queen 1990 in view of the PDB database does not render the challenged claims obvious.

For Grounds 2, 4, and 7, Pfizer contends that Queen 1990 combined with the PDB database renders obvious the substitutions required by the challenged claims. However, just as with Queen 1989, Pfizer's obviousness theory cannot be reconciled with what Queen 1990 teaches. Moreover, even under Pfizer's theory, combining Queen 1990 with the PDB database would have led to numerous possible substitutions. Pfizer has failed to explain why a skilled artisan would have selected the specific substitutions required by the challenged claims. Accordingly, the Board should deny Grounds 2, 4, and 7.

a) Queen 1990 contradicts Pfizer's obviousness theory.

Rather than rely on any framework substitution disclosed in Queen 1990, Pfizer argues that Queen 1990's "detailed criteria" for creating humanized antibodies would have led a skilled artisan to make the '213 patent's claimed substitutions. (Paper 1 at 36-37.) But Pfizer's obviousness theory is contrary to the criteria provided in Queen 1990.

For example, Queen 1990's "Criterion I" instructs using "a framework from a particular human immunoglobulin that is unusually homologous to the donor immunoglobulin to be humanized" as critical to preserving antibody activity and providing "a smaller chance of changing an amino acid near the CDR's [sic] that distorts their conformation." (Ex. 1550, 12:17-35.) In its petition, however, Pfizer selected nine different antibodies as the starting point for its analysis without considering how similar those sequences are to an original non-human antibody (or even identifying a non-human antibody for humanization—a necessary first step under Queen 1990's approach). (Paper 1 at 33-34; Ex. 1503 ¶¶ 261-68.) Pfizer has offered no reason why a skilled artisan would have ignored Queen 1990's teachings and followed the opposite approach underlying its obviousness theory.

Pfizer argues that its obviousness theory is supported by Queen 1990's "Criterion IV," which states that "the known antibody structures" from the PDB database "can be used if necessary as rough models of other antibodies." (Paper 1 at 36; Ex. 1550, 14:32-36.) But Queen 1990 makes clear that "Criterion IV" is "typically" applied to a model of "the original donor antibody," and that PDB structures merely serve as "rough models" only "if necessary." (Ex. 1550, 14:14-19, 14:32-36.) Pfizer does not explain why a skilled artisan would have ignored Queen 1990's instruction to create a model of the "original donor antibody," and instead resorted to "rough models" from other antibodies.

Moreover, even if a skilled artisan would have looked to the PDB database, Queen 1990 does not describe ***combining*** multiple antibody structures from that database—let alone suggest selecting the nine specific structures that Pfizer cites. Queen 1990's only discussion of the PDB database is in the context of using individual antibody structures as "rough models of other antibodies," with no mention of combining data from different structures as Pfizer does. (*Id.*)

The Board should deny Grounds 2, 4, and 7 because they rest on an analysis contrary to what Queen 1990 teaches.

b) Pfizer's proposed combination of Queen 1990 with the PDB database results in a broad genus that would not have led to the claimed substitutions.

Pfizer identifies 42 possible substitutions by analyzing 9 antibody structures from the PDB database (supposedly following Queen 1990's criteria). (Paper 1 at 37.) But Pfizer has not explained why a skilled artisan would have selected ***any*** specific substitutions claimed in the '213 patent from that group of 42—the vast majority of which do not correspond with the challenged claims. Pfizer cannot rely on a "laundry list" disclosure of potential substitutions to render obvious the specific substitutions recited in the challenged claims. *Insite Vision*, 783 F.3d at 863.

Accordingly, the Board should deny Grounds 2, 4, and 7.

3. Grounds 1 and 2: Queen 1989 and Queen 1990 do not render obvious claim 63.

Pfizer challenges claim 63 in Grounds 1 and 2. Claim 63 requires "[a] humanized antibody which lacks immunogenicity compared to a non-human parent antibody." Pfizer has not shown that these functional limitations would have been obvious in view of Queen 1989 or Queen 1990.

Pfizer points to no data showing that an antibody produced according to Queen 1989 or Queen 1990 "lacks immunogenicity," as required by claim 63. (Paper 1 at 41-42.) Instead, merely relies on aspirational statements in both references. (Paper 1 at 41; *e.g.*, Ex. 1534 at 1 ("[S]equence homology and molecular modeling were used to select a combination of mouse and human sequence elements that would reduce immunogenicity while retaining high binding affinity."); Ex. 1550 at 1 (abstract) ("[T]he humanized immunoglobulins of the present invention will be substantially non-immunogenic in humans.").)

During prosecution of the '213 patent, the examiner considered similar statements from another reference (Riechmann): "[T]he use of human rather than mouse isotypes should minimize the anti-globulin [*i.e.*, immunogenic] responses during therapy by avoiding anti-isotypic antibodies." (Ex. 1569 at 1; *see* Ex. 1502 at 2485.) However, a follow-on publication showed that 3 out of 4 patients treated with the antibody nevertheless "developed antiglobulins." (Ex. 2025 at 751.) And

the applicants successfully distinguished those aspirational statements in the prior art from the actual functional result achieved by the '213 invention. (Ex. 1502 at 2502, 3431-3432.) The same result should apply here. The aspirational statements in the Queen references that the authors hoped to address the problem of immunogenicity does not make it obvious how to achieve that result.

For these additional reasons, the Board should deny Grounds 1 and 2 for claim 63.

4. Grounds 1-4: Queen 1989 and Queen 1990 do not render obvious claim 65.[8]

Claim 65 requires the humanized antibody to have a binding affinity "up to 3-fold more" than the parent non-human antibody. Pfizer again points to no data showing that actual antibodies produced according to Queen 1989 or Queen 1990 will have "up to 3-fold more" binding affinity. Instead, Pfizer argues that the Queen 1989 and Queen 1990 teach the limitation. (Paper 1 at 51-52.) This argument fails.

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[8] Pfizer did not identify claim 65 as challenged under Grounds 1-2 (Paper 1 at 5), but presented argument concerning claim 65 for these grounds (*id.* at 51-52). To the extent that Pfizer is challenging claim 65 in Grounds 1-2, its arguments fail as explained in this section.

For Grounds 1 and 3, Pfizer points to nothing in Queen 1989 suggesting its humanized antibodies had greater binding affinity than the original non-human antibody. Instead, Pfizer relies entirely on Dr. Foote's bare assertion that "it would not have been surprising that a small improvement in affinity would be achieved." (Paper 1 at 51; Ex. 1503 ¶ 308.) Such unsupported assertions are insufficient to carry Pfizer's burden. *See, e.g.*, *Innogenetics, N.V. v. Abbott Labs*., 512 F.3d 1363, 1373-74 (Fed. Cir. 2008). And in any case, Pfizer's argument is contrary to the record evidence showing that humanized antibodies produced starting from the most homologous human sequence (as taught by Queen 1989) had ***reduced*** binding affinity. (Ex. 2033 at 1 (abstract).)

For Grounds 2 and 4, Pfizer argues that Queen 1990 discloses the "up to 3-fold more" limitation by stating that the binding affinity of the humanized antibodies "may be within about 4 fold of the donor immunoglobulin's original affinity to the antigen." (Paper 1 at 51; Ex. 1550, 6:26-28.) But Queen 1990 does not indicate that the humanized antibody's binding affinity is ***more*** than the non-human parent antibody, as claim 65 requires. The binding affinity could be lower. Indeed, Kurrle—like Queen 1990—also started from a best-fit human antibody sequence. (Ex. 1571, 8:16-18.) Yet, Kurrle saw a significant ***decrease*** in binding affinity. (Ex. 2033 at 1 (abstract).) Nothing in the record demonstrates that use of

the analogous technique described in Queen 1990 would result in an increase in binding affinity as required by claim 65.

For these additional reasons, the Board should deny Grounds 1-4 for claim 65.

5. Grounds 2, 5, and 7: Pfizer's asserted references do not render obvious the "consensus" sequence limitations of claims 4, 33, 62, 64, and 69.

The asserted references do not teach the "consensus human variable domain" required by claims 4, 33, 62, and 69, or the "human variable domain comprising the most frequently occurring amino acid residues at each location in all human immunoglobulins of a human heavy chain immunoglobulin subgroup" required by claim 64.

a) Grounds 2 and 7: Queen 1990 does not render obvious the claimed "consensus" sequence.

For Ground 2 (claims 4, 62, and 64) and Ground 7 (claim 33), Pfizer alleges that the consensus sequence limitation is satisfied by Queen 1990's statement that "a consensus framework from many human antibodies" may be used. (Paper 1 at 40-42; Ex. 1550, 12:17-20.) But that is Queen 1990's only mention of a "consensus framework." And even from that single statement, it is clear that Queen 1990 is not referring to the type of consensus sequence expressly defined and claimed in the '213 patent—which "comprises the most frequently occurring

amino acid residues at each location in all human immunoglobulins of any particular subclass or subunit structure." (Ex. 1501, 11:32-40.)

First, Queen 1990's "Criterion I"—the only place in Queen 1990 that mentions a "consensus" framework—emphasizes the importance of selecting a human antibody sequence "most homologous" to the non-human antibody sequence. Indeed, Queen 1990 explains that choosing the "most homologous" human sequence is critical to retaining binding affinity because it presents "a smaller chance of changing an amino acid near the CDR's [sic] that distorts their conformation." (Ex. 1550, 12:26-36.) The '213 patent takes the ***opposite*** approach; it does not consider whether the consensus sequence is homologous to any particular non-human sequence and instead applies the same sequence for all antibodies to be humanized.

Second, Queen 1990's "Criterion II" specifically pertains to "unusual" or "rare" amino acid residues, which occur "in no more than about 10%" of human sequences. (Ex. 1550, 13:22-32.) Criterion II would make no sense if Queen 1990 disclosed a "consensus" sequence as claimed by the '213 patent, which "comprises the most ***frequently*** occurring amino acid residues at each location" (Ex. 1501, 11:32-40)—*i.e.*, by definition, it contains ***no*** "unusual" or "rare" residues.

Third, there is nothing in Queen 1990's claims or working examples that would have led a skilled artisan to the '213 patent's consensus sequence approach.

On the contrary, Queen 1990's claims recite methods that require selecting "one of the about three most homologous sequences" for the human framework (claim 18) or making substitutions for "rare" amino acids in the human sequence (claim 19). And Queen 1990's only working example involves selecting a human antibody sequence "more homologous to the heavy chain of this antibody than to any other heavy chain sequence in the [database]." (Ex. 1550, 26:6-13.)

These deficiencies in Queen 1990 are not cured by the PDB database, which merely collects individual protein structures. (Ex. 1580 at 1.) The database does not disclose "the most frequently occurring amino acid residues at each location in all human immunoglobulins of any particular subclass or subunit structure." (Ex. 1501, 11:32-40.) Indeed, even Pfizer does not allege that the PDB database discloses a "consensus" sequence.

For these additional reasons, the Board should deny Grounds 2 and 7 for claims 4, 33, 62, and 64.

b) Ground 5: Queen 1989 in view of Kabat 1987 does not render obvious the claimed "consensus" sequence.

Nor does the combination of Queen 1989 with Kabat 1987 render obvious the "consensus" sequence claims challenged in Ground 5 (claims 4, 62, 64, and 69). The term "consensus" sequence does not appear anywhere in Queen 1989. In fact, Queen 1989's reliance on identifying a human sequence "most homologous"

to the specific non-human sequence to be humanized is the ***opposite*** of a consensus sequence—which is a generally applicable sequence that does not depend upon homology to any particular sequence.

Pfizer argues that Queen 1989 "taught moving towards a consensus framework region, observing that replacing amino acid residues with ones that are 'more typical' and common would make the resulting antibody more human and less immunogenic." (Paper 1 at 55.) But ***modifying*** a sequence to include "more typical" residues is not the consensus sequence approach of the '213 patent. The '213 patent's consensus sequence starts with "the most frequently occurring amino acid residues at each location" (Ex. 1501, 11:32-40) and adds ***less common*** residues from the non-human sequence (*id.*, 20:41-21:3). The discussion in Queen 1989 of adding "more typical" residues does not suggest moving toward the '213 patent's consensus sequence approach. If anything, this passage suggests a different approach from the '213 patent.

Kabat 1987 does not cure Queen 1989's deficiencies. Kabat 1987 is a reference book of antibody sequences; it does not disclose any techniques for humanizing an antibody. Kabat 1987 included statistics on the "most common" amino acids for a given type of immunoglobulin. (Ex. 1552 at 8.) But Kabat 1987's tabulation of the "most common" amino acids was simply to assist scientists evaluate "the probability that a given amino acid at a given position may

not be correct" when sequencing an antibody. (Ex. 2026 at 3.) Nothing in Kabat 1987 suggests using those values to engineer ***entirely new*** antibody sequences.

Moreover, in some instances, Kabat 1987 identifies more than one amino acid for each position where there are several amino acids that frequently occur at a given position. (*E.g.*, Ex. 1552 at 8 (residues 1, 3, 6, 17, etc.).) There is thus no reason a skilled artisan would have been led from Kabat 1987 to a "consensus" sequence consisting only of the single "most frequently occurring amino acid residues at each location." (Ex. 1501, 11:32-40.)

For these additional reasons, the Board should deny Ground 5.

6. Grounds 3 and 4: Claims 75-77 and 79[9] would not have been obvious in view of Pfizer's proposed combinations.

a) Claim 75

In Grounds 3 and 4, Pfizer asserts an obviousness theory against claim 75, which requires a substitution at 71H.

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[9] Although Pfizer identifies claim 65 as challenged under Grounds 3-4 (Paper 1 at 5), and includes a summary sentence that claim 65 is obvious in view of Queen 1989 or Queen 1990, the PDB Database, and Tramontano (*id.* at 54), Pfizer presented no substantive argument concerning claim 65 for these grounds (*id.* at 53-54). To the extent that Pfizer is challenging claim 65 in Grounds 3-4, its arguments fail as explained above.

Pfizer argues that a skilled artisan would have substituted 71H based upon the teachings of Queen 1989 (Ground 3) or Queen 1990 (Ground 4). (Paper 1 at 53-54.) Pfizer, however, points to no antibody sequence in Queen 1989 or Queen 1990 that contains a substitution at 71H. Instead, Pfizer argues that the general teachings of those references when combined with 9 structures from the PDB database "would have readily identified residue 71H for substitution." (Paper 1 at 53; Ex. 1503 ¶¶ 289-91.) But as discussed above, Pfizer argues that those references would have disclosed numerous possible substitutions—20 total from Queen 1989, and 42 from Queen 1990. (Paper 1 at 34, 37.) Pfizer does not explain why a skilled artisan would have selected residue 71H among the numerous other positions supposedly identified by applying the techniques described in those references.

Lacking support in the Queen references, Pfizer attempts to bolster its argument based upon Tramontano. (*Id.* at 53-54.) Tramontano analyzed several antibody structures and found that "the major determinant of the position of H2 is the size of the residue at site 71." (Ex. 1551 at 1 (abstract).) Although Tramontano referenced potential "applications" of that discovery "to antibody engineering" (*id.* at 7), it did not suggest that substitutions at 71H are desirable when designing new antibody structures. On the contrary, Tramontano highlighted the unpredictability of substitutions at that position.

For example, Tramontano reported that substituting 71H reduced binding affinity by "approximately tenfold" for one antibody. (Ex. 1551 at 7.) Tramontano also noted that a different antibody substituted at 71H had "an affinity close to that of the rat original." (*Id.*) Tramontano acknowledged that it could not explain those divergent results. (*Id.*) A skilled artisan would have had no reason to substitute 71H given the mixed success and unexplained results reported in Tramontano, let alone a reasonable expectation of success in doing so. *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1208-09 (Fed. Cir. 1991) (rejecting obviousness challenge where there was no reasonable expectation of success based upon the state of the art).

For these additional reasons, the Board should deny Grounds 3 and 4 for claim 75.

b) Claims 76-77 and 79

Pfizer's challenge to claims 76, 77, and 79—which also require a substitution at 71H—fails for all the reasons discussed above for claim 75. In addition, these three claims require ***additional*** framework substitutions: 73H (claim 76); 73H and 78H (claim 77); and 73H, 78H, and 93H (claim 79). As discussed above, Pfizer contends that the asserted references would have disclosed many potential substitutions—20 from Queen 1989, and 42 from Queen 1990—resulting in thousands of combinations and permutations of possible substitutions.

Pfizer provides no analysis why a skilled artisan would have been led to the specific combinations of substitutions required by claims 76, 77, and 79 based upon the asserted references. Given the breadth of the genus that Pfizer contends is disclosed by its asserted references, Pfizer's obviousness argument with respect to the specific claimed combinations of substitutions fails. *See Insite Vision*, 783 F.3d at 863.

Accordingly, for these additional reasons, the Board should deny Grounds 3 and 4 for claims 76, 77, and 79.

7. Grounds 6 and 7: Claims 30, 31, 33, 42, and 60 would not have been obvious in view of Pfizer's proposed combinations.

For Grounds 6 and 7, Pfizer argues that Queen 1989 or Queen 1990 would have led a skilled artisan to make substitutions at 66L, 98L, and 36H, which are recited in claims 30, 31, 33, and 42. (Paper 1 at 56-61.) However, as discussed above (pp. 43, 48), Pfizer has not identified any antibody disclosed in Queen 1989 or Queen 1990 that contains those substitutions; instead, Pfizer relies upon the general techniques disclosed in those Queen references, which Pfizer admits encompasses numerous substitutions—20 total for Queen 1989 and 42 total for Queen 1990. (Paper 1 at 34, 37.) Pfizer has failed to provide any reason why a skilled artisan would have been drawn to the specific residue substitutions recited in the challenged claims, which is fatal to Pfizer's obviousness argument.

Pfizer also relies on Hudziak, even though that reference does not mention antibody humanization, or provide any guidance on possible framework substitutions. Pfizer does not suggest otherwise. Pfizer relies on Hudziak solely for its disclosure of $p185^{HER2}$ as a potential drug target. (*Id.* at 56-57.) But knowledge of the biological ***target*** does not render the ***specific humanized sequences*** claimed here obvious. *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1074 (Fed. Cir. 2012) ("[K]nowledge of the goal does not render its achievement obvious.").

For these additional reasons, the Board should deny Grounds 6 and 7.

C. Objective Indicia Of Non-Obviousness Confirm The Patentability Of The Challenged Claims.

Evidence concerning the real-world impact of a patented invention is a critical safeguard against hindsight reasoning. *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010). Here, several objective indicia confirm the non-obviousness of the challenged claims.

1. Unexpected results

Unexpected results are powerful evidence of non-obviousness. *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) ("[T]hat which would have been surprising to a person of ordinary skill in a particular art would not have been obvious."). Here, the challenged claims reflect at least two different unexpected results.

First, it would not have been expected before the invention of the '213 patent that it was possible to develop a broadly-applicable platform that could be used to humanize different antibodies starting from the same sequence. Before the '213 invention, scientists believed that it was necessary to identify a sequence most homologous to the non-human antibody as a starting point. For example, Queen 1989 emphasized that choosing a human sequence "as homologous as possible to the original mouse antibody to reduce any deformation of the mouse CDRs" was one of its key "ideas that may have wider applicability." (Ex. 1534 at 5.) The '213 patent's consensus sequence approach unexpectedly allowed numerous different antibodies to be humanized from a single consensus sequence—without regard to how similar that consensus sequence is to the original non-human antibody. (Ex. 1502 at 456-58, ¶¶ 2-9 (describing antibodies made according to the '213 invention that were effective against numerous disease targets).)

Pfizer argues that the broad applicability of the '213 invention is irrelevant because the claims relate to antibody products, not methods of making them. (Paper 1 at 62-63.) But the broad applicability of the '213 invention is reflected in the claims—for example, which recite specific framework substitutions that the inventors determined could be used in many different humanized antibodies. (Ex. 2017, Carter Decl. ¶¶ 75-79.)

Second, the '213 patent's approach results in antibodies with unexpectedly superior properties compared to those made by prior art methods. For example, humanized antibodies made using prior art techniques often produced an immunogenic response (*e.g.*, Ex. 2025 at 751 (3 out of 4 patients suffered immunogenic response)) or had reduced binding affinity (*e.g.*, Ex. 2033 at 1 (abstract) (2.5-fold reduction in binding affinity)). Humanized antibodies made according to the '213 invention unexpectedly solved both problems. Antibodies for a variety of disease conditions made using the '213 invention lacked immunogenicity even after prolonged use and demonstrated ***superior*** binding affinity to the original non-human antibody. (Ex. 1502 at 3439-41, ¶¶ 2-9; Ex. 1501, 51:50-53 ("This antibody binds the $p185^{HER2}$ ECD 3-fold more tightly than does muMAb4D5 itself.").) That these desirable properties could be obtained using a broadly-applicable consensus sequence that was not specifically designed to be similar to the original non-human antibody was a surprising result, given the prior art teachings emphasizing the importance of starting from the most homologous human sequence for each individual antibody.

Pfizer argues that those unexpected properties are not commensurate with the scope of the claims, since only claims 63 and 65 specifically recite those properties. (Paper 1 at 62.) But those properties are a result of the inventors' novel consensus sequence approach, which is reflected in the specific framework

substitutions that are recited in the challenged claims. (Ex. 2017, Carter Decl. ¶¶ 75-79; Ex. 2016, Presta Decl. ¶¶ 51-53.) There is no requirement that the unexpected results be recited in the claims themselves. *In re Merchant*, 575 F.2d 865, 869 (C.C.P.A. 1978) (noting "no law requiring that unexpected results relied upon for patentability be recited in the claims").

2. Commercial success

Some of Genentech's most successful antibodies embody the claims of the '213 patent, including Herceptin®, Perjeta®, Avastin®, Lucentis®, and Xolair®, together generating billions of revenue annually. (Ex. 2029 at 2.) The success of these drugs is attributable, in part, to their unique amino acid sequences provided using the '213 patent's consensus sequence approach, which allows good binding affinity while minimizing immunogenicity. This commercial success confirms the non-obviousness of the challenged claims. *See Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1379 (Fed. Cir. 2011).

Pfizer argues that the commercial success of Herceptin® is not relevant because the drug contains additional substitutions that are not recited in the claims. (Paper 1 at 65.) But Pfizer does not dispute that Herceptin® embodies the challenged claims. And Pfizer's argument that Herceptin® somehow is not coextensive with the claimed features because it contains additional unclaimed substitutions is incorrect. (*Id.*) The challenged claims recite ***framework*** region

substitutions. The two unclaimed substitutions in Herceptin® (55L and 102H[10]), however, are in the ***CDRs***, not the framework region. (*See, e.g.*, *id.* at 13 (showing CDRs).) There are no unclaimed framework substitutions in Herceptin®. Because Herceptin® is both an embodiment of the claims and coextensive with the claimed features, a nexus between its commercial success and the challenged claims is presumed. *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000).

D. *Inter Partes* Review Proceedings Are Unconstitutional.

The Board should deny institution because this proceeding would violate Patent Owner's constitutional rights. Adversarial challenges to an issued patent—like inter partes reviews—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, 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 is currently considering the constitutionality of *inter partes* reviews. *Oil States Energy Servs., LLC v. Greene's Energy Grp., LLC*, 137 S. Ct. 2239 (2017). Patent

[10] Pfizer erroneously identifies this position as 102L.

Owner presents this constitutional challenge now to preserve the issue pending the Supreme Court's decision.

VIII. CONCLUSION

The Board should deny institution.

Respectfully submitted,

Date: September 6, 2017

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CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Patent Owner's Preliminary Response contains 13,765 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: September 6, 2017

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CERTIFICATE OF SERVICE

I hereby certify that, on September 6, 2017, I caused a true and correct copy of the following materials:

- Patent Owner's Preliminary Response
- Patent Owner's Motion to Seal
- Exhibits 2001-2033
- Patent Owner's Exhibit List

to be served electronically via File Transfer Protocol (FTP), as previously agreed by the parties, on the following attorneys of record:

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IPR2017-01489
Patent Owner's Exhibit List

Patent Owner's Exhibit Number	Exhibit Name
2001	Genentech, Inc. Laboratory Notebook No. 10098 (Leonard Presta) PROTECTIVE ORDER MATERIAL
2002	Genentech, Inc. Laboratory Notebook No. 10823 (Leonard Presta) PROTECTIVE ORDER MATERIAL
2003	Genentech, Inc. Laboratory Notebook No. 11268 (Paul Carter) PROTECTIVE ORDER MATERIAL
2004	Genentech, Inc. Laboratory Notebook No. 11643 (Paul Carter) PROTECTIVE ORDER MATERIAL
2005	Genentech, Inc. Laboratory Notebook No. 10840 (John Brady) PROTECTIVE ORDER MATERIAL
2006	Genentech, Inc. Laboratory Notebook No. 11162 (John Brady) PROTECTIVE ORDER MATERIAL
2007	Excerpts from Genentech, Inc. Laboratory Notebook No. 11008 (Ann Rowland) PROTECTIVE ORDER MATERIAL
2008	Excerpts from Genentech, Inc. Laboratory Notebook No. 11297 (Tim Hotaling) PROTECTIVE ORDER MATERIAL
2009	Excerpts from Genentech, Inc. Laboratory Notebook No. 11568 (Monique Carver) PROTECTIVE ORDER MATERIAL
2010	Genentech, Inc. Interoffice Memorandum from Paul Carter to Leonard Presta and Dennis Henner PROTECTIVE ORDER MATERIAL
2011	Genentech, Inc. Interoffice Memorandum from Paul Carter to Leonard Presta PROTECTIVE ORDER MATERIAL
2012	Genentech, Inc. Synthetic DNA Requests PROTECTIVE ORDER MATERIAL
2013	Genentech, Inc. Synthetic DNA Requests PROTECTIVE ORDER MATERIAL

Patent Owner's Exhibit Number	Exhibit Name
2014	Genentech, Inc. Protein Engineering of 4D5 Status Report PROTECTIVE ORDER MATERIAL
2015	Genentech, Inc. Interoffice Memorandum re: RCC Minutes and Recommendations PROTECTIVE ORDER MATERIAL
2016	Declaration of Dr. Leonard G. Presta PROTECTIVE ORDER MATERIAL
2017	Declaration of Dr. Paul J. Carter PROTECTIVE ORDER MATERIAL
2018	Declaration of John Ridgway Brady PROTECTIVE ORDER MATERIAL
2019	Declaration of Irene Loeffler
2020	Paul Carter, et al., *Humanization of the Anti-p185 Antibody for Human Cancer Therapy*, 89 PROC. NATL. ACAD. SCI. 4285-4289 (1992)
2021	Leonard Presta, et al., *Humanization of an Anti-Vascular Endothelial Growth Factor Monoclonal Antibody for the Therapy of Solid Tumors and Other Disorders*, 57 CANCER RESEARCH 4593-4599 (1997)
2022	Marianne Brüggerman, et al., *The Immunogenicity of Chimeric Antibodies*, 170 J. EXP. MED. 2153-2157 (1989)
2023	Jatinderpal Kalsi, et al., *Structure-function Analysis and the Molecular Origins of Anti-DNA Antibodies in Systemic Lupus Erythematosus*, EXPERT REVIEWS IN MOLECULAR MEDICINE 1-28 (1999)
2024	Scott Gorman, et al., *Reshaping a Therapeutic CD4 Antibody*, 88 PROC. NATL. ACAD. SCI. 4181-4185 (1991)
2025	John Isaacs, et al., *Humanised Monoclonal Antibody Therapy for Rheumatoid Arthritis*, 340 THE LANCET 748-752 (1992)
2026	Elvin Kabat, et al., *Sequences of Proteins of Immunological Interest* 1-23 (4th ed. 1987)
2027	Anna Tramontano, et al., *Framework Residue 71 Is a Major Determinant of the Position and Conformation of the Second Hypervariable Region in the VH Domains of Immunoglobulins*, 215 J. MOL. BIOL. 175-182 (1990)

Patent Owner's Exhibit Number	**Exhibit Name**
2028	H.M. Shepard, et al., *Herceptin*, *in* THERAPEUTIC ANTIBODIES. HANDBOOK OF EXPERIMENTAL PHARMACOLOGY 183-219 (Y. Chernajovsky & A. Nissim, eds. 2008)
2029	Excerpt from Roche Finance Report 2016
2030	Modified Default Standing Protective Order and Patent Owner's Certification of Agreement to Terms
2031	Modified Default Standing Protective Order – Redline
2032	File History for U.S. Patent Application No. 07/715,272 *Immunoglobulin Variants* (filed June 14, 1991)
2033	Shearman, et al. *Construction, expression and characterization of humanized antibodies directed against the human a/b T cell receptor*. J. Immunol. 147(12):4366-4373, (December 15, 1991)