Filed on behalf of Patent Owner Genentech, Inc. by:

David L. Cavanaugh (Reg. No. 36,476)
Owen K. Allen (Reg. No. 71,118)
Robert J. Gunther, Jr. (*Pro Hac Vice to be filed*)
Lisa J. Pirozzolo (*Pro Hac Vice to be filed*)
Kevin S. Prussia (*Pro Hac Vice to be filed*)
Andrew J. Danford (*Pro Hac Vice to be filed*)
WILMER CUTLER PICKERING
HALE AND DORR LLP
1875 Pennsylvania Ave., NW
Washington, DC 20006

Adam R. Brausa (Reg. No. 60,287)
Daralyn J. Durie (*Pro Hac Vice to be filed*)
DURIE TANGRI LLP
217 Leidesdorff Street
San Francisco, CA 94111

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-01488
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 ten different anticipation or obviousness grounds, but fails to demonstrate a reasonable likelihood of success for any of them.

As an initial matter, the primary references underlying each proposed ground—Kurrle (Ex. 1071) and Queen 1990 (Ex. 1050)—are not prior art. The '213 inventors reduced their invention to practice before the publication of Kurrle and Queen 1990 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 Kurrle or Queen 1990, Pfizer has failed to demonstrate a reasonable likelihood of success for claim 63 in Ground 1 and all claims challenged in Grounds 2-10 for several additional reasons.

First, Pfizer has not demonstrated that certain claim limitations are disclosed or would have been obvious, including (i) "lacks immunogenicity" in claim 63 (Grounds 1-3); (ii) "up to 3-fold more" binding affinity in claim 65 (Ground 7); and (iii) "consensus" sequence in claims 4, 33, 62, 64, and 69 (Grounds 2, 3, and 8). Pfizer's arguments with respect to these claims rest on speculation and are not supported by the disclosure of the asserted references.

Second, for its anticipation argument in Ground 2, Pfizer has not shown that Queen 1990 teaches each limitation of any challenged claim. Pfizer does not contend that Queen 1990 discloses ***any*** antibody that reads on ***any*** challenged claim. Instead, Pfizer argues that Queen 1990 discloses general criteria that supposedly would have led a skilled artisan to arrive at the challenged claims. But Pfizer's own arguments confirm that Queen 1990 encompasses thousands of possibilities, and Pfizer has not explained why a skilled artisan supposedly would have pursued the specific amino acid substitutions recited in the challenged claims.

Third, Pfizer's obviousness arguments (Grounds 3-10) fail for similar reasons. Pfizer presents a hindsight-driven analysis that selectively focuses on some potential amino acid substitutions without explaining 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.

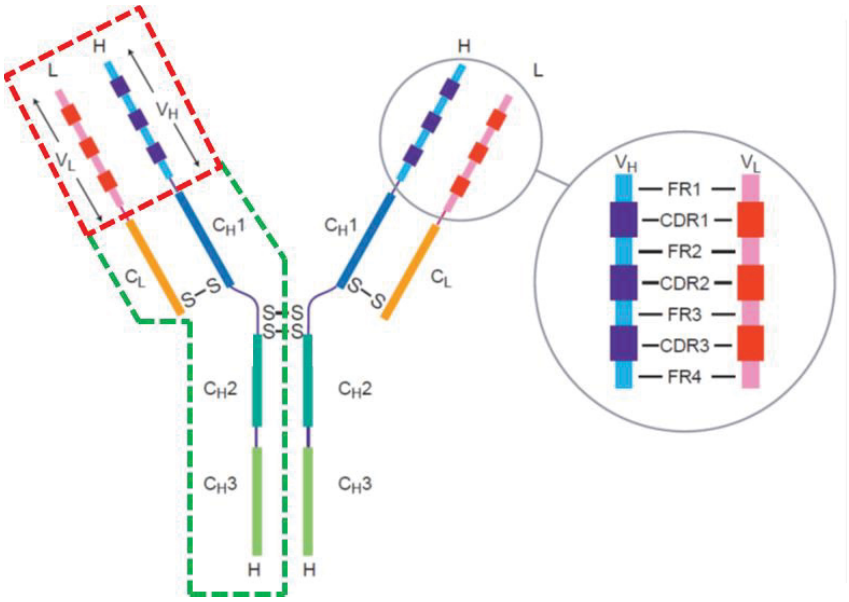
Finally, for Grounds 3-7, Pfizer contends the challenged claims would have been obvious over the combination of Queen 1990 and Kurrle. Pfizer, however, never identifies any claim limitation lacking from Queen 1990 that is disclosed in Kurrle, or vice versa—let alone explains how the references would be combined. Pfizer cannot cure the deficiencies in its anticipation theory with such conclusory assertions of "obviousness."

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. 1082 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. 1001, 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. 1001, 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. 1001, 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. 1028 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. 1001, 2:20-52.) But that approach could reduce the antibody's ability to bind to specific antigens. (Ex. 1034 at 5 ("Unfortunately, in some cases the humanized antibody had significantly less binding affinity for antigen than did the original mouse antibody.").)[1]

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. 1034) selected a human

[1] In this proceeding, Patent Owner uses "chimeric" and "humanized" as defined in the '213 patent. (Ex. 1001, 1:59-62 ("chimeric" antibodies have "an 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").)

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. 1034 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. 1001, 3:50-52.) 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. 1002 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. 1001, 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. 2016,

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. 1001, 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. 1002 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. 1001, coversheet.) The challenged claims issued over hundreds of references considered during prosecution, including every reference that Pfizer relies upon in its proposed grounds. (Ex. 1001 at 1-6.) The examiner did not make any rejection based upon any reference underlying Pfizer's proposed grounds.

Pfizer asserts that Kurrle (Ex. 1071), Chothia & Lesk (Ex. 1062), and Chothia 1985 (Ex. 1063) were not considered during prosecution. (Paper 1 at 14.)

That is incorrect. Each reference is cited on the face of the patent. (*See* Ex. 1001 at 1 (Kurrle: "EP 403156"); *id.* at 2 (Chothia & Lesk: right column, ninth from top); *id.* (Chothia 1985: right column, twelfth from top).) And Chothia & Lesk and Chothia 1985 are even discussed in the '213 specification; indeed, Chothia 1985 is the first reference cited in the specification, and Chothia & Lesk is cited no fewer than nine times. (*Id.*, 1:27-30 (Chothia 1985); *id.*, 3:1-3, 3:31, 7:7-8, 7:45, 10:38, 20:22-23, 20:29-30, 47:42-43, 48:66-67 (Chothia & Lesk).)

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. 1002 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 Kurrle (December 19, 1990) or Queen 1990 (July 26, 1990).

IV. PFIZER'S ASSERTED REFERENCES

A. Kurrle

Kurrle is a European Patent Application published on December 19, 1990. Because it was published after the '213 inventors conceived and reduced their invention to practice, Kurrle is not prior art. (*See infra* pp. 20-42.)

Unlike the '213 patent's consensus sequence approach, Kurrle used a best-fit approach for antibody humanization. Starting from the murine antibody sequence, Kurrle searched a database of human antibody sequences to identify "the most homologous human antibody" to provide the variable domain. (Ex. 1071, 8:16-18.) Kurrle incorporated the CDRs from the mouse antibody into the human antibody sequence (*id.*, 3:8-11), and then made further substitutions of murine residues "in the sequence immediately before and after the CDRs" and "up to 4 amino acids away" (*id.*, 8:25-29).

Kurrle's technique thus involved making substitutions in any of up to 24 different amino acid residues per antibody chain—*i.e.*, 4 amino acid residues on either side of the 3 CDRs. Kurrle provided no guidance on which substitutions may be beneficial for any given antibody. Kurrle also highlighted the unpredictable and "potential[ly] adverse consequences" of modifying the human antibody sequence to incorporate amino acids from the murine antibody. (*Id.*, 8:40-43 ("[E]xtreme caution must be exercised to limit the number of changes.").)

Kurrle disclosed the sequence for four humanized antibodies: BMA 031-EUCIV1, BMA 031-EUCIV2, BMA 031-EUCIV3, and BMA 031-EUCIV4. (*Id.*, Tables 6A-B.)

B. Queen 1990

Queen 1990 is a PCT application published July 26, 1990. It is not prior art. (*See infra* pp. 20-42.)

Like Kurrle, 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. 1050, 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 34-40.)

C. Furey

Furey (Ex. 1125) is a 1983 publication describing the crystal structure of a Bence-Jones protein fragment (an immunoglobulin light chain). Furey does not describe antibody humanization or discuss substitutions beneficial when humanizing an antibody.

Furey identified "11 side chain-side chain hydrogen bonds" of which 6 "may be common to all V_L domains." (Ex. 1125 at 14.) According to Furey, the "most important" of those six hydrogen bonds "seem to be the two involved in the salt-bridge" between residue 61L (Arg62) and residue 82L (Asp83). (*Id.*)[2]

D. Chothia & Lesk

Chothia & Lesk (Ex. 1062) is a 1987 publication that analyzed known antibody structures to identify the amino acid positions "primarily responsible for the main-chain conformations observed in the hypervariable regions." (Ex. 1062 at

[2] This shorthand follows the convention of Kabat 1987 (Ex. 1052), which assigns standardized numbers to the amino acid positions in antibody heavy ("H") and light ("L") chains. (Ex. 1001, 10:46-57.) For example, "61L" refers to the 61st amino acid position in the light chain. Furey identifies these positions using a different numbering convention (*i.e.*, Arg62 or Asp83).

902.) Chothia & Lesk does not describe antibody humanization or discuss substitutions beneficial when humanizing an antibody.

Chothia & Lesk noted that "[t]he major determinants of the tertiary structure of the frameworks are the residues buried within and between the domains." (*Id.* at 903.) Table 4 identifies 50 amino acid positions "commonly buried within V_L and V_H domains"—26 from the light chain and 24 from the heavy chain. (*Id.* at 906.) Chothia & Lesk does not indicate that any of those 50 amino acid positions has more importance than any other to determine antibody structure.

E. Chothia 1985

Chothia 1985 (Ex. 1063) is a 1985 publication that analyzes "the structure of the interface between VL and VH domains in three immunoglobulin fragments." (Ex. 1063 at 2 (abstract).) Chothia 1985 does not describe antibody humanization or discuss substitutions beneficial when humanizing an antibody.

Table 4 of Chothia 1985 identifies 20 amino acid positions at the V_L-V_H interface. (*Id.* at 11.) Chothia 1985 does not indicate that any of those 20 positions has more importance than any other to determine antibody structure.

F. Hudziak

Hudziak (Ex. 1021) 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. 1021 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 15-16), 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. 1001, 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 16-18.) 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 All Grounds Because Neither Kurrle Nor Queen 1990 Is Prior Art.

Each of Pfizer's proposed grounds rests on Kurrle and/or Queen 1990. Yet neither Kurrle (published December 19, 1990) nor Queen 1990 (published July 26, 1990) is prior art.

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

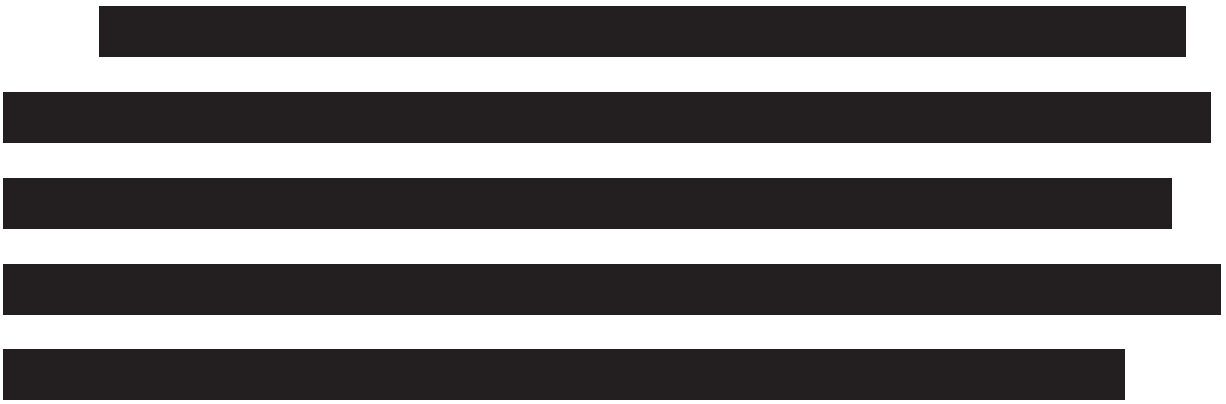
a) Consensus sequence

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. 1021 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]

[redacted]

(i) First humanized 4D5 variable domain fragment

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[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]

[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 (pp. 22-25), 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. 20-25), 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. 25-26, 29-31), 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. 1002 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. 1001, 51:48-53 ("[HuMAb4D5-8] binds the p185^{HER2} ECD 3-fold more tightly than does muMAb4D5 itself.").)[7]

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

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. 27-

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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 Kurrle and/or Queen 1990.

31), 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. 27-31.) 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. Kurrle and Queen 1990 are not prior art.

Kurrle (published December 19, 1990) and Queen 1990 (published July 26, 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.

Kurrle and Queen 1990 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.*, 75:31-93:19.)

"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 Kurrle and Queen 1990 are not prior art, they cannot render any challenged claim invalid. The Board should thus deny institution of all grounds.

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

The prior invention of the challenged claims before the publication of Kurrle and Queen 1990 defeats ***all*** proposed grounds. However, as noted at the outset, there are additional reasons why Pfizer has not demonstrated a reasonable likelihood of success for certain challenged claims even under its incorrect attempt to treat Kurrle and Queen 1990 as prior art.

First, Pfizer has not shown that the following limitations are disclosed and/or would have been obvious: (i) "lacks immunogenicity" in claim 63 (Grounds 1-3); (ii) "up to 3-fold more" binding affinity in claim 65 (Ground 7); and (iii) "consensus" sequence in claims 4, 33, 62, 64, and 69 (Grounds 2, 3, 8). Pfizer's cited references do not contain data for any humanized antibody satisfying the "lacks immunogenicity" and "up to 3-fold more" binding affinity limitations. Nor do they describe a "consensus" sequence as the '213 patent defines the term.

Second, all claims challenged in Grounds 2-10 require specific framework substitutions that Pfizer has not shown are anticipated and/or 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.

Third, Grounds 3-7 present obviousness arguments that rest on the combination of Kurrle and Queen 1990. But Pfizer's conclusory assertions of motivation to combine cannot cure the deficiencies in its anticipation arguments for those references. The Board should therefore not institute Grounds 3-7, and it should also deny Ground 3 (which rests solely on the combination of Kurrle and Queen 1990) for the separate reason that it is redundant of Pfizer's anticipation arguments in Grounds 1-2.[8]

[8] For this preliminary response, Patent Owner relies solely on antedation in response to Pfizer's challenge to claims 1-2, 25, 29, 66-67, 71-72, 75-76, and 80-81 in Ground 1. Patent Owner reserves the right to challenge other aspects of Pfizer's argument with respect to those claims if this proceeding is instituted.

1. Grounds 1, 2, and 3: Kurrle and Queen 1990 do not anticipate or render obvious the "lacks immunogenicity" limitation of claim 63.

In Grounds 1, 2, and 3, Pfizer challenges claim 63, which requires "[a] humanized antibody which lacks immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient."

Pfizer points to no data showing that the antibodies produced according to Kurrle and/or Queen 1990 will result in humanized antibodies that "lack immunogenicity compared to a non-human parent antibody." (Paper 1 at 30-31, 38.) Instead, Pfizer argues that this limitation is inherent to humanized antibodies. (*Id.*) That is incorrect; even humanized antibodies may produce an immunogenic response. (Ex. 2025 at 751 (3 out of 4 patients "developed antiglobulins" when treated with humanized antibody).)

Pfizer also relies on aspirational statements of intended results to argue that Kurrle and/or Queen 1990 teach the "lacks immunogenicity" limitation. (Paper 1 at 31, 38; *e.g.*, Ex. 1050 at 1 (abstract) ("[T]he humanized immunoglobulins of the present invention will be substantially non-immunogenic in humans."); Ex. 1071, 3:11-12 ("The resulting mAb of the present invention is thus essentially a human antibody with a much lower immunogenicity in patients.").) These unsupported predictions are insufficient to show that antibodies produced according to techniques disclosed in the publications will ***necessarily*** lack immunogenicity—

which Pfizer must establish to show inherent anticipation. *See Bettcher Indus., Inc. v. Bunzl USA, Inc.*, 661 F.3d 629, 639-40 (Fed. Cir. 2011).

Those same unsupported predictions also do not render obvious the "lacks immunogenicity" limitation of claim 63. During prosecution of the '213 patent, the examiner considered similar statements contained in 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. 1069 at 1; *see* Ex. 1002 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. 1002 at 2502, 3431-3432.) The same result should apply here. The aspirational statements in Kurrle and Queen 1990 that the authors hoped to address the problem of immunogenicity does not make it obvious how to achieve that result.

Accordingly, the Board should deny Grounds 1, 2, and 3 for claim 63.

2. <u>Grounds 2, 3, and 8</u>: Pfizer's asserted references do not anticipate or render obvious the "consensus" limitations of claims 4, 33, 62, 64, and 69.

The asserted references do not teach the "consensus human variable domain" limitation 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" limitation required by claim 64.

a) Queen 1990

For Grounds 2, 3, and 8, 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 36, 37, 39; Ex. 1050, 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. 1001, 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. 1050, 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. 1050, 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. 1001, 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. 1050, 26:6-13.)

Because Queen 1990 does not disclose or suggest a "consensus" sequence that "comprises the most frequently occurring amino acid residues at each

location" (Ex. 1001, 11:32-40), the Board should deny Grounds 2, 3, and 8 for claims 4, 33, 62, 64, and 69.

b) Kurrle

For Ground 3, Kurrle does not cure the deficiencies in Queen 1990. Like Queen 1990, Kurrle relies on a best-fit approach, which is very different from the consensus sequence approach of the '213 patent, as discussed above. (Ex. 1071, 8:16-18 ("[T]he murine BMA 031 amino acid sequence was used to search the NBRF data base for the most homologous human antibody.").) Because Pfizer does not point to any disclosure in Kurrle that supposedly suggests the consensus sequence required by claims 4, 33, 62, 64, and 69, Pfizer's challenge to those claims in Ground 3 fails for this additional reason.

c) Hudziak

For Ground 8, Hudziak also does not cure Queen 1990's deficiencies. Hudziak does not even mention the possibility of humanizing antibodies, and Pfizer does not point to any disclosure in Hudziak supposedly teaching the '213 patent's consensus sequence approach. Accordingly, Pfizer's challenge to claim 33 in Ground 8 fails for this reason as well.

3. <u>Ground 2</u>: Queen 1990 does not anticipate the challenged claims.

For Ground 2, Pfizer argues that Queen 1990 anticipates claims 1-2, 4, 29, 62-64, and 80-81. But Pfizer does not point to any antibody sequence disclosed in

Queen 1990 that contains the claimed framework substitutions. Instead, Pfizer contends that Queen 1990's "Criterion III" discloses those substitutions. (Paper 1 at 35, 39-40.) Queen 1990's "Criterion III" allows for substitutions "[i]n the positions immediately adjacent to the 3 CDR's [sic] in the humanized immunoglobulin chain." (Ex. 1050, 14:1-3.) That broad rule encompasses substitutions at any of 23 different positions (Ex. 1003 ¶ 179)—literally ***thousands*** of different combinations and permutations of possible substitutions, only a small fraction of which overlap with the challenged claims.

That disclosure of a large genus is insufficient to teach the ***specific*** claimed substitutions. Indeed, where a reference discloses a genus that encompasses the claims, and no specific examples falling within the claims, the genus anticipates only if it contains "sufficient specificity" pointing to the claimed species. *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006) (finding no anticipation of a narrower claimed species by a broader prior art genus). Pfizer has not explained how Queen 1990's broad disclosure provides "sufficient specificity"

to lead a skilled artisan to the particular substitutions required by the challenged claims.[9]

Pfizer quotes Queen 1990's statement that "[e]ach humanized immunoglobulin chain may comprise about 3 or more amino acids from the donor immunoglobulin in addition the CDR's [sic], usually at least one of which is immediately adjacent to a CDR in the donor immunoglobulin." (Paper 1 at 35; Ex. 1050 at 1 (abstract).) But that statement does not meaningfully narrow the number of possible substitutions or otherwise lead specifically to the substitutions of the challenged claims. For example, even if only 3 substitutions were made, there are over 2,000 different permutations and combinations of the 23 residues that Pfizer identifies as satisfying Queen 1990's Criterion III.

Because Pfizer has not explained how the broad genus encompassed by Queen 1990 would have led to the specific substitutions claimed in the '213 patent, the Board should deny Ground 2.

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[9] In contrast to Queen 1990's generic guidance, the '213 patent claims specific substitutions that the inventors' identified using their consensus sequence approach. (*See supra* pp. 20-25.)

4. Grounds 3-7: Pfizer has failed to explain how a skilled artisan would combine Queen 1990 and Kurrle.

Grounds 3-7 each depend upon the combination of Queen 1990 and Kurrle. Pfizer argues that a skilled artisan, considering Kurrle, would look to Queen 1990 "in order to gather as much information as they could to guide their selection of specific residues for substitution in order to maintain the affinity and strength of a particular non-human antibody." (Paper 1 at 43.) However, Pfizer never says what teaching absent from Kurrle is supposedly remedied by Queen 1990, or vice versa—let alone explains how the skilled artisan would purportedly combine the teachings of these two references. (*Id.* at 43-55.) Instead, Pfizer's "obviousness" grounds simply rehash the same arguments that Pfizer presented concerning Kurrle and Queen 1990 in support of its anticipation arguments in Grounds 1-2. (*Id.* at 41-55.) Pfizer's summary assertions that a skilled artisan would combine Queen 1990 and Kurrle to arrive at the claimed inventions do not cure the deficiencies in its anticipation proof. *See, e.g.*, *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1372 (Fed. Cir. 2000) (conclusory assertions of obviousness are insufficient). Accordingly, the Board should deny Grounds 3-7.

5. Ground 3: The Board should deny Ground 3 as duplicative of Grounds 1 and 2.

The Board also should deny Ground 3 because it is duplicative of Grounds 1 and 2, in which Pfizer argues anticipation by Kurrle and Queen 1990, respectively.

The only references asserted in Ground 3 are Queen 1990 and Kurrle—the same references cited for Grounds 1 and 2. Indeed, the vast majority of claims challenged in Ground 3 are also challenged in Grounds 1 and/or 2, and Pfizer's explanation of how the limitations are supposedly satisfied is the same. The Board should refuse to institute these duplicative grounds. *See, e.g.*, *Oracle Corp. v. Clouding IP, LLC*, IPR2013-00088, Paper 13 at 2-3 (June 13, 2013).

There are only two claims that Pfizer challenges in Ground 3 not also addressed in Grounds 1 and/or 2: claims 69 and 78. Pfizer's arguments confirm that Ground 3 should be denied as duplicative even for those two claims.

Claim 69: Claim 69 requires that "the human antibody variable domain is a consensus human variable domain." As discussed above (pp. 47-49), neither Queen 1990 nor Kurrle discloses a "consensus" sequence as defined by the '213 patent. (Ex. 1001, 11:32-40.) Combining the two references in Ground 3 does not cure that deficiency.

Claim 78: Claim 78 requires "an antibody comprising the humanized variable domain of claim 66." Pfizer did not allege that either Kurrle or Queen 1990 anticipates claim 78, and offers no explanation what the combination of the two supposedly adds. (*See* Paper 1 at 49-50.)

6. Ground 4: Claim 12 would not have been obvious over Queen 1990 and Kurrle in view of Furey.

The only claim challenged in Ground 4 is claim 12, which requires a substitution at residue 66L. Pfizer does not contend that Queen 1990 and/or Kurrle teach that limitation; rather, Pfizer argues that a skilled artisan would have made a substitution at residue 66L because it is among "a handful of framework residues contacting the CDR side chain residues via side chain-side chain hydrogen bond interactions" that Furey identified. (Ex. 1003 ¶ 233.)

However, Furey states that the "most important" hydrogen-bonding interactions "seem to be the two involved in the salt-bridge between Arg62 [*i.e.*, 61L] and Asp83 [*i.e.*, 82L]," not 66L. (Ex. 1125 at 14.) Pfizer provides no explanation why a skilled artisan supposedly would have selected 66L for substitution when Furey itself emphasizes the importance of other positions. Pfizer also does not explain why a skilled artisan would have selected 66L instead of the five other hydrogen bonding interactions that Furey identified in addition to 66L. (*Id.*)

Finally, Pfizer's arguments about 66L cannot be reconciled with its other arguments highlighting the large number of potential substitutions supposedly suggested by Kurrle (31 residues) and Queen 1990 (23 residues). (Paper 1 at 49-50; Ex. 1003D (indicating 31 substitutions in Kurrle's sequences).) Pfizer does not

explain why a skilled artisan would have ignored these supposed teachings and selected 66L instead. Because Pfizer does not explain why a skilled artisan would have substituted 66L, as opposed to the numerous other substitutions supposedly suggested by Pfizer's cited references, the Board should deny Ground 4.

7. Grounds 5-7: Claims 73, 74, 77, 79, and 65 would not have been obvious over Queen 1990 and Kurrle in view of Chothia & Lesk and/or Chothia 1985.

Claims 73, 74, 77, 79, and 65 each recite specific substitutions, which are neither recited nor suggested in any of the references. Because these references would not lead a skilled artisan to the claimed substitutions, the Board should reject Grounds 5-7.

a) Claim 73 (Ground 5)

Claim 73 requires a specific substitution at 78H (claim 73), which Pfizer argues would have been obvious based upon Table 4 of Chothia & Lesk, Table 4 of Chothia 1985, and Queen 1990. (Paper 1 at 53-54; Ex. 1062 at 7; Ex. 1063 at 11.) This argument rests on hindsight.

The only explanation that Pfizer offers for why a skilled artisan would have substituted 78H is because Chothia & Lesk states that "residues buried within and between the [V_L and V_H] domains" are important determinants of antibody structure, and identifies 78H as one such position, and Queen 1990 recognizes the importance of FR residues "accessible from the antigen binding site [or] essential

for inter-chain interactions." (Paper 1 at 53; Ex. 1003 ¶ 236.) But neither Kurrle nor Queen 1990 identifies "residues buried within and between the [V_L and V_H] domains" as desirable to substitute. A skilled artisan would have had no reason to substitute position 78H based upon Pfizer's proposed combinations of references.

And in any case, even if a skilled artisan would have considered buried residues relevant, Chothia & Lesk identifies ***49 other positions*** "commonly buried within V_L and V_H domains." (Ex. 1062 at 7 (Table 4).) Pfizer has not explained why a skilled artisan would have singled out 78H from all the others. Pfizer cannot prove obviousness by ignoring the other potential substitutions disclosed in the very reference underlying its obviousness theory.

Moreover, Pfizer's obviousness theory conflicts with arguments made elsewhere in its petition. For example, Pfizer argues that Kurrle supposedly discloses 31 positions where substitutions could be made and that Queen 1990 discloses 23 such positions—none of which is 78H. (Paper 1 at 19-23; Ex. 1003D.) Pfizer has failed to explain why a skilled artisan would have modified 78H, as opposed to the numerous other possibilities disclosed in the cited references.

b) Claim 77 (Ground 5)

Claim 77, requiring substitutions at 71H and 73H in addition to 78H, fails for the same reasons as Claim 73, and also because Pfizer provides no analysis as

to why a skilled artisan purportedly would have been motivated to make these substitutions at 78H ***in addition*** to the substitutions at 71H and 73H supposedly disclosed by Kurrle. (Paper 1 at 53-54.) Nor could it in view of Kurrle's warning that "extreme caution must be exercised to limit the number of changes." (Ex. 1071, 8:42-43.) Pfizer cannot demonstrate obviousness based on Kurrle by disregarding Kurrle's own teaching.

c) Claim 74 (Ground 6)

Claim 74 recites a substitution at 93H. Pfizer argues that this claim is invalid because "Chothia 1985 identified residue **93H** as important for maintaining V_L:V_H interactions." (Paper 1 at 54.) But Chothia 1985 identifies 19 other "[r]esidues buried in VL-VH interfaces" (Ex. 1063 at 11 (Table 4)), and Pfizer has not explained why a skilled artisan would have focused on 93H from that list as opposed to the numerous other residue substitutions supposedly suggested by Pfizer's cited references.

d) Claims 79 (Ground 7)

Claim 79 recites substitutions at 71H, 73H, 78H, and 93H. Pfizer argues that a skilled artisan would have combined (i) the substitutions at 71H and 73H from Kurrle with (ii) 78H from Chothia & Lesk ***and*** (iii) 93H from Chothia 1985. (Paper 1 at 54-55.) This argument fails for the same reasons as Grounds 5 and 6—Pfizer provides no explanation why a skilled artisan would have made that specific

combination of substitutions, which again conflicts with Kurrle's admonition "to limit the number of changes." (Ex. 1071, 8:42-43.) Only in hindsight can Pfizer selectively identify the specific combination of substitutions recited in claims 79.

e) Claim 65 (Ground 7)

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 Kurrle and/or Queen 1990 have "up to 3-fold more" binding affinity. Instead, Pfizer argues that this limitation is obvious over Queen 1990 and Kurrle in view of Chothia & Lesk and/or Chothia 1985 because Queen 1990 states 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 55-56; Ex. 1050, 6:26-28.)

This argument fails. 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 and saw a significant ***decrease*** in binding affinity. (Ex. 1071, 8:16-18; Ex. 2033 at 1 (abstract) ("The relative affinity of BMA 031-EUCIV3 was about 2.5 times lower than BMA 031.").) Nothing in the record demonstrates that the use of the analogous

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

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For these reasons, the Board should deny Grounds 5-7 for claims 73, 74, 77, 79, and 65.

8. Ground 8: Queen 1990 would not have led a skilled artisan to make the substitutions required by claims 30, 31, and 33.

Pfizer argues that Queen 1990 would have led a skilled artisan to make substitutions at residues 66L, 98L, and 36H, which are recited in claims 30, 31, and 33. (Paper 1 at 57.) However, Pfizer has not identified an antibody sequence disclosed in Queen 1990 that contains those substitutions. Pfizer attempts to fill that gap by relying on the broad criteria described in Queen 1990. But Pfizer admits that Queen 1990's disclosure encompasses any of ***23*** different substitutions (Ex. 1003 ¶ 179)—leading to ***thousands*** of possible combinations and permutations of substitutions. Pfizer provides no explanation why a skilled artisan

supposedly would have selected the substitutions at 66L,[10] 98L, and 36H from the numerous other possibilities.

Hudziak does not cure Queen 1990's deficiencies. Hudziak does not mention the humanization of any antibody, or provide any guidance on possible substitutions to make while humanizing an antibody. Pfizer does not suggest otherwise; it relies on Hudziak solely for its disclosure of $p185^{HER2}$ as a potential drug target. (Paper 1 at 55-58.) Knowledge of the biological target, however, does not render the specific framework substitutions recited in claims 30, 31, 33, and 42 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.").

Accordingly, the Board should deny Ground 8.

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[10] Pfizer identifies 66L as a substitution supposedly suggested by Queen 1990. (Paper 1 at 60-61.) But Pfizer does not explain how Queen 1990 taught a substitution at 66L, and even Dr. Foote does not identify 66L among the 23 substitutions supposedly suggested by Queen 1990. (Ex. 1003 ¶ 179.)

9. Ground 9: Claim 42 would not have been obvious over Queen 1990 and Kurrle in view of Furey and Hudziak.

Ground 9 is similar to Ground 6, except that Pfizer adds Furey for its supposed disclosure of a substitution at 66L. As discussed above for Ground 4 (pp. 54-55), Queen 1990 combined with Furey would not have led a skilled artisan to make a substitution at 66L, and Pfizer does not contend that Hudziak adds anything that would have motivated a substitution at 66L. (Paper 1 at 61-62.) Accordingly, the Board should deny Ground 9.

10. Ground 10: Claim 60 would not have been obvious over Queen 1990 in view of Chothia & Lesk and Hudziak.

For Ground 10, Pfizer alleges that claim 60 (which depends from claim 30 and specifically requires a framework substitution at 78H) would have been obvious based on the same combination of Queen 1990 and Chothia & Lesk asserted in Ground 5. That argument fails for the same reasons discussed above for Ground 5 (pp. 55-56)—*i.e.*, Pfizer has not explained why a skilled artisan would have substituted 78H based upon Queen 1990 in view of Chothia & Lesk, as opposed to the 49 other residues identified by Chothia & Lesk or the 23 residues that Pfizer contends are taught by Queen 1990. Pfizer does not contend that Hudziak adds anything to motivate a substitution at 78H. (Paper 1 at 62.) Accordingly, the Board should deny Ground 10.

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. 1034 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. 1002 at 3439-41, ¶¶ 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 64-65.) 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. 1002 at 3439-41, ¶¶ 2-9; Ex.

1001, 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 63-64.) 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 67.) 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[11]), however, are in the ***CDRs***, not the framework region. (*See, e.g.*, *id.* at 13 (showing CDRs).) 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).

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

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 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 5, 2017

/David L. Cavanaugh/
David L. Cavanaugh
Registration No. 36,476

Robert J. Gunther, Jr.
Pro Hac Vice Motion To Be Filed

Counsel for Patent Owner

WILMER CUTLER PICKERING HALE AND DORR LLP
1875 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20006
TEL: 202-663-6000
FAX: 202-663-6363
EMAIL: david.cavanaugh@wilmerhale.com

CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Patent Owner's Preliminary Response, contains 13,605 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 5, 2017

/David L. Cavanaugh/
David L. Cavanaugh
Registration No. 36,476

CERTIFICATE OF SERVICE

I hereby certify that, on September 5, 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:

Amanda Hollis
KIRKLAND & ELLIS LLP
amanda.hollis@kirkland.com
300 North LaSalle, Chicago, IL 60654

Stefan M. Miller, Ph.D.
Stefan.miller@kirkland.com
601 Lexington Avenue, New York, NY 10022

Karen Younkins
karen.younkins@kirkland.com
333 South Hope Street, Los Angeles, CA 90071

Pfizer_Genentech_IPRs@kirkland.com

/Michael H. Smith/
Michael H. Smith
Reg. No. 71,190
WILMER CUTLER PICKERING
HALE AND DORR LLP
1875 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20006

IPR2017-01488
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)