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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2016-01693
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 sequence 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 either suffered from reduced binding affinity or still resulted in an immunogenic response when administered to humans. Given those challenges, which continued throughout the late 1980s, there were no humanized antibodies on the market, and some scientists doubted it would ever be possible to develop one that could be used therapeutically.

In the late 1980s, scientists at Genentech 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. And since then, their invention has been used to develop numerous other highly successful therapeutic antibodies for a wide range of diseases.

In this proceeding, Mylan has challenged certain claims of the '213 patent on eight different anticipation or obviousness grounds, but has failed 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 even 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.

And even if Mylan could rely on Kurrle or Queen 1990, Mylan has failed to demonstrate a reasonable likelihood of success for claim 63 in Ground 1 and all claims challenged in Grounds 2-8 for several additional reasons.

First, Mylan 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 (Grounds 2-3); and (iii) "consensus" sequence in claims 4, 33, 62, 64, and 69 (Grounds 2, 3, and 6). Mylan'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, Mylan has not shown that Queen 1990 teaches each limitation of any challenged claim. Indeed, even Mylan does not contend that Queen 1990 discloses ***any*** antibody that reads on ***any*** challenged claim. Instead, Mylan argues that Queen 1990 discloses general criteria that supposedly would have led a person of ordinary skill to arrive at the challenged claims. But Mylan's own arguments confirm that Queen 1990 encompasses thousands of possibilities, and Mylan has not explained why a skilled artisan supposedly would have pursued the specific amino acid substitutions recited in the challenged claims.

Third, Mylan's obviousness arguments (Grounds 3-8) fail for similar reasons. Mylan 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 Mylan admits a skilled artisan would have had to confront.

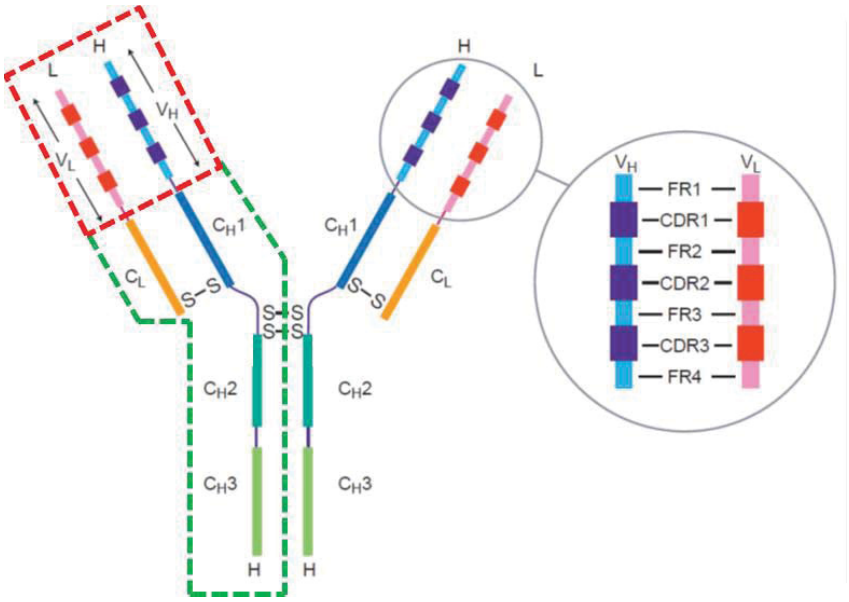
Finally, for Grounds 3-5, Mylan contends the challenged claims would have been obvious over the combination of Kurrle and Queen 1990. Mylan, however, never explains why (or even how) a skilled artisan would have combined the teachings of those two references. Mylan cannot carry its burden by relying on such conclusory assertions of obviousness.

The Board should not institute any proposed ground.

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 together to form a "Y" shape, as shown below:



(Ex. 2022 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 binding to an antigen and typically have similar amino acid sequences across all antibodies within a subclass. (Ex. 2029, 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. 2021 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] For purposes of this proceeding, Patent Owner uses "chimeric" and "humanized" as the '213 patent describes those terms. (Ex. 1001, 1:59-62 ("chimeric" antibodies are those "in which an animal antigen-binding variable domain 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 amino acid 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.) After selecting the most homologous human sequence as a starting point, the humanized sequence was 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.*) Queen 1989's 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. 2023 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 548-50, ¶¶ 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. 2019, 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 individual murine (or other non-human) 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 548-50, ¶¶ 2-9.) In fact, using the '213 invention, Genentech has developed 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. 2030, Carter Decl. ¶ 4; Ex. 2029, 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 Mylan

relies upon in its proposed grounds for this petition. (Ex. 1001 at 1-6.) Notably, the examiner did not make any rejection based upon any of the references underlying Mylan's proposed grounds.

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 802-03.) The examiner allowed the claims after accepting that antedation evidence. (*Id.* at 813.) 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. MYLAN'S ASSERTED REFERENCES

A. Kurrle

Kurrle is a European Patent Application published on December 19, 1990. Because that reference was published after the '213 inventors conceived and reduced their invention to practice, Kurrle is not prior art to the challenged claims. (*See infra* pp. 20-43.)

Kurrle describes producing a humanized antibody "against an epitope within the constant region of the human alpha/beta T-cell receptor." (Ex. 1071, 2:1-2.) 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. (*Id.*, 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. And Kurrle provided no guidance on which specific amino acid 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 also is not prior art to the '213 patent. (*See infra* pp. 20-43.)

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, Mylan does not contend that any antibody sequence disclosed in Queen 1990 anticipates or renders obvious the challenged '213 claims. Instead, Mylan 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 2 at 30-32.)

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.

From reviewing a Bence-Jones crystal structure, 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 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

[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).

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 the humanization of any antibody 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.

Mylan's proposed definition is similar, but imposes too high of a skill level because it requires individuals to have experience with the "humanization of antibodies for therapeutic development and use in humans." (Paper 2 at 12.) At the time of the '213 invention, no one had yet developed a humanized antibody approved for therapeutic use, and techniques for creating humanized antibodies were still under development. Mylan's proposed definition would thus apply only to the handful of highly skilled artisans at the absolute forefront of the field.

In any event, the challenged claims would not have been obvious to a person of ordinary skill 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.").

Mylan has proposed constructions of: (i) "humanized" (claims 1, 30, 62-64, 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 2 at 13-16.) No construction of those terms is necessary, but Patent Owner does not dispute Mylan'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. As Mylan notes, the '213 patent's priority application relies only on Kabat 1987. (Paper 2 at 15 n.3.)

VII. ARGUMENT

A. The Board Should Deny All Proposed Grounds Because Neither Kurrle Nor Queen 1990 Is Prior Art.

Each of Mylan'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 even prior art.

1. The inventors produced and tested humanized 4D5 antibodies using their consensus sequence approach before July 26, 1990.

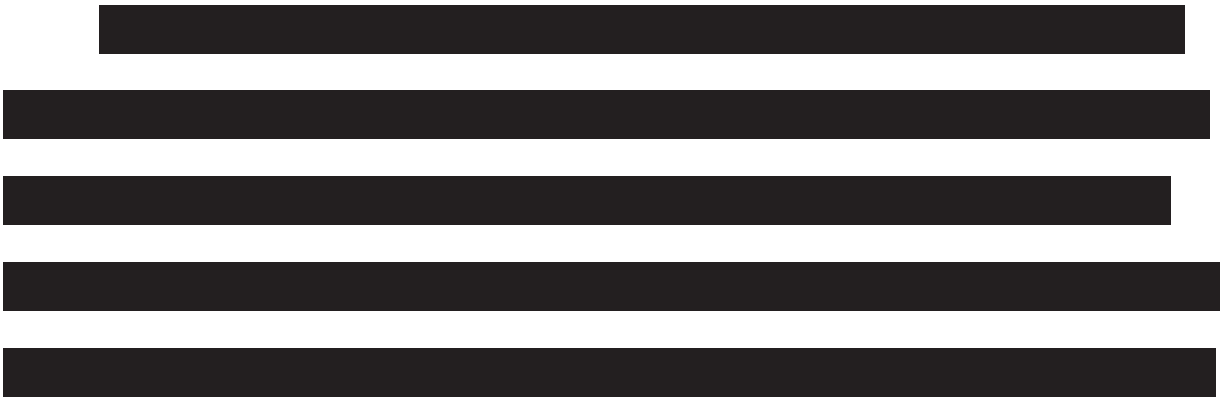
a) Consensus sequence

In 1989, Dr. Paul Carter started his own laboratory at Genentech. (Ex. 2030, 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. 2029, 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. 2030, Carter Decl. ¶ 19; Ex. 2029, Presta Decl. ¶¶ 16-21.)

Drs. Carter and Presta, however, conceived of a novel strategy for minimizing immunogenicity. Rather than starting from a specific 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. 2030, Carter Decl. ¶¶ 19-20; Ex. 2029, 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. 2030, Carter Decl. ¶ 19; Ex. 2029, 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. 2030, Carter Decl. ¶ 19; Ex. 2029, 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. 2030, 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.)



[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. 2016, 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]

[4] Those other five variants are called HuMAb4D5-3, HuMAb4D5-4, HuMAb4D5-6, HuMAb4D5-7, and HuMAb4D5-8 in the '213 patent. (Ex. 2030, Carter Decl. ¶¶ 67, 76; Ex. 2029, Presta Decl. ¶ 50.)

[redacted]

***

The inventors' success 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]

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. 2030, Carter Decl. ¶ 79; Ex. 2029, Presta Decl. ¶ 53.)

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

(i) Limitations common to all claims

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. 2029, Presta Decl. ¶¶ 45, 47; Ex. 2030, 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. 2029, Presta Decl., ¶¶ 45, 47; Ex. 2030, 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. 2029, Presta Decl. ¶¶ 40, 45-47; Ex. 2030, 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. 2029, Presta Decl. ¶¶ 40, 45-47; Ex. 2030, 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: 4L, 38L,	HuMAb4D5-5 contains substitutions at 66L, 71H, 73H, 78H, and 93H. (Ex. 2029, Presta Decl. ¶¶ 45, 47; Ex. 2002 at 34-36.)	HuMAb4D5-8 contains substitutions at 55L, 66L, 71H, 73H, 78H, 93H, and 102H. (Ex. 2029, 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
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]

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. 23-24), 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. 2029, 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. 2029, Presta Decl. ¶¶ 45, 47; Ex. 2030, 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. 2029, 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] The reduction to practice of humanized 4D5 antibodies containing framework substitutions derived

[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. 2029, Presta Decl. ¶ 52; Ex. 2020.)

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. 2029, 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. 24-25, 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 548-49, ¶¶ 2-4; Ex. 2027 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 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.

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. 2030, 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. 2030, 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. 29-31), 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.

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.

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. *See* 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. 1094, 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 Kurrle and Queen 1990—which Mylan relies on for all grounds—are not prior art, they cannot render any challenged claim invalid. The Board should deny institution of all grounds for this reason alone.

B. Mylan'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 for certain challenged claims why Mylan has not demonstrated a reasonable likelihood of success even under its incorrect attempt to treat Kurrle and Queen 1990 as prior art.

First, Mylan 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 (Grounds 2-3); and (iii) "consensus" sequence in claims 4, 33, 62, 64, and 69 (Grounds 2, 3, 6). Mylan'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 2-8 require specific framework substitutions that Mylan has not shown are anticipated and/or obvious. Mylan's own arguments confirm that its asserted references encompass numerous possible

substitutions, and Mylan has not explained why a skilled artisan would have been led to the substitutions required by the challenged claims for Grounds 2-8.

Third, Grounds 3, 4, and 5 present obviousness arguments that rest on the combination of Kurrle and Queen 1990. However, Mylan has not explained why, or even how, a skilled artisan would have combined Kurrle and Queen 1990. Mylan cannot rely on conclusory assertions of "obviousness" to cure the deficiencies in its anticipation arguments for those references. The Board should not institute Grounds 3, 4, and 5 given Mylan's failure to explain its proposed combination of Kurrle and Queen 1990, and it should also deny Ground 3 (which rests solely on the combination of Kurrle and Queen 1990) as redundant of Mylan's anticipation arguments in Grounds 1-2.[8]

[8] For purposes of this preliminary response, Patent Owner relies solely on antedation in response to Mylan's challenge to claims 1-2, 25, 29, 66, 71, 75-76, 78, and 80-81 in Ground 1. Patent Owner reserves the right to challenge other aspects of Mylan's argument with respect to those claims depending on the Board's determination in the Decision on Institution.

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, Mylan 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."

Mylan 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 2 at 27-28, 34, 42.) Instead, Mylan merely relies on aspirational statements of intended results in both references. (*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 Mylan 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 417.) However, a follow-on publication showed that 3 out of 4 patients treated with the antibody nevertheless "developed antiglobulins." (Ex. 2024 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 434, 507-12.) 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 and 3</u>: Kurrle and Queen 1990 do not anticipate or render obvious the "up to 3-fold more" binding affinity limitation of claim 65.

Claim 65 requires the humanized antibody to have a binding affinity "up to 3-fold more" than the parent non-human antibody. Mylan 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, Mylan argues that this limitation is either disclosed by Queen 1990 (Ground 2), or obvious in view of Kurrle and Queen 1990 (Ground 3), 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 2 at 37, 43-44; Ex. 1050, 6:26-28.) That argument fails.

First, Mylan has not argued that Kurrle and/or Queen 1990 anticipate or render obvious claim 79 (from which claim 65 depends), which requires framework substitutions at 71H, 73H, 78H, and 93H. (Ex. 1001, Certificate of Correction.) Mylan cannot succeed in showing that claim 65 is anticipated or obvious without addressing the limitations of the claim from which it depends. 35 U.S.C. § 112, ¶ 4 (pre-AIA) ("A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.").

Second, Queen 1990 does not indicate that the humanized antibody's binding affinity is ***improved***, as claim 65 requires. The reference merely states that the humanized antibody is "***within*** about 4 fold of the donor immunoglobulin's original affinity to the antigen." (Ex. 1050, 6:26-28.) Queen 1990's binding affinity could be ***worse*** than the non-human parent antibody and still be "within about 4 fold" of the non-human antibody's binding affinity. Indeed, Kurrle—like Queen 1990—also started from a best-fit human antibody sequence. (Ex. 1071, 8:16-18.) Yet, Kurrle saw a significant ***decrease*** in binding affinity. (Ex. 1072 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 Queen 1990's analogous technique improved binding affinity as required by claim 65.

Therefore, the Board should deny Grounds 2 and 3 for claim 65.

3. Grounds 2, 3, and 6: Mylan'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 6, Mylan 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 2 at 32, 36, 41, 43, 46, 56; 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 6 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 Mylan does not point to any disclosure in Kurrle that supposedly suggests the consensus sequence required by claims 4, 33, 62, 64, and 69, Mylan's challenge to those claims in Ground 3 fails for this additional reason.

c) Hudziak

For Ground 6, Hudziak also does not cure Queen 1990's deficiencies. Hudziak does not even mention the possibility of humanizing antibodies, and

Mylan does not point to any disclosure in Hudziak supposedly teaching the '213 patent's consensus sequence approach. Accordingly, Mylan's challenge to claims 4, 33, 62, 64, and 69 in Ground 6 fails for this reason as well.

4. Ground 2: Queen 1990 does not anticipate the challenged claims.

For Ground 2, Mylan argues that Queen 1990 anticipates claims 1-2, 4, 29, 62-65, and 80-81. But Mylan does not point to any antibody sequence disclosed in Queen 1990 that contains the claimed framework substitutions. Instead, Mylan contends that Queen 1990's "Criterion III" discloses those substitutions. (Paper 2 at 31-33, 35-37.) 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 ¶ 165)—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*** substitutions claimed in the '213 patent. 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). Mylan 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]

Mylan 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 2 at 30-31; 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 Mylan identifies as satisfying Queen 1990's Criterion III.

Because Mylan 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.)

5. Grounds 3, 4, and 5: Mylan has failed to explain how or why a person of ordinary skill would combine Queen 1990 and Kurrle.

Grounds 3, 4, and 5 each depend upon the combination of Queen 1990 and Kurrle. Mylan argues that Queen 1990 and Kurrle describe similar techniques for humanizing antibodies. (Paper 2 at 39-40.) However, Mylan offers no explanation how or why a person of ordinary skill would combine the teachings of those two references, or what teaching absent from Queen 1990 is supposedly provided by Kurrle, or vice versa. (*Id.* at 37-51.) Mylan cannot sustain its burden to demonstrate obviousness without providing some reason a skilled artisan would have combined the teachings of Kurrle and Queen 1990, or even explaining how those references supposedly would have been combined to arrive at the claimed invention. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (explaining that the patent challenger must provide "an apparent reason to combine" the teachings of multiple references and "this analysis should be made explicit"); *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.").

Indeed, Mylan's "obviousness" grounds simply rehash the same arguments that Mylan presented concerning Kurrle and Queen 1990 in support of its

anticipation arguments in Grounds 1-2. (Paper 2 at 37-51.) But Mylan cannot rely on vague assertions of obviousness to cure 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).

Grounds 3, 4, and 5 should be denied for this reason alone.

6. 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 Mylan 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 (claims 1-2, 4, 25, 29, 62-66, 71, 75-76, 78, 80-81), and Mylan'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).

Indeed, there are only three claims that Mylan challenges in Ground 3 not also addressed in Grounds 1 and/or 2: claims 67, 69, and 72. Mylan's arguments confirm that Ground 3 should be denied as duplicative even for those three claims.

Claim 67: Claim 67 requires that "the substituted residue is the residue found at the corresponding location of the non-human antibody from which the non-human CDR amino acid residues are obtained." Because Mylan alleges that "[b]oth Queen 1990 and Kurrle disclosed this additional limitation" (Paper 2 at 45), it is not clear what combining the two references adds in Ground 3.

Claim 69: Claim 69 requires that "the human antibody variable domain is a consensus human variable domain." As discussed above (pp. 48-50), 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 72: Claim 72 requires an amino acid substitution "at site 76H." But Mylan did not allege in Ground 1 that Kurrle anticipates claim 72, and it is not clear what the combination with Queen 1990 supposedly adds.

7. 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. Mylan does not contend that Queen 1990 and/or Kurrle teach that limitation; rather, Mylan 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 ¶ 203.)

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 the interaction at 66L. (Ex. 1125 at 14.) Mylan provides no explanation why a person of ordinary skill supposedly would have selected 66L for substitution when Furey itself emphasizes the importance of other residues. Mylan also does not explain why a skilled artisan would have selected residue 66L instead of the five other hydrogen bonding interactions that Furey identified in addition to 66L. (*Id.*)

Finally, Mylan's arguments about residue 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 2 at 17, 19; Ex. 1003, Padlan Ex. B (indicating 31 residue substitutions in Kurrle's sequences).) Mylan does not explain why a person of ordinary skill would have ignored these supposed teachings and selected residue 66L instead. Because Mylan does not explain why a skilled artisan would have substituted residue 66L, as opposed to the numerous other residue substitutions supposedly suggested by Mylan's cited references, Mylan has not shown a reasonable likelihood of success for Ground 4.

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

For Ground 5, Mylan challenges claims 73, 74, 77, and 79, which require the following specific substitutions: 78H (claim 73); 93H (claim 74); 71H, 73H, and 78H (claim 77); and 71H, 73H, 78H, and 93H (claim 79).

Mylan does not contend that Kurrle and/or Queen 1990 disclose or suggest substitutions at 78H and/or 93H. Mylan instead argues that a substitution at both residues would have been obvious based upon Table 4 of Chothia & Lesk and Table 4 of Chothia 1985. (Paper 2 at 49-50; Ex. 1062 at 7; Ex. 1063 at 11.) Neither argument is correct.

a) Claims 73 and 74

Mylan's identification of position 78H (claim 73) based upon Chothia & Lesk rests on hindsight. The only explanation that Mylan offers for why a person of ordinary skill 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. (Paper 2 at 49.) But neither Kurrle nor Queen 1990 identifies "residues buried within and between the [V_L and V_H] domains" as desirable to substitute. A person of ordinary skill would have had no reason to substitute position 78H based upon Mylan's proposed combinations of references.

And in any case, even if a person of ordinary skill 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).) Mylan has not explained why a skilled artisan would have singled out 78H from all the others. Mylan cannot prove obviousness by ignoring the other potential substitutions disclosed in the very reference underlying its obviousness theory.

Similarly, Mylan argues that a person of ordinary skill would have made a substitution at residue 93H (claim 74) because "Chothia 1985 identified residue **93H** as important for maintaining V_L:V_H interactions." (Paper 2 at 50.) But Chothia 1985 identifies 19 other "[r]esidues buried in VL-VH interfaces" (Ex. 1063 at 11 (Table 4)), and Mylan has not explained why a person of ordinary skill would have focused on 93H from that list.

Moreover, Mylan's obviousness theory for claims 73 and 74 conflicts with arguments made elsewhere in its petition. For example, Mylan argues that Kurrle supposedly discloses 31 residues where substitutions could be made and that Queen 1990 discloses 23 such residues—none of which are residues 78H or 93H. (Paper 2 at 17, 19; Ex. 1003, Padlan Ex. B.) Mylan has failed to explain why a person of ordinary skill would have modified residues 78H (claim 73) or 93H (claim 74), as opposed to the numerous other possibilities disclosed in Mylan's cited references.

Because Mylan has failed to meet its burden to explain why a person of ordinary skill would have substituted residues 78H or 93H, as opposed to the numerous other residue substitutions supposedly suggested by Mylan's cited references, the Board should deny Ground 5 based on claims 73 and 74.

b) Claims 77 and 79

The problems with Mylan's obviousness arguments are compounded for claims 77 and 79, which require multiple substitutions: (i) 71H, 73H, and 78H for claim 77; and (ii) 71H, 73H, 78H, and 93H for claim 79.

For claim 77, Mylan provides no analysis as to why a person of ordinary skill purportedly would have been motivated to make the substitution at 78H ***in addition*** to the substitutions at 71H and 73H supposedly disclosed by Kurrle. (Paper 2 at 50.) 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.) Mylan cannot attempt to demonstrate obviousness based on Kurrle by disregarding Kurrle's own teaching.

For claim 79, Mylan argues that a person of ordinary skill would have combined (i) the substitutions at 71H and 73H from Kurrle with (ii) residue 78H from Chothia & Lesk ***and*** (iii) 93H from Chothia 1985. (Paper 2 at 51.) Mylan 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 with the benefit of hindsight can Mylan selectively identify the specific combination of substitutions recited in claims 77 and 79. The Board should deny Ground 5 based on claims 77 and 79 for these additional reasons.

9. Ground 6: Queen 1990 would not have led a person of ordinary skill to make the substitutions required by claims 30, 31, 33, and 42.

Mylan argues that Queen 1990 would have led a person of ordinary skill to make substitutions at residues 66L, 98L, and 36H, which are recited in claims 30, 31, 33, and 42. (Paper 2 at 54-56.) However, Mylan has not identified an antibody sequence disclosed in Queen 1990 that contains those substitutions. Mylan attempts to fill that gap by relying on the broad criteria described in Queen 1990. But Mylan admits that Queen 1990's disclosure encompasses any of ***23*** different substitutions (Ex. 1003 ¶ 165)—leading to ***thousands*** of possible combinations and permutations of substitutions. Mylan 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. Mylan does not suggest otherwise; it relies on Hudziak solely for its disclosure of $p185^{HER2}$ as a potential drug target. (Paper 2 at 52-55.) 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, Mylan has not demonstrated a reasonable likelihood of success for any claim challenged in Ground 6.

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[10] Mylan identifies residue 66L as a substitution supposedly suggested by Queen 1990. (Paper 2 at 55.) But Mylan does not explain how Queen 1990 taught a substitution at residue 66L, and even Dr. Padlan does not identify residue 66L among the 23 residues supposedly suggested by Queen 1990. (Ex. 1003 ¶ 165.)

10. Ground 7: Claim 42 would not have been obvious over Queen 1990 in view of Furey and Hudziak.

Ground 7 is similar to Ground 6, except that Mylan adds Furey for its supposed disclosure of a substitution at 66L. As discussed above for Ground 4 (pp. 55-56), Queen 1990 combined with Furey would not have led a person of ordinary skill to make a substitution at residue 66L, and Mylan does not contend that Hudziak adds anything that would have motivated a substitution at residue 66L. (Paper 2 at 56.)

Because Mylan has not demonstrated a reasonable likelihood of success that substituting residue 66L would have been obvious, the Board should not institute proposed Ground 7.

11. Ground 8: Claim 60 would not have been obvious over Queen 1990 in view of Chothia & Lesk and Hudziak.

For Ground 8, Mylan 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 in connection with Ground 5 (pp. 57-60)—*i.e.*, Mylan has not explained why a person of ordinary skill 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 Mylan contends are taught by Queen 1990. Mylan does not

contend that Hudziak adds anything to motivate a substitution at residue 78H. (Paper 2 at 57.)

Therefore, the Board should deny Mylan's proposed Ground 8.

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) ("Secondary considerations can be the most probative evidence of non-obviousness in the record, and enables the ... court to avert the trap of hindsight." (internal quotation marks omitted)). 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 548-50, ¶¶ 2-9 (describing antibodies made according to the '213 invention that were effective against numerous disease targets).)

Second, the '213 patent's approach results in antibodies with unexpectedly superior properties compared to those made by prior art methods. For example, those prior art humanized antibodies often produced an immunogenic response (*e.g.*, Ex. 2024 at 751 (3 out of 4 patients suffered immunogenic response)) or had reduced binding affinity (*e.g.*, Ex. 1072 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 548-50, ¶¶ 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.

2. Commercial success

Some of Genentech's most successful antibodies embody the claims of the '213 patent, including Herceptin®, Perjeta®, Avastin®, Lucentis®, and Xolair®. Those drugs together generate billions of revenue annually. (Ex. 2028 at 10-11.) And there is a direct nexus between the success of those drugs and the challenged claims. Indeed, their success is attributable, in part, to their unique amino acid sequences provided using the '213 patent's consensus sequence approach, which allows these drugs to have 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).

VIII. CONCLUSION

The Board should deny institution of all grounds.

Respectfully submitted,

Date: December 16, 2016

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CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Patent Owner's Preliminary Response, contains 13,746 words as measured by the word processing software used to prepare the document, in compliance with 37 C.F.R. § 42.24(d).

Respectfully submitted,

Dated: December 16, 2016

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CERTIFICATE OF SERVICE

I hereby certify that, on December 16, 2016, I caused a true and correct copy of the following materials:

- Patent Owner's Preliminary Response
- Patent Owner's Motion to Seal
- Exhibits 2001-2031
- 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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IPR2016-01693
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 Irene Loeffler
2017	Modified Default Standing Protective Order – Redline
2018	Declaration of John Ridgway Brady PROTECTIVE ORDER MATERIAL
2019	Paul Carter, et al., *Humanization of the Anti-p185 Antibody for Human Cancer Therapy*, 89 PROC. NATL. ACAD. SCI. 4285-4289 (1992)
2020	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)
2021	Marianne Bruggerman, et al., *The Immunogenicity of Chimeric Antibodies*, 170 J. EXP. MED. 2153-2157 (1989)
2022	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)
2023	Scott Gorman, et al., *Reshaping a Therapeutic CD4 Antibody*, 88 PROC. NATL. ACAD. SCI. 4181-4185 (1991)
2024	John Isaacs, et al., *Humanised Monoclonal Antibody Therapy for Rheumatoid Arthritis*, 340 THE LANCET 748-752 (1992)
2025	Elvin Kabat, et al., *Sequences of Proteins of Immunological Interest* 1-23 (4th ed. 1987)
2026	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)
2027	H.M. SHEPARD, et al., *Herceptin*, *in* Therapeutic Antibodies. HANDBOOK OF EXPERIMENTAL PHARMACOLOGY 183-219 (Y. Chernajovsky & A. Nissim, eds. 2008)
2028	Excerpt from Roche Finance Report 2015

Patent Owner's Exhibit Number	**Exhibit Name**
2029	Declaration of Dr. Leonard G. Presta PROTECTIVE ORDER MATERIAL
2030	Declaration of Dr. Paul J. Carter PROTECTIVE ORDER MATERIAL
2031	Modified Default Standing Protective Order and Patent Owner's Certification of Agreement to Terms