IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the *Inter Partes* Review of: Trial Number: To Be Assigned

U.S. Patent No. 6,407,213

Filed: November 17, 1993

Issued: June 18, 2002

Inventor(s): Paul J. Carter, Leonard G. Presta

Assignee: Genentech, Inc.

Title: Method for making humanized antibodies Panel: To Be Assigned

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Mail Stop *Inter Partes* Review
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PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 6,407,213
UNDER 35 U.S.C. § 311 AND 37 C.F.R. § 42.100

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1187	Declaration of Amanda Hollis
1188	Declaration of Christopher Lowden

I. INTRODUCTION

Pursuant to 35 U.S.C. § 311 and 37 C.F.R. § 42.100, Petitioner Pfizer, Inc. petitions for *Inter Partes* Review ("IPR") of claims 1, 2, 4, 12, 25, 29–31, 33, 42, 60, 62–67, 69 and 71–81 ("Challenged Claims") of U.S. Patent No. 6,407,213 ("'213 patent," Ex. 1001). With this Petition is a Power of Attorney pursuant to 37 C.F.R. § 42.10(b); and pursuant to 37 C.F.R. § 42.103, the fee set forth in § 42.15(a).

By a preponderance of the evidence, this Petition proves the prior art renders the Challenged Claims unpatentable. Prior art disclosing methods of making humanized antibodies—including the detailed roadmaps taught in Kurrle[1] and Queen 1990[2]—anticipate and render obvious the Challenged Claims to a person of

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[1] Kurrle *et al*., EP Publication Number 0403156, *Improved monoclonal antibodies against the human alphabeta T-Cell receptor, their production and use* (published December 19, 1990) ("Kurrle") (Ex. 1071).

[2] Queen, International Publication No. WO 1990/07861 (published July 26, 1990) ("Queen 1990") (Ex. 1050).

ordinary skill in the art ("POSITA") as of the priority date of the '213 patent.[3]

II. MANDATORY NOTICES – 37 C.F.R. § 42.8(A)(1) AND (B)

A. 37 C.F.R. § 42.8(b)(1): Real Party-In-Interest

Pfizer, Inc. ("Pfizer" or "Petitioner") is the real party-in-interest for Petitioner.

B. 37 C.F.R. § 42.8(b)(2): Related Matters

Petitioner concurrently files two IPR petitions for claims of the '213 patent. Petitioner is aware of two earlier IPR proceedings for the '213 patent, both filed by third-party Mylan Pharmaceuticals Inc.: IPR2016–01693 and IPR2016–01694. These proceedings were terminated by the Board on March 10, 2017 after the parties filed a Joint Motion to Terminate. Paper No. 24, IPR2016–01693; Paper No. 23, IPR2016–01694 (March 10, 2017). Petitioner is also aware of two current IPR proceedings for the '213 patent, both filed by third-party Celltrion, Inc.: IPR2017-01373 and IPR2017-01374. Petitioner is not aware of any other judicial or administrative matters that would affect, or be affected by, a decision in the proceeding.

The '213 patent is related to the following patents: U.S. Patent No.

[3] All references herein to the knowledge or understanding of a POSITA or a POSITA's interpretation or understanding of a prior art reference are as of the earliest possible priority date unless specifically stated otherwise.

6,639,055 (expired due to nonpayment of maintenance fees); U.S. Patent No. 6,800,788 (expired due to nonpayment of maintenance fees); U.S. Patent No. 6,719,971 (expired due to nonpayment of maintenance fees); and U.S. Patent No. 8,075,890 (patented).

C. 37 C.F.R. § 42.8(b)(3): Lead and Back-Up Counsel

Petitioner designates the following counsel:

Lead Counsel	**Back-up Counsel**
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D. 37 C.F.R. § 42.8(b)(4): Service Information

Please address all correspondence to lead counsel at the contact information above. Petitioner consents to service by electronic mail at

Pfizer_Genentech_IPRs@kirkland.com. A Power of Attorney is being filed concurrently herewith. 37 C.F.R. § 42.10(b).

III. PAYMENT OF FEES – 37 C.F.R. § 42.103

The undersigned authorizes the PTO to charge the fee set forth in 37 C.F.R. § 42.15(a) for this Petition and any additional fees that may be due in connection with this Petition to Deposit Account No. 506092.

IV. GROUNDS FOR STANDING – 37 C.F.R. § 42.104(A)

Petitioner certifies that the '213 patent is available for IPR and that the Petitioner is not barred or estopped from requesting IPR on the grounds identified herein. 35 U.S.C. § 315.

V. IDENTIFICATION OF CHALLENGE – 37 C.F.R. § 42.104(B)

Petitioner requests IPR and cancellation of the Challenged Claims under pre-AIA 35 U.S.C. §§ 102 and 103, as set forth in Petitioner's detailed "Statement of Reasons for Relief Requested." Petitioner provides copies of the exhibits, and this Petition is supported by the Declarations of Dr. Jefferson Foote (Ex. 1003) and Mr. Timothy Buss (Ex. 1004).

Dr. Foote is the Chief Science officer of Arrowsmith Technologies, a biotechnology startup developing immunologic cancer treatments. He received his B.A. in Biochemical Sciences from Harvard College in 1977 and his Ph.D. in Biochemistry from the University of California in 1985. Dr. Foote has well over thirty years of experience in the antibody engineering field, particularity with

respect to antibody humanization. From 1985 to 1992, Dr. Foote was a part of the earliest antibody humanization efforts at the Medical Research Council Laboratory of Molecular Biology under Dr. Gregory Winter, the pioneer in the field.

Mr. Buss is an antibody engineering consultant. He received his Higher National Certificate in Applied Biology from Cambridgeshire College of Arts and Technology. Mr. Buss also has over thirty years of experience in the antibody engineering field, particularly with respect to cancer treatments. From 1991 to 1993, Mr. Buss was a part of Dr. Winter's team at the Laboratory of Molecular Biology, working on various antibody engineering issues. Mr. Buss later helped develop and prepare humanized antibodies at the Fred Hutchinson Cancer Research Center, the Sidney Kimmel Cancer, Ambrx, Inc., and the California Institute for Biomedical Research. As a consultant, Mr. Buss advises his clients on a variety of antibody engineering issues, including identifying framework substitutions for antibody humanization and generating humanized constructions.

This Petition is also supported by Declarations from Mr. Christopher Lowden, Ms. Amanda Hollis, and Ms. Karen Younkins, which authenticate various exhibits.

The Challenged Claims generally involve humanized antibodies and humanized antibody variable domains (Ex. 1003 ¶¶44–65) and are unpatentable as follows:

Ground	Proposed Statutory Rejection of the '213 Patent
1	Claims 1–2, 25, 29, 63, 66–67, 71–72, 75–76, 80–81 are invalid under 35 U.S.C. § 102(a) as anticipated by: **Kurrle**
2	Claims 1–2, 4, 29, 62–64, 80–81 are invalid under 35 U.S.C. §102(a) as anticipated by: **Queen 1990**
3	Claims 1–2, 4, 25, 29, 62–64, 66–67, 69, 71–72, 75–76, 78, 80–81 are invalid under 35 U.S.C. § 103(a) as obvious in view of: **Queen 1990** and **Kurrle**
4	Claim 12 is invalid under 35 U.S.C. § 103(a) as obvious in view of: **Queen 1990**, **Kurrle** and **Furey**
5	Claims 73 and 77 are invalid under 35 U.S.C. § 103(a) as obvious in view of: **Queen 1990**, **Kurrle** and **Chothia & Lesk**
6	Claim 74 invalid under 35 U.S.C. § 103(a) as obvious in view of: **Queen 1990**, **Kurrle** and **Chothia 1985**
7	Claims 79 and 65 are invalid under 35 U.S.C. § 103(a) as obvious in view

Ground	Proposed Statutory Rejection of the '213 Patent
	of: **Kurrle**, **Queen 1990**, **Chothia & Lesk** and **Chothia 1985**
8	Claims 30, 31, 33 and 42 are invalid under 35 U.S.C. § 103(a) as obvious in view of: **Queen 1990** and **Hudziak**
9	Claim 42 is invalid under 35 U.S.C. § 103(a) as obvious in view of: **Queen 1990**, **Hudziak** and **Furey**
10	Claim 60 is invalid under 35 U.S.C. § 103(a) as obvious in view of: **Queen 1990**, **Hudziak** and **Chothia & Lesk**

VI. THRESHOLD REQUIREMENT FOR *INTER PARTES* REVIEW

A petition for IPR must demonstrate "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). This Petition meets and exceeds this threshold. As explained below, there is more than a reasonable likelihood that Petitioner will prevail with respect to at least one of the challenged claims.

VII. STATEMENT OF REASONS FOR THE RELIEF REQUESTED

A. ’213 Patent Background

The ’213 patent issued June 18, 2002 from a continuation-in-part of an earlier-abandoned U.S. Patent Appl. No. 07/715,272 filed on June 14, 1991, the ’213 patent’s earliest possible priority date.

The ’213 patent has 82 claims. Claims 1, 30, 62–64, 66, 79 and 80 are independent, and all claim a “humanized antibody,” “antibody,” “humanized variant of a non-human parent antibody” or “humanized antibody variable domain” comprising a “non-human…CDR,” and a “Framework Region [FR] amino acid substitution” reverting a substituted human framework residue back to, ***e.g.***, a mouse at “a site selected from the group consisting of” certain recited residues.

Claim 1 requires the FR substitution be located at any one of 14 FR light chain residues (4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, and 98L) or 10 heavy chain residues (2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, and 92H) using Kabat’s numbering system. Ex. 1001 at 86:44–52.

Independent **Claims 30, 62 and 63** add four FR residues to claim l’s list (46L, 75H, 76H and 78H). Claim 30’s antibody “binds $p185^{HER2}$ and comprises a humanized antibody variable domain.” *Id*. at 87:18–28. Claim 63’s humanized antibody “lacks immunogenicity compared to a non-human parent antibody upon

repeated administration to a human patient" when treating chronic disease. ***Id.*** at 88:37–48.

Independent **Claim 66** requires substitution at one of 5 FR residues: 24H, 73H, 76H, 78H and 93H. ***Id.*** at 88:66–89:6. Independent **Claim 79** recites "substitutions at heavy chain positions 71H, 73H, 78H and 93H." ***Id.*** at 90:3–10. Independent **Claim 80** requires substitution at any one of the residues recited in claims 1 and 66, and adds that the substituted FR residue: "(a) noncovalently binds antigen directly; (b) interacts with a CDR; or (c) 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." ***Id.*** at 90:11–25.

Independent **Claim 64**'s "humanized variant of a non-human parent antibody" includes a consensus domain wherein amino acid residues forming Complementarity Determining Regions ("CDRs") thereof "comprise non-human antibody amino acid residues." Claim 64 also requires a substituted FR residue 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." ***Id***. at 88:49–62.

The challenged dependent claims recite specific residues (claims 12, 25, 42, 60 and 71–77); that the substituted mouse residue is from the corresponding

location as the replaced human residue[4] (claims 2, 31, 67 and 81); that the human antibody variable domain is a consensus domain (claims 4, 33 and 69); or an antibody comprising the claimed humanized variable domain of claims 1 or 66 (claim 29 and claim 78, respectively).

The claimed humanization concepts were neither novel nor inventive. The '213 patent acknowledges the widely held view that the "function of the antibody is dependent on its three dimensional structure, and that amino acid substitutions can change the three-dimensional structure of an antibody" near the CDRs. *Id.* at 3:40–44. It acknowledges that "molecular modeling" had increased "the antigen binding affinity of a humanized antibody" in the past. *Id.* at 3:44–48. Indeed, the '213 patent applies the same cloning and analysis tools and techniques that Kurrle (Ex. 1071) and Queen 1990 (Ex. 1050) already described, including site-directed mutagenesis, molecular modeling and antibody functionality analysis. The '213 patent likewise recognizes the known promise of 4D5 as a therapeutic anticancer agent whose murine origin may render it "immunogenic in humans." Ex. 1001 at 3:56–4:23.

B. Summary of the Argument

In 1975, the journal *Nature* published Köhler and Milstein's ground-breaking study manufacturing "predefined specific antibodies by means of

[4] *E.g.*, Human residue 4L is replaced with mouse residue 4L.

permanent tissue culture cell lines" Ex. 1022 at 3. Mouse monoclonal antibodies exhibited therapeutic and diagnostic promise, but researchers discovered that patients receiving them experienced a human anti-mouse antibody (HAMA) immunogenicity response. Exs. 1003 ¶¶97–100; 1004 ¶35.

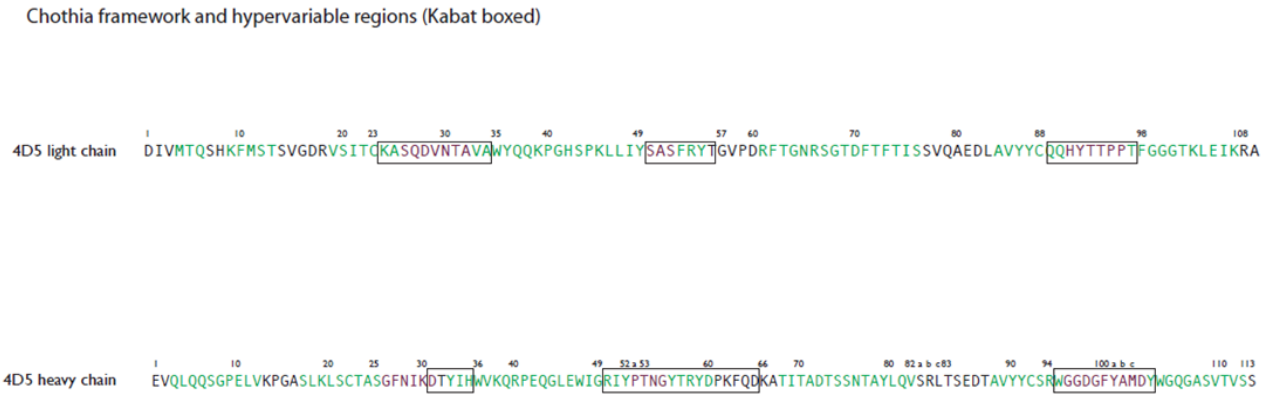
To neutralize the HAMA response, mouse antibodies were re-engineered to make them "more human" by replacing parts of the mouse antibody with human counterparts. First generation (early 1980s) versions replaced only portions of the mouse antibody sequence known as constant regions with corresponding human antibody residues. Exs. 1003 ¶¶99–100; 1004 ¶¶38–40. While these "chimeric" antibodies retained the parent mouse's affinity (*i.e.*, the strength of the interaction between the antibody and target receptor) and specificity (*i.e.*, selectivity for an antigen), patients still experienced HAMA responses from the mouse variable domain. Next, scientists replaced mouse variable domain framework regions (FR) flanking the complementarity determining regions (CDR) with human sequences. Ex. 1003 ¶101–106.

However, because adding human FRs to the regions between the mouse CDRs was known to disrupt binding affinity, the next logical step in the evolution of humanized antibody technology was to switch select residues in the human FRs back to the mouse residue. Ex. 1003 at ¶¶103–106, 108–109. These techniques were well-known and well mapped out prior to the earliest priority date (June 14,

1991) of the ’213 patent. *Id.* at ¶110–12. Kurrle (Ex. 1071) is just one example disclosing combining human FRs with mouse CDRs, wherein select residues in the human FRs were switched back to mouse. Kurrle’s switched residues include claimed residues **4L**, **69H**, **71H**, **73H** and **76H**.[5] Ex. 1071 at 3:9–10. Kurrle’s result was “essentially a human antibody with a much lower immunogenicity in patients.” *Id.* at 3:11–12. Kurrle thus anticipates claims 1, 2, 25, 29, 63, 66, 71, 75, 76, 78, 80 and 81. Ex. 1003 at ¶¶110–111, 155–172.

Queen 1990 established a humanization roadmap with four specific yet universal criteria for producing humanized antibodies from non-human monoclonal antibodies, including substituting for the mouse monoclonal antibody residue in the Framework Regions (FR) “immediately adjacent to one or more of the 3 CDR’s in the primary sequence” according to the Kabat numbering system. Queen 1990 (Ex. 1050), Kabat (Ex. 1052) and Chothia & Lesk (Ex. 1062) had earlier classified the antibody variable domain structure, including defining the boundaries of the Kabat CDRs, the Chothia hypervariable regions and FRs:

[5] Petitioner has attempted to use bold font for claimed residues in this petition to facilitate the Board’s review.



Ex. 1003 ¶¶91–96, 115–20.

These boundaries would have allowed a POSITA, given Queen 1990's instruction to substitute CDR-adjacent FR residues, to readily identify at least claimed residues **36H** and **98L** (*see* claims 1, 2, 4, 29, 62, 63, 64, 80 and 81) for substitution. Thus, Queen 1990 anticipates at least claims 1, 2, 4, 29, 62, 63, 64, 80 and 81. *Id*. ¶¶173–199.

Moreover, all Challenged Claims are obvious given the prior art, including Queen 1990; Kurrle; and others. *Id*. ¶¶200–251, 342–349. For example, a number of prior art references taught the importance of specific claimed residues (including **93H**, **78H** and **66L**) because of their predicted contribution to antigen binding. *Id*. ¶¶35, 116, 139. The inclusion of residues **93H**, **78H**, and **66L** in the challenged claims was not a patentable advance in the field, but obvious.

The prior art also disclosed p185^{HER2} as a promising therapeutic target, and a specific mouse monoclonal antibody (4D5) against the p185^{HER2} target. Dr. Foote and Mr. Buss both agree that the next logical and necessary step in the

development of 4D5 was humanizing it. *Id*. ¶¶40, 333–36; Ex. 1004 ¶¶63–70. Queen 1990 provided the motivation and a sufficient roadmap to accomplish this humanization. Ex. 1003 ¶¶342–49. Others gave further details on specific residues. *Id.* Thus, humanizing 4D5 and claims 30, 31, 33, 42, and 60 are also obvious.

C. Prosecution History and Related Proceedings

'206 Application Prosecution. The '213 patent issued from Application No. 08/146,206 (the "'206 application"). During prosecution, the PTO rejected the '206 application's claims for anticipation, obviousness, lack of written description, lack of enablement, indefiniteness and non-statutory obviousness-type double patenting. *See generally* Ex. 1002. The Examiner allowed the claims on December 18, 2001 without giving any reasons for their allowance. *See id.* at 4462–71 (Notice of Allowability).

Of the references asserted in this Petition, Kurrle, Chothia & Lesk, and Chothia 1985 were not considered during prosecution. Ex. 1001 ("References Considered"). Queen 1990, Furey, and Hudziak were considered by the Examiner (*see id.*) but were not used by the Examiner in any rejections of the claims (*see generally* Ex. 1002).

Interference with Application No. 11/284,261. Applicants for Application No. 11/284,261 ("Adair") requested an interference with the '213 patent. The interference count was drawn to humanized antibodies with non-human

substitutions at specific variable domain framework positions. The Board declared the interference but determined Adair's claim was barred under 35 U.S.C. § 135(b)(1). *Adair*, Interference No. 105,744, Declaration of Interference at 4 (Feb. 2, 2010) (Ex. 1095, Vol. 13), at 1588-89 (Decision on Motions at 9–10), *aff'd*, *Adair v. Carter*, 101 U.S.P.Q.2d 1625, 1630 (Fed. Cir. 2012).

D. Level of Ordinary Skill in the Art

The alleged invention relates to humanizing non-human antibodies, ***e.g.***, mouse monoclonal antibodies. A POSITA would have held a Ph.D. or equivalent (for example, knowledge gained through 4–5 years of work experience) in molecular biology, immunology, biochemistry or a closely related field, and may work as a member of a team. A team member or advisor or consultant would have an M.D. with clinical experience in the disease or disease area (***e.g.***, oncology) for which the antibody development is intended. *See*, ***e.g.***, Exs. 1003 ¶¶29–32; 1004 ¶¶30–33. Such a person would have the educational background above with experience in common laboratory techniques in molecular biology. ***Id.*** Such experience can include three dimensional computer modeling of protein structures, domain and sequence manipulation and swapping, construction and expression of recombinant proteins, antibody binding assays (for specificity and affinity), immunogenicity testing and the like. ***Id.*** Such person may have consulted with one or more team members of experienced professionals to develop a humanized

monoclonal antibody for therapeutic use, including consulting with others to select non-human monoclonal antibodies (such as a mouse monoclonal antibody) for humanization, as well as subsequent testing of the humanized antibody and its intermediates. *Id.* Such a person would also have been well-versed in the world-wide literature that was available as of the priority date. *Id.*

E. Claim Construction

The Challenged Claims possess their "broadest reasonable construction in light of the specification" of the '213 patent. 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs.*, *LLC*, 793 F.3d 1268 (Fed. Cir. 2015) (affirming broadest reasonable construction standard in IPR) ("BRI").

1. "a humanized antibody variable domain" (claims 1, 62 and 80), "an antibody" (claim 30) or "a humanized antibody" (claim 63), "a humanized variant of a non-human parent antibody" (claims 64 and 79) or "a humanized antibody heavy chain variable domain" (claim 66).

The independent claims of the '213 patent each contain a variation of the preamble phrase, "a humanized antibody" set forth above. A POSITA would understand "a humanized antibody" to include an antibody or antibody fragment that has been humanized, *i.e.*, made more human-like. A POSITA would also understand that none of the claims relate to a single, specific antibody or antibody fragment. Even in claim 30, where the phrase "[a] humanized antibody" is

modified with "which binds $p185^{HER2}$," the claim is not limited to a particular antibody.

2. "and further comprising a Framework Region (FR) amino acid substitution at a site selected from the group consisting of…"

Independent claims 1, 30, 62, 63, 66, 79 and 80 include a Markush Group list of amino acid residues from which a framework region substitution is chosen. Markush Group members are accorded functional equivalency status for purposes of claim construction. *See Ecolochem, Inc. v. Southern California Edison Co.*, 91 F.3d 169 (Fed. Cir. 1996) ("By claiming a Markush group…members of the claimed group are functionally equivalent"), citing *In re Skoll*, 523 F.2d 1392, 1397 (C.C.P.A. 1975).

As none of the claims are limited to a specific antibody, and all Markush Group members are functional equivalents of each other for the purpose of creating a humanized antibody, the BRI would be that any of the recited residues can be equally substituted for any given antibody. Thus, it is assumed for the purposes of claim construction in this proceeding that each of the recited substitutions is available for humanization of an antibody.

3. "numbering system set forth in Kabat"

Independent claims 1, 30, 62, 63, 66, 79 and 80 recite "utilizing the numbering system set forth in Kabat." The '213 patent specifically ties its

numbering system to two references: Kabat 1987 (Ex. 1052) and Kabat 1991 (Ex. 1055). *See* Ex. 1001 at 10:45–49. As noted, the Kabat 1987 and 1991 data derives from a database of publicly available antibody sequences, formatted to display the sequences in alignment with each other and in a numerical sequence order. Kabat 1987 and 1991 also show boundaries of known antibody regions, including the three CDRs and four Framework Regions (FRs) in each antibody chain variable domain. The BRI of "utilizing the numbering system set forth in Kabat" encompasses the Kabat 1987 and Kabat 1991 designations, including the amino acid residue positions set forth in Kabat and the boundary designations for CDR and FR structures.

4. "up to 3-fold more"

Claim 65, which depends from claim 79,[6] requires a "humanized variant...bind[ing] the antigen up to 3-fold more in the binding affinity than the parent antibody binds antigen" (emphasis added). The BRI of this claim includes all binding affinity values "up to" 3-fold more, *i.e.,* any value no matter how small and greater than zero "up to" 3-fold more.

[6] The Patent Owner filed a Certificate of Correction dated June 18, 2002, which modified claim 65 to depend from claim 79, stating that it incorrectly depended from claim 63 as a result of a printing error. Ex. 1002, Vol. 9 at 4487–90.

F. Prior Art

Petitioner relies on the following patents and printed publications:

1. Kurrle (Ex. 1071)

Kurrle, published on December 19, 1990, detailed the humanization of a mouse monoclonal antibody (BMA 031) against the human alpha/beta T-cell receptor. Ex. 1071 at 1, Abstract. Kurrle provided guidance to a POSITA regarding a "further refinement" of the variable domain FR region, making "essentially a human antibody with a much lower immunogenicity in patients." *See id.* at 3:8–12 ("A further refinement involves humanization of the variable regions. Only the complementarity determing [sic] regions and *selected framework amino acids necessary for antigen binding* are maintained murine. The remaining framework regions are converted to human sequences").[7]

Further, Kurrle taught the four amino acids on either side of a CDR contribute to antibody binding:

> Molecular models of antibodies have shown that the actual CDR loops can contain amino acids up to 4 amino acids away from the 'Kabat' CDRs. Therefore, maintaining at least the major amino acid differences (in size or charge) within 4 amino acids of the CDRs as murine may be beneficial.

[7] All emphasis is added unless otherwise indicated.

Id. at 8:27–29. Such "differences within four amino acids of the CDRs should be maintained murine." *Id.* at 8:28–31. Kurrle further recommended using a simplified computer model based on sequence homology with solved antibody structures to judge the proximity of framework amino acid residues with the CDRs. *Id.* at 8:32–36. Existing human framework residues could be switched to a consensus human residue at such positions. *Id.* at 1:38–46.

Kurrle made four humanized versions of their antibody (CIV-1, CIV-2, CIV-3 and CIV-4), each time substituting select FR residues in the human antibody for the corresponding residue in the non-human (mouse) antibody. *See id.* at 25–26, Tables 6A and 6B.[8] Using their roadmap, Kurrle made several FR substitutions in the light and heavy chain, including at positions **4L, 69H, 71H, 73H** and **76H**. *See* Ex. 1003 ¶¶123, 155–172. The '213 patent claims these very residue substitutions. *Id.*

2. Queen 1990 (Ex. 1050)

Queen 1990 is a PCT application filed December 28, 1989 and published July 26, 1990. Queen 1990 advanced four explicit criteria for humanizing non-

[8] Kurrle did not use the Kabat numbering system in Tables 6A and 6B for the antibody heavy chain. Ex. 1003 ¶124, n.14. To follow the "numbering system set forth in Kabat," the amino acid sequences in Table 6A (heavy chain) were aligned with the Kabat numbering system. *See* Ex. 1003D.

human antibodies. Criterion I of Queen 1990 relates to the choice of the acceptor human framework:

> **Criterion I**: As acceptor, use a framework from a particular human immunoglobulin that is unusually homologous to the donor immunoglobulin to be humanized, or use a consensus framework from many human antibodies.

Exs. 1050 at 12:17–13:20; 1003 ¶¶131–137.

Next, if a human FR residue is rare or unusual in humans, while the mouse residue is common (or conserved) in humans, substitute for the conserved mouse residue at that sequence position:

> **Criterion II**: If an amino acid in the framework of the human acceptor immunoglobulin is unusual (*i.e.*, "rare", which as used herein indicates an amino acid occurring at that position in no more than about 10% of human heavy (respectively light) chain V region sequences in a representative data bank), and if the donor amino acid at that position is typical for human sequences (i.e., "common", which as used herein indicates an amino acid occurring in at least about 25% of sequences in a representative data bank), then the [mouse] donor amino acid rather than the [human] acceptor may be selected.

Exs. 1050 at 13:21–37. The prior art thus knew maintaining highly conserved residues was important to minimize immunogenicity. Ex. 1003 ¶¶133, 134.

Queen 1990's Criterion III suggests substituting at CDR-adjacent positions:

> **Criterion III**: In the positions immediately adjacent to one or more of the 3 CDR's in the humanized immunoglobulin chain, the [mouse] donor amino acid[s] rather than [human] acceptor amino acid may be selected. These amino acids are particularly likely to interact with the amino acids in the CDR's and, if chosen from the [human] acceptor, distort the donor CDR's and reduce affinity. Moreover, the adjacent amino acids may interact directly with the antigen (Amit et al., Science, 233, 747–753 (1986), which is incorporated herein by reference) and selecting these amino acids from the [mouse] donor may be desirable to keep all the antigen contacts that provide affinity in the original antibody.

Id. at 14:1–12. As mentioned above, Kabat and Chothia identified the CDR boundaries,[9] both in sequence and structurally. Residues "immediately adjacent" to Kabat's CDRs are limited: 30H, **36H**, 49H, 66H, 94H, 103H in the heavy chain; and 23L, 35L, 49L, 57L, 88L, and **98L** in the light chain; residues "immediately adjacent" to Chothia's hypervariable regions include: 25L, 33L, 49L, 53L, 90L, 97L, 25H, 33H, 52H, 56H, 95H and 102H. The '213 patent claims include **36H** and **98L**. Exs. 1052; 1003 ¶¶110–115.

Criterion IV calls for pinpointing framework residues that possess an atom that is within about 3Å of a CDR atom and thus likely to make a CDR contact:

[9] As discussed above in Section VII.A (Summary of the Argument), Chothia calls CDRs "hypervariable regions".

> **Criterion IV**: A 3-dimensional model, typically of the original [mouse] donor antibody, shows that certain amino acids outside of the CDR's are close to the CDR's and have a good probability of interacting with amino acids in the CDR's by hydrogen bonding, Van der Waals forces, hydrophobic interactions, etc. At those amino acid positions, the [mouse] donor amino acid rather than the [human] acceptor immunoglobulin amino acid may be selected. Amino acids according to this criterion will generally have a side chain atom within about 3 angstrom units of some site in the CDR's and must contain atoms that could interact with the CDR atoms according to established chemical forces, such as those listed above. Computer programs to create models of proteins such as antibodies are generally available and well known to those skilled in the art.

Ex. 1050 at 14:14–31 (citations omitted). Queen 1990 further teaches deriving these "contact" residues from known antibody structures. *Id.* Such framework residues are more likely to be important in influencing how CDRs interact with the antigen.

3. Furey (Ex. 1125)

Well prior to Queen 1990 and Kurrle's humanization efforts, Furey *et al.* established the structural importance of framework residues that established tight hydrogen bonding with CDR residues, including at claimed position **66L** in the light chain variable domain, to maintain CDR2 conformation. Ex. 1125 at 16, Table 4. Furey therefore taught well before the alleged priority date that claimed

residue **66L** contacted CDR2 residues via hydrogen bonds, and thus readily identifiable for substitution according to the teachings of Kurrle and Queen 1990.

4. Chothia & Lesk (Ex. 1062)

Chothia & Lesk also established certain residues are important for maintaining antibody structure, disclosing that "[t]he major determinants of the tertiary structure of the framework are the residues buried within and between the [V_L and V_H] domains." Ex. 1062 at 5. These residues are summarized in Table 4:

Table 4

Residues commonly buried within V_L and V_H domains

V_L domains			V_H domains		
Position	Residues in known structures	A.S.A.[a] (Å²)	Position	Residues in known structures	A.S.A.[a] (Å²)
4	L,M	6	4	L	14
6	Q	12	6	Q,E	16
19	V	11	18	L	21
21	I,M	1	20	L	0
23	C	0	22	C	0
25	G,A,S	13	24	S,V,T,A	8
33	V,L	3	34	M,Y	4
35	W	0	36	W	0
37	Q	30	38	R	13
47	L,I,W	8	48	I,V	1
48	I	24	49	A,G	0
62	F	11	51	I,V,S	4
64	G,A	13	69	I,V,M	13
71	A,F,Y	2	78	L,F	0
73	L,F	0	80	L	0
75	I,V	0	82	M,L	0
82	D	4	86	D	2
84	A,S	11	88	A,G	3
86	Y	0	90	Y	0
88	C	0	92	C	0
90	A,S,Q,N	7	104	G	11
97	V,T,G	18	106	G	19
99	G	3	107	T,S	17
101	G	11	109	V	2
102	T	1			
104	L,V	2			

[a] Mean accessible surface area (A.S.A.) of the residues in the Fab structures NEWM, MCPC603, KOL and J539 and in the V_L structures REI and RHE.

Id. at 8, Table 4. These residues, which maintain tertiary structure (immunoglobulin chain interactions) of the framework, overlap with important

CDR contact residues already disclosed in the prior art as well as known highly conserved residues, *see* Ex. 1003 ¶¶150–52, 238 n.17, narrowing the list of substitutable residues significantly. Since such residues—including claimed residues **4L, 62L, 73L, 4H, 36H, 69H, 78H and 92H**—help maintain structure of the framework, they are readily identifiable for substitution according to the teachings of Kurrle and Queen 1990. *Id.*

5. Chothia 1985 (Ex. 1063)

Chothia 1985 disclosed "buried" residues involved in the "packing of the VL and VH β-sheets in the conserved 'framework'…" Ex. 1063 at 3, Abstract. According to Chothia 1985:

> When the VL and VH domains pack together, residues from these edge strands form the central part of the interface and give what we call a three- layer packing; *i.e.*, there is a third layer composed of side-chains inserted between the two backbone side-chain layers that are usually in contact. *The 12 residues that form the central part of the three observed VL-VH packings are absolutely or very strongly conserved in all immunoglobulin sequences.*

Id. One of the buried residues in the V_L-V_H interface is residue **93H**. *See id.* at 12, Table 4.

6. Hudziak (Ex. 1021)

Hudziak confirmed $p185^{HER2}$'s role in carcinoma development. Ex. 1021 at 8, Abstract. Hudziak had already shown high $p185^{HER2}$ levels correlated to negative

prognoses and high relapse probability in carcinoma development; and amplifying $p185^{HER2}$ *in vitro* created resistance to cytotoxic (TNF-α) treatment. *Id.* Hudziak "prepared [murine] monoclonal antibodies against the extracellular domain of $p185^{HER2}$…" and chose "[o]ne monoclonal antibody (4D5)," which "was characterized in more detail and was shown to inhibit in vitro proliferation of human breast tumor cells overexpressing $p185^{HER2}$ and, furthermore, to increase the sensitivity of these cells to the cytotoxic effects of TNF-α." *Id.* In growth inhibition studies, "*[m]aximum inhibition* was obtained with monoclonal antibody 4D5, which inhibited cellular proliferation by 56%." *Id.* at 12 (emphasis added). Hudziak confirmed "the combination of TNF-α and monoclonal antibody 4D5 reduced the [listed] tumor cell number to a level below that initially plated," and "indicat[ed] the induction of a cytotoxic response." *Id*. at 13.

TABLE 1. Inhibition of SK-BR-3 proliferation by anti-$p185^{HER2}$ monoclonal antibodies[a]

Monoclonal antibody	Relative cell proliferation[b]
7C2	79.3 ± 2.2
2C4	79.5 ± 4.4
7D3	83.8 ± 5.9
4D5	44.2 ± 4.4
3E8	66.2 ± 2.4
6E9	98.9 ± 3.6
7F3	62.1 ± 1.4
3H4	66.5 ± 3.9
2H11	92.9 ± 4.8
40.1.H1	105.8 ± 3.8
4F4	94.7 ± 2.8

Id. at 11, Table 1.

Hudziak concluded that "[m]onoclonal antibodies specific for $p185^{HER2}$ may therefore be useful therapeutic agents for the treatment of human neoplasias, including certain mammary carcinomas, which are characterized by the overexpressing of $p185^{HER2}$." *Id*. at 14.

VIII. THE PRIOR ART RENDERS THE CHALLENGED CLAIMS UNPATENTABLE

Detailed instructions for humanizing antibodies were widely available before earliest possible priority date. Multiple research institutions—including Genzyme Corp. (Ex. 1071), Protein Design Labs (Ex. 1050), the Medical Research Council and the National Institutes of Health—published efforts to humanize antibodies to avoid the immunogenic reactions observed with non-human monoclonal antibody therapeutics before the '213 patent's filing date. *See* Exs. 1071 at 3:8–12; 1050 at 1, Abstract; 1003 ¶¶122, 163; 1004 ¶¶38–45. The field recognized that earlier efforts (*e.g.*, chimeric antibodies, CDR grafting) often resulted in non-or poor binding, with immunogenicity remaining a concern. *See* Exs. 1050 at 3:30–33; 1073 at 9:12–19; 1003 ¶¶252-253; 1004 ¶¶38–41.

Queen 1990 detailed the importance of preserving certain mouse framework positions in a humanized antibody in order to maintain CDR conformation and antigen binding. Ex. 1050 at 14:1–12. Kurrle used logic similar to Queen 1990's, replacing several human FR sites with mouse residues within the variable region of the light and heavy chains. Exs. 1071 at 25–26, Tables 6A and 6B; 1003 ¶¶159–

161. The prior art, thus, already provided detailed pathways to humanize antibodies for therapeutic use which would "be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen." Ex. 1071 at 6:23-25; Ex. 1003 at ¶¶173–199.

Furey, Chothia & Lesk, Chothia 1985, and Hudziak provide additional teachings that confirm the Challenged Claims are unpatentable. Furey, Chothia & Lesk, and Chothia 1985 teach that a number of claimed residues constitute potential substitution candidates according to the teachings of Kurrle and Queen 1990. Further, Hudziak provides motivation for creating monoclonal antibodies specific to $p185^{HER2}$. The copious prior art demonstrates that modification and humanization, as claimed in each Challenged Claim, was anticipated and/or plainly obvious.

A. Ground 1: Claims 1–2, 25, 29, 63, 66, 67, 71–72, 75–76 and 80–81 Are Anticipated by Kurrle

1. Claim 1

Independent claim 1 recites "[a] humanized antibody variable domain comprising," the elements (1) "non-human Complementarity Determining Region (CDR) amino acid residues which bind an antigen incorporated into a human antibody variable domain," and (2) FR substitutions at "a site selected from the group consisting of: 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."

The "humanized antibody variable domain" element is disclosed in Kurrle, which taught "humanised and civilised versions of [mouse monoclonal] antibodies." Exs. 1071 at 1, Abstract; 1003 at ¶¶155, 156. Kurrle also disclosed "non-human Complementarity Determining Region (CDR) amino acid residues which bind an antigen" and "a Framework Region (FR) amino acid substitution" incorporated into a human antibody variable domain, referring to the "civilised" antibodies as those where "[o]nly the *complementarity determining regions* and *selected framework amino acids* necessary for antigen binding are maintained *murine*." Exs. 1071 at 3:9–10 (emphasis added); 1003 ¶156–158.

Further, Kurrle substituted several corresponding murine amino acids for human framework residues under Kabat's numbering system, including **4L** and **69H**, as found in claim 1. *See* Ex. 1071 at 25–26, Tables 6A and 6B; Ex. 1003 at ¶¶155–158, Exhibit B. Claim 1 is anticipated.

2. Claims 2, 25 and 29

Claim 2 depends on claim 1, and recites, "wherein 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." This is precisely what Kurrle did. *See* Ex. 1071 at 8:45–47 ("In one position…the human consensus

sequence is the same as [in the mouse sequence]. One could rationalize changing [the human acceptor antibody residue] back to [mouse], so this change was incorporated…"). This is a basic step in the humanization process taught by Kurrle. *See* Ex. 1003 ¶159. Claim 2 is also anticipated by Kurrle.

Claim 25 depends on claim 1, and recites "wherein the residue at site 69H has been substituted." Because framework residue **69H** was substituted with the murine residue in Kurrle's humanized anti-T-cell receptor antibody, *see* claim 1 (§VIII.A.1), Kurrle anticipates claim 25. Ex. 1003 ¶160.

Claim 29 depends on claim 1, and recites "[a]n antibody comprising the humanized variable domain of claim 1." Kurrle created an antibody comprising the humanized variable domain: "The resulting mAb of the present invention is thus essentially a human antibody with a much lower immunogenicity in patients." Ex. 1071 at 3:11–12; *see also* 2:2–4; Ex. 1003 ¶161. Kurrle anticipates Claim 29.

3. Claim 63

Independent claim 63 is drawn to an antibody with structural components substantially identical to those of claim 29, *i.e.*, the same "humanized antibody" incorporating the same claimed non-human CDRs and completely overlapping substituted framework residues as in claim 1. *See* §VIII.A.2, *supra*. Accordingly, because the structural components are the same, the same function (*i.e.*, "which 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") is also present. *See Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999) ("'[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer.'"); Ex. 1003 ¶¶162–66.

Not only is lacking immunogenicity compared to a non-human parent an inherent aspect of the claimed humanized antibodies, this is explicitly stated in Kurrle. *See* Exs. 1071 at 3:8–12 ("A further refinement involves humanization of the variable regions…the resulting mAb of the present invention is thus essentially a human antibody with a much lower immunogenicity in patients."); 1003 at ¶¶162–63. One of ordinary skill in the art would thus know that Kurrle's humanized antibodies would "lack immunogenicity compared to a non-human parent antibody upon repeated administration…" Claim 63 is anticipated.

4. Claims 66, 67, 71, 72, 75 and 76

Independent ***claim 66*** shares elements with claims 1 and 63, which are met by Kurrle as demonstrated above. *See* §§VIII.A.1, 3, *supra*; Ex. 1003 ¶¶165–66. Claim 66 requires an "amino acid substitution at a site selected from the group consisting of: 24H, 73H, 76H, 78H, and 93H," under Kabat's numbering system.

As Kurrle substituted residues **73H** and **76H**, Ex. 1003D; Ex. 1003 ¶¶165–66, it anticipates claim 66.

Claim 67 depends from claim 66 and recites "wherein the substituted residue is the residue found at the corresponding location of the nonhuman antibody from which the non-human CDR amino acid residues are obtained." Kurrle taught this limitation. *See* Ex. 1071 at 8:45–47 ("In one position…the human consensus sequence is the same as [in the mouse sequence]. One could rationalize changing [the human acceptor antibody residue] back to [mouse], so this change was incorporated…"); *see also* §VIII.A.2 (claim 2); Ex. 1003 ¶167.

Dependent Claims 71, 72, 75 and 76 recite the humanized variable domain of claim 66 "wherein the residue at site 73H has been substituted" (***claim 71***), "wherein the residue at site 76H has been substituted" (***claim 72***), "which further comprises an amino acid substitution at site 71H" (***claim 75***), and "which further comprises amino acid substitutions at sites 71H and 73H" (***claim 76***). Kurrle substituted amino acid residues **71H**, **73H** and **76H** in their humanized anti-T-cell receptor monoclonal antibody. *See* Exs. 1071 at 26, Table 6B; 1003D; 1003 ¶168. Accordingly, and in view of the discussion for claims 1 and 66, *see* §§VIII.A.1, 3, *supra*; Ex. 1003 ¶¶155–58, 168, Kurrle anticipates claims 71, 72, 75 and 76.

5. Claims 80 and 81

Claim 80: Independent claim 80 recites "[a] humanized antibody variable domain comprising non-human Complementarity Determining Region (CDR) amino acid residues which bind an antigen incorporated into a human antibody variable domain, and further comprising a Framework Region (FR) amino acid substitution." Claim 80 further recites the "substituted FR residue: (a) noncovalently binds antigen directly; (b) interacts with a CDR; or (c) 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…" Claim 80 then recites "the substituted FR residue is at a site selected from the group consisting of 4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 24H, 36H, 39H, 43H, 45H, 69H, 70H, 73H, 74H, 76H, 78H, 92H and 93H, utilizing the numbering system set forth in Kabat." As discussed above, Kurrle substituted residues **4L**, **69H**, **73H** and **76H.** *See* §§VIII.A.1, 3, *supra*.

The additional recited elements, which are noted functions of the substituted residues, do not add anything new to the claim. *See* claim 63, §VIII.A.3; Ex. 1003 ¶¶162–164; *see also Atlas Powder Co.*, 190 F.3d at 1347. Even if the inherency of these functions were discounted (they should not be), Kurrle teaches interaction of the framework residues with the CDR as a reason for substitutability. *See* Exs. 1071 at 8:28–29, 32–40 (use of a "simplified computer model" to determine

whether or not FR residues were close enough to CDRs to influence binding); 1003 ¶¶169–171. Accordingly, Kurrle at least teaches substitution of a framework residue that "interacts with a CDR," *i.e.*, limitation "(b)" from claim 80, and therefore anticipates claim 80.

Claim 81: Claim 81 depends on claim 80, and further recites, "wherein 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." As discussed above, this is taught by Kurrle. *See* claim 2, §VIII.A.2, *supra*, Exs. 1071 at 25–26, Tables 6A and 6B; 1003 ¶¶162–64; 172. Kurrle anticipates claim 81.

B. Ground 2: Claims 1, 2, 4, 29, 62–64 and 80–81 Are Anticipated by Queen 1990

1. Claim 1

The first part of claim 1, "[a] humanized antibody variable domain," is disclosed in Queen 1990. Queen 1990 disclosed creating "a humanized antibody variable domain" by not only swapping CDRs, but also manipulating the framework region of the variable domain, as claim 1 of the '213 patent recites. Queen provided "novel methods for designing humanized immunoglobulins having one or more complementarity determining regions (CDR's) from a donor immunoglobulin and a framework region from a human immunoglobulin…." Exs. 1050 at 1, Abstract; 1003 ¶174.

Queen 1990 further provided a detailed roadmap with specific criteria that could be used in making humanized immunoglobulins. Exs. 1050 at 12:11–12; 1003 ¶¶173–183. For example, Queen 1990 emphasized the importance of framework positions adjacent to the CDR: "Each humanized immunoglobulin chain may comprise about 3 or more amino acids from the donor immunoglobulin in addition to the CDR's, *usually at least one of which is immediately adjacent to a CDR in the donor immunoglobulin*…" Ex. 1050 at 1, Abstract. A POSITA could have readily envisioned such locations. *See* Ex. 1003 ¶¶177–79.

Queen 1990 encapsulated this rule in Criterion III, which states:

> *In the positions immediately adjacent to one or more of the 3 CDR's in the humanized immunoglobulin chain, the donor [mouse] amino acid(s) rather than acceptor [human] amino acid may be selected.* These amino acids are particularly likely to interact with the amino acids in the CDR's and…[m]oreover, the adjacent amino acids may interact directly with the antigen…and selecting these amino acids from the donor may be desirable to keep all the antigen contacts that provide affinity in the original antibody.

Exs. 1050 at 14:1–12 (citations omitted); 1003 ¶178.

Dr. Foote explained that "one of ordinary skill in the art at the time of the '213 patent…would have readily understood that Queen 1990 (specifically Criterion III) explicitly taught the substitution of framework sites **immediately adjacent** to CDRs." Ex. 1003 ¶179. Using the numbering system set forth by

Kabat 1987, claimed framework residues **98L** and **36H** are "immediately adjacent" to CDRs. *See* Exs. 1003E; 1003 ¶¶173–83; §VII.F.2, *supra*.

Thus, Queen 1990's teaching to substitute CDR-adjacent framework region amino acid positions would inevitably include substitutions at claimed amino acid residues **98L** and **36H**. Queen 1990 thus anticipates claim 1.

2. Claims 2, 4 and 29

Claim 2's additional limitation "wherein 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" is also disclosed by Queen 1990. *See* Exs. 1050 at 5:36–6:2 ("substitutions of a human framework amino acid of the acceptor (*i.e.*, human) immunoglobulin with a corresponding amino acid from a donor (*i.e.*, non-human) immunoglobulin"); 1003 ¶184. Queen 1990 anticipates claim 2.

Claim 4 recites "wherein the human antibody variable domain is a consensus human variable domain." Queen 1990 expressly teaches this by disclosing in Criterion I that "[a]s acceptor…use a *consensus framework* from many human antibodies." *See* Exs. 1050 at 12:17–20 (Criterion I); 1003 ¶¶132, 184. Queen 1990 anticipates claim 4.

Claim 29 depends on claim 1, and further recites "[a]n antibody comprising the humanized variable domain of claim 1." As Dr. Foote explains, the goal of

antibody humanization programs was to create antibodies with humanized variable domains. *See*, ***e.g.***, Exs. 1050 at 4:21–25 ("mouse complementarity determining regions, with or without additional naturally-associated mouse amino acid residues, can be used to produce human-like antibodies…"); 1003 ¶186. A POSITA would thus recognize that Queen 1990 teaches creating therapeutic-quality antibodies with a humanized variable domain in order to maintain a high level of binding and affinity. Ex. 1003 ¶186. Queen 1990 anticipates claim 29.

3. Claim 62

Independent Claim 62 is identical to claim 1 except that it requires the amino acid residues "bind an antigen incorporated into a consensus human variable domain" and adds residues 46L, 75H, 76H and 78H to claim l's list of FR substitutable residues list. As discussed above for claim 1, *see* §VIII.B.1, *supra*, Queen 1990 discloses claimed residues **98L** and **36H** as inevitably requiring substitution. As with claim 1, claim 62 only requires substitution at one of the recited list of residues.

Regarding the "consensus human variable domain," Queen 1990 disclosed in Criterion I that "[a]s acceptor…use *a consensus framework* from many human antibodies." *See* Exs. 1050 at 12:17–20; 1003 ¶187–88; §VIII.B.2, *supra*. Queen 1990 anticipates claim 62.

4. Claim 63

Independent Claim 63 differs from claim 62 by reciting "[a] humanized antibody" (as opposed to claim 62's "humanized antibody variable domain") and by describing the claimed humanized antibody as lacking "immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient."

As above, lacking immunogenicity compared to a non-parent antibody is a non-patentable distinction. *See* §VIII.B.3, citing to *Atlas Powder Co.*, 190 F.3d 1342; Ex. 1003 ¶176. Regardless, Queen 1990 taught: "When combined into an intact antibody, the humanized immunoglobulins of the present invention *will be substantially non-immunogenic* in humans…." Exs. 1050 at 1, Abstract; 1003 at ¶189–91. Further, Queen 1990 taught a humanized antibody. *Id*. Claim 63 is also anticipated by Queen 1990.

5. Claim 64

Independent Claim 64 recites "[a] humanized variant of a non-human parent antibody which binds an antigen; comprising a 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; wherein amino acid residues forming Complementarity Determining Regions (CDRs) thereof comprise non-human antibody amino acid residues, and further comprises a

Framework Region (FR) substitution where the substituted FR residue: (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."

Queen 1990 anticipates claim 64. As with claims 1, 4 and 29, Queen 1990 disclosed an antibody incorporating a humanized variable domain with a consensus sequence (*i.e.*, "most frequently occurring amino acid residues at each location in all human immunoglobulins of a human heavy chain immunoglobulin subgroup"). *See* §§VIII.B.2, 3, *supra*; Exs. 1003 ¶¶192–94; 1050 at 12:17–20.

While the remaining limitations are merely inherent functions of the humanized antibody, *see* §VI.G.3, *supra*, Queen 1990 disclosed at least functions (a) and (b) above in Criterion III: "immediately adjacent…amino acids are *particularly likely to interact with the amino acids in the CDR's*….Moreover, *the adjacent amino acids may interact directly with the antigen*…." Exs. 1050 at 14:1–12; 1003 ¶194. Because Queen 1990 teaches to substitute "immediately adjacent" residues **98L** and **36H**, *see* §VIII.B.1 *supra*, and because Queen 1990 teaches those residues "are particularly likely to interact with the amino acids in the CDR's and…may interact directly with the antigen," Queen 1990 anticipates claim 64. Ex. 1003 ¶¶192–94.

6. Claims 80 and 81

Independent ***Claim 80*** is also anticipated by Queen 1990. As discussed with claims 1 and 64, Criterion III of Queen 1990 explicitly teaches the selection of framework residues immediately adjacent to CDRs for substitution—this would include claimed residues **36H** and **98L**. *See* §§VIII.B.1 & 5, *supra*; Exs. 1003E; 1003 ¶¶195–98 (citing Ex. 1050 at 14:4–8). Queen 1990 explains that "selecting these amino acids from the donor may be desirable to keep all the antigen contacts that provide affinity in the original antibody." Exs. 1050 at 14:9–12; 1003 at ¶196.

Moreover, Criterion IV teaches "interact[ion] with a CDR" by disclosing that "certain amino acids outside of the CDR's are close to the CDR's and have a good probability of interacting with amino acids in the CDR's by hydrogen bonding, Van der Waals forces, hydrophobic interactions, etc." Exs. 1050 at 14:15–19; 1003 ¶197. Queen 1990 anticipates Claim 80.

Claim 81 (dependent on claim 80) is also taught by Queen 1990, which disclosed "substitutions of a human framework amino acid of the acceptor (*i.e.*, human) immunoglobulin with a corresponding amino acid from a donor (*i.e.*, non-human) immunoglobulin." *See* Exs. 1050 at 5:36–6:2; 1003 ¶199. Queen 1990 anticipates Claim 81.

C. Ground 3: Claims 1–2, 4, 25, 29, 62–64, 66–67, 69, 71–72, 75–76, 78 and 80–81 Are Unpatentable as Obvious over Queen 1990 and Kurrle

1. Claim 1

Queen 1990 disclosed a detailed pathway for humanizing non-human monoclonal antibodies, with the expectation that the resulting humanized antibodies "will be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen…," including:

- Criterion I: Choose an acceptor human framework antibody, including one that is "unusually homologous to the donor immunoglobulin to be humanized, or use a consensus framework from many human antibodies." Exs. 1050 at 12:17–13:20; 1003 ¶¶132, 203;
- Criterion II: Once the human antibody is selected, evaluate whether amino acid residues in the framework of the human acceptor antibody are "rare" amongst human antibodies. If the residue is "rare" and the donor [mouse] antibody is more "typical for human sequences," choose the donor residue. Criterion II "helps ensure that an atypical amino acid in the human framework does not disrupt the antibody structure" Exs. 1050 at 13:22–37; 1003 ¶¶133–34, 203;

- Criterion III: "In the positions immediately adjacent to the 3 CDR's in the humanized immunoglobulin chain, the donor [mouse] amino acid rather than acceptor [human] amino acid may be selected." Exs. 1050 at 14:1–12; Ex. 1003 ¶¶135, 203; and
- Criterion IV: Generate a 3-dimensional model of the original donor antibody, and select amino acid positions where:

> [C]ertain amino acids outside of the CDR's are close to the CDR's and have a good probability of interacting with amino acids in the CDR's….Amino acids according to this criterion will generally have a side chain atom within about 3 angstrom units of some site in the CDR's and must contain atoms that could interact with the CDR atoms according to established chemical forces, such as those listed above.

Exs. 1050 at 14:14–15:2; 1003 ¶¶136, 203.

Queen 1990 concludes that when the humanized variable regions are "combined into an intact antibody, the humanized light and heavy chains of the present invention will be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen…" Exs. 1050 at 6:21–26; 1003 ¶204. Queen 1990 thus provided motivation to humanize monoclonal antibodies along with a detailed roadmap for production of humanized monoclonal antibodies. Ex. 1003 ¶¶203–204.

Kurrle employed a similar roadmap to obtain a "humanized antibody variable domain" as claimed in claim 1, including the steps of: choosing the most similar human acceptor sequence (Criterion I of Queen 1990, Ex. 1050 at 12:17–13:21; *see* Ex. 1071 at 8:16–18); accounting for the adjacent residue rules of Queen 1990 (Criterion III of Queen 1990, Ex. 1050 at 14:1–12; *see* Ex. 1071 at 8:25–31); substituting CDR-contact residues using computer models based on solved structures (Criterion IV of Queen 1990, Ex. 1050 at 14:16–15:2; *see* Ex. 1071 at 8:32–36); and substituting "rare" amino acids in the human acceptor framework for "common" (consensus) amino acid residues (Criterion II of Queen 1990, Ex. 1050 at 13:22–37; *see* Ex. 1071 at 8:36–40). Ex. 1003 ¶¶121–124, 205.

Using these guidelines, Kurrle made a total of 13 substitutions in the light chain framework region and 18 substitutions in the heavy chain framework region according to the Kabat numbering system, including claimed residues **4L** and **69H**. *See* §§VII.F.1 & VIII.A.1, *supra*, Exs. 1003D; 1003 ¶¶155–58, 206.

A POSITA considering Kurrle would have looked to other references disclosing the successful humanization of non-human antibodies, including 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. Kurrle and Queen 1990 were published less than six months apart. Exs. 1071 at 1; 1050 at 1. International Publication No. WO

92/05274, published on April 2, 1992, lists both references in the International Search Report. Ex. 1183 at 71, 73. Additionally, the International Search Report for both Kurrle and Queen 1990 include International Publication No. WO 89/01783 entitled "Recombinant Antibody and Method." Exs. 1071 at 44; 1050 at 48; 1182 at 1. Given the interrelated teachings of Kurrle and Queen 1990, it would have been obvious to a POSITA to have incorporated the teachings of Queen 1990 when humanizing the antibody of Kurrle in order to ensure successful humanization. Ex. 1003 at ¶207.

The combination of Queen 1990 and Kurrle provided ample motivation and a reasonable expectation of success that a humanized monoclonal antibody could be obtained with "a much lower immunogenicity in patients", Ex. 1071 at 3:11–12, while maintaining the binding affinity and specificity of the donor monoclonal antibody. Claim 1 is obvious over Queen 1990 and Kurrle. Ex. 1003 ¶¶203–207.

2. Claims 2, 25 and 29

Claim 2 is also taught by Queen 1990 and Kurrle. As discussed above, claim 2 recites a basic step in humanization, followed by many in the field, including Queen 1990 (Ex. 1050 at 5:36–6:2) and Kurrle (Ex. 1071 at 8:28–29). *See* §VIII.A.2, VIII.B.2 *supra*, Ex. 1003 ¶209. Claim 2 is obvious over Queen 1990 and Kurrle.

Claim 25 recites "wherein the residue at site 69H has been substituted." Residue **69H** was substituted in Kurrle's humanized anti-T-cell receptor antibody. *See* §§VIII.A.1 & 2, *supra*, Ex. 1003 ¶210. Accordingly, claim 25 is also obvious over Queen 1990 and Kurrle.

Claim 29 recites "[a]n antibody comprising the humanized variable domain of claim 1." Queen 1990 and Kurrle created antibodies comprising a humanized variable domain. Ex. 1050 at 6:21–26 ("the humanized light and heavy chains of the present invention will be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen"); *see also* Exs. 1071 at 3:26–28, 2:2–4; 1003 at ¶211. Claim 29 is also obvious over Queen 1990 and Kurrle.

3. Claim 4

Claim 4 recites: "wherein the human antibody variable domain is a consensus human variable domain." Queen 1990 teaches the use of a human consensus variable domain as the human acceptor framework antibody, *see* Ex. 1050 at 12:17–20 ("As acceptor…use a consensus framework from many human antibodies."), which would have motivated a POSITA to use the human "acceptor" framework together with the humanization methods of Kurrle. Ex. 1003 ¶¶132, 212. Claim 4 is also obvious over Queen 1990 and Kurrle.

4. Claim 62

As discussed above, claim 62 differs from claim 1 by adding that the human variable domain is a "consensus human variable domain." *See* §§VII.A, VIII.C.1, *supra*. Queen 1990 discloses the use of a consensus human variable domain in Criterion I. Exs. 1050 at 12:17–20 ("As acceptor…use *a consensus framework* from many human antibodies."); 1003 ¶¶213–214. As discussed above, this would have motivated a POSITA to use the human "acceptor" framework together with the humanization methods of Kurrle. *See* §VIII.C.3, *supra*.

Queen 1990 and Kurrle provided both the motivation and a reasonable expectation of success to make and use the remaining limitations, including substituting at claimed positions **98L** and **36H** (Ex. 1050; §C.1) and **4L**, **69H** and **76H** (Ex. 1071; §B.l). Ex. 1003 ¶214. Claim 62, as for claims 1 and 4 (see §§VIII.C.1 & 2, *supra*), is obvious over Queen 1990 and Kurrle.

5. Claim 63

As discussed above, claim 63 differs from claim 62 by reciting "[a] humanized antibody" and by describing the claimed humanized antibody as lacking "immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient." Both Queen 1990 and Kurrle disclose these features. *See, e.g.*, Exs. 1050 at 1, Abstract ("the humanized immunoglobulins of the present invention *will be substantially non-immunogenic in humans*…"); 1071

at 3:11–12 ("The resulting mAb of the present invention is thus essentially a human antibody with a much lower immunogenicity in patients."); 1003 ¶¶215–218. Claim 63 is obvious over Queen 1990 and Kurrle.

6. Claim 64

Queen 1990 and Kurrle also disclose the limitations of claim 64. Queen 1990 discloses an antibody incorporating a humanized variable domain comprising a consensus sequence. *See* §§VIII.B.2 & 5, *supra*; Exs. 1050 at 12:17–20 ("As acceptor…use *a consensus framework* from many human antibodies."); 1003 ¶¶219–222. Both Queen 1990 and Kurrle also taught humanized antibodies containing a non-human CDR and substituted FR residues. *See*, ***e.g.***, Exs. 1071 at 3:9–11 ("Only the complementarity determing [sic] regions and selected framework amino acids necessary for antigen binding are maintained murine. The remaining framework regions are converted to human sequences."); 1003 ¶219.

While the remaining limitations are merely stated functions of the humanized antibody, *see* §§VIII.A.3, & VIII.B.5 *supra*, both Queen 1990 and Kurrle disclosed that certain framework residues were important because of their proximity to neighboring CDRs. *See* Ex. 1050 at 14:1–12 ("These amino acids are *particularly likely to interact with the amino acids in the CDR's* and, if chosen from the acceptor, distort the donor CDR's and reduce affinity."); *see also* Exs. 1071 at 8:27–29; 1003 ¶220. Queen 1990 and Kurrle provided the motivation

and reasonable expectation of success to make the claimed "humanized variant of a non-human parent antibody." Claim 64 is obvious over Queen 1990 and Kurrle.

7. Claim 66

Both Queen 1990 and Kurrle disclose the claimed "humanized antibody heavy chain variable domain comprising non-human Complementarity Determining Region (CDR) amino acid residues which bind antigen incorporated into a human antibody variable domain," which is also essentially recited in claims 1 and 62. *See* §§VIII.C.1 & 4, *supra*. Claim 66 further requires a framework substitution of one of residues 24H, 73H, 76H, 78H and 93H. Kurrle, using Queen 1990's roadmap, substituted FR amino acids at claimed positions **73H** and **76H**, rendering the humanized antibody "essentially a human antibody with a much lower immunogenicity in patients." Exs. 1071 at 3:11–12; 1003 ¶¶223–224.

Both Queen 1990 and Kurrle provide the motivation and a reasonable expectation of success to make "a humanized antibody variable domain" as in claim 66. Ex. 1003 ¶224. Claim 66 is also obvious over Queen 1990 in view of Kurrle.

8. Claims 67, 71, 72, 75, 76 and 78

Claim 67, which depends from claim 66, recites "wherein 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." Both

Queen 1990 and Kurrle disclosed this additional limitation. *See*, ***e.g.***, Exs. 1050 at 5:36–6:2 (disclosing "substitutions of a human framework amino acid of the acceptor (*i.e.*, human) immunoglobulin with a corresponding amino acid from a donor (*i.e.*, non-human) immunoglobulin."); 1003 ¶225. Claim 67 is also obvious over Queen 1990 and Kurrle.

Claims 71, 72, 75 and 76 recite "wherein the residue at site 73H has been substituted" (***claim 71***), "wherein the residue at site 76H has been substituted" (***claim 72***) "which further comprises an amino acid substitution at site 71H" (***claim 75***), and "which further comprises amino acid substitutions at sites 71H and 73H" (***claim 76***). Kurrle substituted the murine amino acid residues at claimed positions **71H**, **73H** and **76H**. Ex. 1003 ¶226. Thus, claims 71, 72, 75 and 76 are also obvious over Queen 1990 in view of Kurrle.

Claim 78: Claim 78 recites an antibody "comprising the humanized variable domain of claim 66." The goal of humanization, including Queen 1990 and Kurrle, was to create a therapeutic antibody comprising a humanized variable domain: "When combined into an intact antibody, the humanized light and heavy chains of the present invention will be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen." *See* Exs. 1050 at 6:21–26; 1071 at 3:26–28; 1003 ¶227. Indeed, both Queen 1990 and

Kurrle created humanized antibodies. Claim 78 is obvious over Queen 1990 and Kurrle.

9. Claim 69

Claim 69 is dependent on claim 66, and further recites "the human antibody variable domain is a consensus human variable domain." Queen 1990 teaches using a consensus sequence as the human acceptor framework antibody. Exs. 1050 at 12:17–20; 1003 ¶228. As discussed above, this would have motivated a POSITA to use the human "acceptor" framework together with the humanization methods of Kurrle. *See* §VIII.C.3, *supra*. Claim 69 is also obvious over Queen 1990 and Kurrle.

10. Claims 80 and 81

Claim 80 recites the same "humanized antibody variable domain" as claim 1 (***i.e.***, "comprising non-human CDR amino acid residues which bind an antigen…and further comprising a Framework Region (FR) amino acid substitution" at residues which completely overlap with claim 1). Like claim 64, claim 80 further recites functional aspects of the humanized antibody, including: (a) noncovalently binds antigen directly; (b) interacts with a CDR; or (c) participates in the V_L-V_H interface...." Ex. 1003 ¶¶169–171, 229–231, 219–222.

The additional recited elements, which are functions of the substituted residues, do not add anything new to the claim. *See* claim 64, §VIII.C.6; Ex. 1003

¶219; *see also Atlas Powder Co.*, 190 F.3d at 1347. Even assuming one could discount the inherency of these functions (which Pfizer disagrees with), both Queen 1990 and Kurrle teach interaction of the framework residues with the CDR as a reason for substitution. *See* Exs. 1050 at 14:4–8; 1071 at 8:28–29, 32–40; 1003 ¶¶229–231. For the same reasons as claims 1 and 64 above, see §§VIII.C.1 & 6 *supra*, including the disclosure of framework region substitutions at **4L**, **69H, 73H** and **76H** (§§VIII.A.1, VIII.A.3 & VIII.C.1, *supra*), as provided by Kurrle, as well as the explicit motivation and reasonable expectation of success provided by both Queen 1990 and Kurrle (*see* §§VIII.A.1 & B.l), claim 80 of the '213 patent is obvious over Queen 1990 and Kurrle.

Claim 81: Claim 81 recites "wherein 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." Both Queen 1990 and Kurrle teach this. *See* Exs. 1050 at 6:21–26; 1071 at 3:26–28; 1003 ¶232. Claim 81 is also obvious over Queen 1990 and Kurrle.

D. Ground 4: Claim 12 Is Obvious over Queen 1990, Kurrle, and Furey

When humanizing an antibody, a POSITA would have been motivated to identify residues important for antibody binding, *e.g.*, CDR contact residues and residues involved in V_L-V_H interaction. Ex. 1003 ¶¶108, 109, 233–234.

Claim 12, which depends on claim 1, recites "wherein the residue at site 66L has been substituted." Furey disclosed the importance of residue **66L** in maintaining antigen binding and specificity. *See* Exs. 1125 at 3, Abstract; 1003 ¶¶233–235. Specifically, Furey identified 66L as interacting with CDR2 of the light chain. Ex. 1125 at 16, Table 4; Ex. 1003 at ¶234.

This directly ties to Queen 1990's and Kurrle's teachings, which provided a POSITA the motivation and reasonable expectation of success to substitute framework region positions that are close enough to interact directly with antigen, as Furey identified with residue **66L**, which a POSITA would have understood as being on a list of substitutable residues in order to maintain antigen binding and specificity. *See* Exs. 1125 at 16, Table 4; 1003 ¶234. A POSITA looking to humanize an antibody according to the teachings of Queen 1990 and Kurrle (including identifying residues close enough to interact with antigen) would have looked to Furey because it disclosed residues that are close enough to interact directly with antigen. Claim 12 is thus obvious over Queen 1990 and Kurrle, and further in view of Furey.

E. Ground 5: Claims 73 and 77 Are Obvious over Queen 1990, Kurrle and Chothia & Lesk

Claims 73 and 77, which both depend on claim 66, recite "wherein the residue at site 78H has been substituted" (***claim 73***), and "which further comprises amino acid substitutions at sites 71H, 73H and 78H (***claim 77***). As discussed

above, claim 66 is obvious in view of Queen 1990 and Kurrle. *See* §VIII.C.7, *supra*. Further, Chothia & Lesk and Queen 1990 taught residue **78H** was already known as important for maintaining antibody conformation, and thus antigen binding and specificity. *See* Ex. 1062 at 3, Abstract; 1003 ¶236. Chothia & Lesk found that "[t]he major determinants of the tertiary structure of the framework are the residues buried within and between the [V_L and V_H] domains," including residue **78H**. Exs. 1062 at 5, 8, Table 4; 1003 ¶¶237–38.

The Background of the '213 patent also recognized the importance of Chothia & Lesk's findings. *See* Ex. 1001 at 3:1–8 (citing to Chothia & Lesk for determining residues "critically affecting the conformation of particular CDRs and thus their contribution to antigen binding."). The inventors of the '213 patent did not discover the importance of residue **78H** for maintaining antigen binding. Ex. 1003 ¶237.

In view of the known importance of **78H** (*i.e.*, the teachings of Queen 1990 and Chothia & Lesk), it would have been obvious for a POSITA to have included **78H** as a substitutable residue. *Id*. ¶238. Claim 73 is obvious over Queen 1990, Kurrle and Chothia & Lesk.

Further, adding residue **78H** to the combination of residues **71H** and **73H** does not confer patentability. *Id*. ¶238. These residues were substituted (**71H** and

73H) in Kurrle, or would have been substituted (**78H**) if necessary. *Id*. Claim 77 is also obvious over Queen 1990, Kurrle and Chothia & Lesk.

F. Ground 6: Claim 74 Is Obvious over Queen 1990, Kurrle and Chothia 1985

Claim 74, which also depends on claim 66, recites "wherein the residue at site 93H has been substituted." As discussed above, claim 66 is obvious in view of Queen 1990 and Kurrle. *See* §VIII.C.7, *supra*. Further, Chothia 1985 identified residue **93H** as important for maintaining V_L-V_H interactions. *See* Exs. 1063 at 12, Table 4; 1003 ¶¶239–40. The inventors of the '213 patent and others recognized the importance of residues that maintain V_L-V_H interface contact. *See* Ex. 1001 at 3:1–8, *supra*, *see also* Ex. 1050 at 16:1–2 (recognizing the importance of "residues essential for inter-chain interactions"). Thus, Kurrle and Queen 1990 provided the explicit motivation as well as reasonable expectation of success to substitute residue **93H** for the non-human (*e.g.*, murine) residue, and thus made obvious that residue **93H** would have been substituted. Ex. 1003 ¶¶239–40. Claim 74 is obvious over Queen 1990, Kurrle and Chothia 1985.

G. Ground 7: Claims 79 and 65 Are Obvious over Queen 1990, Kurrle, Chothia & Lesk and Chothia 1985

Claim 79 recites "a humanized variant of a non-human parent antibody which binds an antigen, wherein the humanized variant comprises Complementarity Determining Region (CDR) amino acid residues of the non-

human parent antibody incorporated into a human antibody variable domain, and further comprises Framework Region (FR) substitutions at heavy chain positions 71H, 73H, 78H and 93H, utilizing the numbering system set forth in Kabat."

As above, Kurrle already substituted positions **71H** and **73H** and it would have been obvious to a POSITA to have incorporated the teachings of Queen 1990 when humanizing the antibody or Kurrle in order to ensure successful humanization. *See* Exs. 1071 at 26, Table 6B; 1003 ¶242, 1003D; §VIII.C.1. Chothia 1985 disclosed residue **93H** as important for maintaining V_L:V_H interactions. Exs. 1063 at 12, Table 4; 1003 ¶¶242–243, 243. Finally, Chothia & Lesk disclosed residue **78H** as one specifically and independently important for maintaining antigen binding. Exs. 1062 at 8, Table 4; 1003 ¶242–243. It would have been obvious to a POSITA to have made substitutions at **71H**, **73H**, **78H** and **93H**, as taught by Queen 1990, Kurrle, Chothia & Lesk and Chothia 1985. *See* §§VIII.A.4, VIII.C.1 & VIII.C.8, *supra*, Ex. 1003 ¶¶241–246. Claim 79 is obvious over Queen 1990 and Kurrle, and further in view of Chothia & Lesk and Chothia 1985.

Claim 65 depends from claim 79, and recites the humanized variant "binds the antigen up to 3-fold more in the binding affinity than the parent antibody binds antigen." Queen 1990 stated "affinity levels can vary…and may be *within about 4 fold* of the donor immunoglobulin's original affinity to the antigen." *See* Ex. 1050

at 6:26–28 (emphasis added). Queen 1990 thus taught that a humanized antibody would have been expected to be "within about 4-fold" in affinity as the original mouse antibody, disclosing a greater increase in affinity than the 3-fold increase recited in claim 65. The range of increase in affinity disclosed in Queen 1990 therefore encompasses the range recited in claim 65. A prior art reference that discloses a range encompassing a narrower claimed range is sufficient to establish a prima facie case of obviousness. *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003); *see also* MPEP § 2144.05. Ex. 1003 ¶¶247–251.

Moreover, Dr. Foote explained that to a POSITA, "it was the expectation when humanizing antibodies…that a similar affinity, *i.e.*, slightly better or worse, would be obtained as compared to the parent (mouse) antibody. Thus…it would not have been unexpected that at least a moderate improvement in affinity would be achieved when humanizing some antibodies." Ex. 1003 ¶308. Dr. Foote further explains that "it was not unexpected [that in this process] one could go beyond the parent antibody's original affinity, *i.e.*, an increase in affinity as claimed in claim 65." *Id*. ¶309. Claim 65 is obvious over Queen 1990 and Kurrle, and further in view of Chothia & Lesk and Chothia 1985.

H. Ground 8: Claims 30–31, 33 and 42 Are Obvious over Queen 1990 in View of Hudziak

Independent ***Claim 30*** of the '213 patent recites "[a]n antibody which binds $p185^{HER2}$ and comprises a humanized antibody variable domain, wherein the

humanized antibody variable domain comprises non-human Complementarity Determining Region (CDR) amino acid residues which bind $p185^{HER2}$ incorporated into a human antibody variable domain and further comprises a Framework Region (FR) amino acid substitution at a site selected from the group consisting of: 4L, 38L, 43L, 44L, 46L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, 75H, 76H, 78H and 92H, utilizing the numbering system set forth in Kabat." ***Claim 42*** depends from claim 30, and further recites "wherein the residue at site 66L has been substituted."

Claim 30 is similar to claim 1, differing in the recitation that the CDRs (and antibody) also bind to $p185^{HER2}$. Claim 30 also includes additional framework sites for substitution at positions 46L, 75H and 76H.

Antibody humanization was developed for a single purpose: realizing the "therapeutic promise of monoclonal antibodies for the treatment of human diseases." Exs. 1003 ¶330; Ex. 1004 ¶¶35–45. While murine monoclonal antibodies were capable of targeting antigens (*e.g.*, proteins) in a highly specific manner, immunogenicity issues severely limited the applicability of this technology to human therapeutics. *See* Exs. 1003 ¶330; Ex. 1004 ¶37.

A prime molecular target was HER*2/c-erbB-2*, whose amplification in breast cancer patients was correlated with poor prognosis and high relapse rate. *See*

Exs. 1021 at 8, Abstract,; 1004 ¶¶46–69; 1003 ¶¶331–332. With respect to the HER*2/c-erbB-2* gene product p185^{HER2}, Hudziak reported that:

- p185^{HER2} was amplified in about 30% of breast cancer tumors; Exs. 1021 at 8; 1004 ¶50; 1003 ¶331;
- p185^{HER2} "correlated with a negative prognosis and high probability of relapse"; Exs. 1021 at 8; 1004 ¶50; 1003 ¶331;
- Increased expression of HER-2/*neu* resulted in cellular transformation of the cells and tumorigenesis when the transformed cells were implanted in athymic mice, Exs. 1021 at 8; 1004 ¶52; 1003 ¶331; and
- High levels of HER-2 gene expression resulted in the cells forming anchorage-independent colonies in soft agar and at low density in low serum concentration, which are characteristics of a transformed phenotype, Exs. 1021 at 8; 1004 ¶58; 1003 ¶331.

In reviewing Hudziak (Ex. 1021) and other literature, Mr. Buss concluded the above findings "strongly suggested that the HER-2/*neu* receptor was a ripe target for therapeutic development." Exs. 1004 ¶53; 1003 ¶¶331–332; 342.

Moreover, a POSITA would have been motivated to develop a monoclonal antibody therapeutic against p185^{HER2} because of its structural similarity to other growth factor receptors, including epidermal growth factor receptor (EGFR). *See* Exs. 1004 ¶56; 1003 ¶333. This similarity was demonstrated well prior to

June 1991 for 4D5, a well-characterized mouse monoclonal antibody targeting $p185^{HER2}$ protein with high affinity, specificity (no cross-reactivity with, for example, EGFR) and efficacy in *in vitro* and *in vivo* studies. Exs. 1004 ¶58; 1003 ¶334. The investigators concluded that 4D5 provided "new potential for diagnostic approaches and therapeutic strategies for treatment of human malignancies." Exs. 1047 at 6; 1004 ¶53; 1003 ¶334.

Given published accounts regarding other monoclonal antibody humanization efforts, and the strength of 4D5 as a clinical target, the logical and necessary next step would have been to humanize 4D5. Exs. 1004 ¶70; 1003 ¶334. Hudziak urged artisans to follow precisely this path:

> The muMAb *4D5 also serves as a template for antibody engineering efforts to construct humanized versions* more suitable for chronic therapy or other molecules which may be directly cytotoxic for tumor cells overexpressing the HER2 protooncogene.

Exs. 1048 at 12; 1004 ¶68 (emphasis added).

Queen 1990 provided detailed steps for humanizing mouse monoclonal antibodies, such as 4D5, and represented the state of the art of antibody humanization by 1991, teaching humanization of antibody variable domains having non-human CDR amino acid residues that bind to an antigen and are incorporated into a human antibody variable framework domain. Ex. 1003 ¶¶131–37, 343.

Further, Queen 1990 disclosed that a POSITA would have had a reasonable expectation that such a humanized antibody would be capable of binding to $p185^{HER2}$. *See* Exs. 1050 at 1, Abstract ("the humanized immunoglobulins of the present invention will be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen…"); 1003 ¶343.

Queen 1990, thus, provided the explicit motivation to make framework substitutions that would, for example, be more representative of a human residue (Ex. 1050 at 13:22–37), residues that are "immediately adjacent" to CDRs that "likely [] interact with…the CDR's…" (*id.* at 14:1–12), and residues that are "in contact", *i.e.*, within about 3 Å of a CDR (*id.* at 14:14–15:2). Ex. 1003 ¶¶131–137.

Hudziak provided explicit motivation to develop 4D5 for therapeutic use, disclosing "monoclonal antibodies specific for $p185^{HER2}$ (*e.g.*, 4D5) [as] useful therapeutic agents for the treatment of human neoplasias." *See* Exs. 1021 at 14; 1003 ¶¶342–345, ; 1004 ¶63. A POSITA would have recognized in June 1991, that 4D5 required humanization before clinical use. *See* Exs. 1048 at 12 ("4D5 also serves as a template for antibody engineering efforts to construct humanized versions more suitable for chronic therapy …"); 1003 ¶¶342–343, 334–336; 1004 ¶68. Therefore, it would have been obvious to humanize 4D5 using the guidelines in Queen 1990. As discussed in §§VII.F.2 & VII.F.3, and VIII.B.1, *supra*, the

particular residues to modify would have included at least **66L**, **98L** and **36H** which likewise appear in claims 30 and 42. Claims 30 and 42 are obvious over Queen 1990 and Hudziak.

Claim 31 recites 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." Queen 1990 disclosed this limitation. *See* Exs. 1050 at 3:36–4:1; 1003 ¶¶131–37, 344; claim 2 §VIII.B.2. Claim 31 is also obvious over Queen 1990 and Hudziak.

Claim 33 further adds that "the human antibody variable domain is a consensus human variable domain," which Queen 1990 also disclosed. *See* Exs. 1050 at 12:17–20 ("As acceptor…use a consensus framework from many human antibodies"); 1003 ¶¶131–37, 345. Claim 33 is also obvious over Queen 1990 and Hudziak.

I. Ground 9: Claim 42 Is Obvious over Queen 1990, Hudziak and Furey

Claim 42, which depends on claim 30, recites "wherein the residue at site 66L has been substituted." Claim 30 is obvious in view of Queen 1990 and Hudziak. *See* §VIII.H. Furey disclosed that residue **66L** forms a hydrogen bond contact with CDR2 of the light chain. *See* Exs. 1125 at 16, Table 4; 1003 ¶¶346–48. Following the detailed roadmap of Queen 1990, a POSITA would have recognized Furey's particular emphasis on 66L to improve binding affinity would

have placed residue 66L on a short list of substitutable residues when humanizing 4D5. Ex. 1003 ¶¶346– 48. Thus, claim 42 is obvious over Queen 1990, Hudziak, and Furey.

J. Ground 10: Claim 60 Is Obvious over Queen 1990, Hudziak and Chothia & Lesk

Claim 60, which also depends on claim 30, recites "wherein the residue at site 78H has been substituted." Chothia & Lesk disclosed a small universe of residues which are "primarily responsible for the main-chain conformations of the hypervariable regions" (*i.e.*, maintaining CDR conformation as Queen 1990 taught), including residue **78H**. *See* Exs. 1062 at 1, Abstract, 8, Table 4; 1003 ¶349. Following the detailed roadmap of Queen 1990, a POSITA would have looked to Chothia & Lesk and identified FR positions that could interact with or influence CDR conformation, and antigen binding and specificity, including residue **78H**. Ex. 1003 ¶349. Claim 60 is obvious over Queen 1990, Hudziak and Chothia & Lesk.

K. Secondary Considerations Cannot Overcome Obviousness

Patent Owner may attempt to assert secondary considerations of nonobviousness, despite no showing of such in the patent. Such evidence would be "insufficient" to "overcome the strong [case] of obviousness" here. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007). Patent Owner cannot show the required nexus between any purportedly novel feature and any secondary

consideration. *See*, *e.g.*, *Merck & Co. v. Teva Pharms. USA*, 395 F.3d 1364, 1376 (Fed. Cir. 2005); *see also Torrent Pharms. Ltd. v. Novartis AG*, 2015 WL 5719630, IPR2014–00784 at 12 (PTAB Sep. 24, 2015) ("If objective indicia of nonobviousness are 'due to an element in the prior art, no nexus exists'") (citing to *Tokai Corp. v. Easton Enters, Inc.*, 632 F.3d 1358, 1369 (Fed. Cir. 2011)). Patent Owner cannot show secondary considerations are commensurate with claim scope given the extraordinary breadth of the challenged claims here. *See*, *e.g.*, *Ex Parte Takeshi Shimono*, 2015 WL 1952506, Appeal 2013–003410 (PTAB Apr. 29, 2015). Pfizer nonetheless preliminarily addresses potential Patent Owner theories below.

1. The Challenged Claims Produced No Relevant Unexpected Results

During prosecution, Genentech argued that the claimed methods achieved unexpected results. *See, e.g.*, Ex. 1002, Vol. 7 at 3431–37. Specifically, Genentech stated:

> The unexpected properties…include: lack of significant immunogenicity of the claimed humanized antibodies upon repeated administration to a human patient, e.g., to treat a chronic disease in the patient…

Id. at 3431.

But Genentech's arguments are not reasonably commensurate with the full scope of the Challenged Claims. *See Ex Parte Takeshi Shimono*, 2015 WL 1952506, at *4 ("Evidence of secondary considerations must be reasonably commensurate with the scope of the claims," *citing In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011)). Only challenged claim 63 even mentions immunogenicity and none recites a method. Ex. 1001 at 88:36–38 (claim 63: "humanized antibody which lacks immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient"). Claim 63 does not require a "lack of ***significant*** immunogenicity."

Genentech also argued that:

> The unexpected properties…include…binding affinities superior to those of the non-human parent antibody; and the ability to use the same consensus human variable domain to make many strong affinity antibodies, thus avoiding tailoring each human FR to each non-human antibody to be humanized.

Id. at 3431.

But only challenged dependent claim 65 even mentions binding affinity. ***Id.*** at 88:63–65 (claim 65: "The humanized variant of claim 63 which binds the antigen up to 3-fold more in the binding affinity than the parent antibody binds antigen."). Further, ***no Challenged Claim*** requires "use of the same consensus

human variable domain" or the making of "many strong affinity antibodies." Moreover, this argument appears to relate to a ***method*** of making numerous antibodies as opposed to the ***products*** recited in the Challenged Claims. *See In re Kubin*, 561 F.3d 1351, 1356 (Fed. Cir. 2009) ("the obviousness inquiry requires this court to review the Board's decision that the claimed sequence, not appellants' unclaimed cloning technique, is obvious.").

These properties were also not unexpected based on the teachings of the prior art. For example, the '213 patent recognizes with respect to affinity that residues important for maintaining CDR conformation and binding were well known prior to June 1991. *See* Exs. 1001 at 2:63–3:8; 1003 ¶¶110–6, 280, 347–348. In addition, Dr. Foote observes that a modest increase in binding affinity (which is all claim 65 requires) was not unexpected given the prior art. Ex. 1003 ¶¶248–250, 307–308. Indeed, Queen 1990 taught that an increase in affinity would have been expected. Exs. 1050 at 6:26–28 ("[A]ffinity levels can vary…and may be within about 4 fold of the donor immunoglobulin's original affinity to the antigen.").

Successful antibody humanization was readily achievable, not surprising or unexpected, as of the earliest priority date of the '213 patent. Exs. 1003 ¶350–351; 1004 ¶¶38–45, 68–70.

2. The ’213 Patent Satisfied No Long-Felt but Unmet Need

There was no long-felt but unmet need for humanized mouse monoclonal antibody 4D5. First, the full scope of the Challenged Claims exceeds antibody 4D5. Further, if 4D5 satisfied any need, the mouse monoclonal antibody 4D5 disclosures, which claimed and disclosed the original mouse monoclonal antibody, satisfied it. *See*, *e.g.*, Exs. 1096; 1003 at ¶352.

Patent Owner cannot even show the purported invention solved the problem that the specification identified. *See*, *e.g.*, *Norgren Inc. v. ITC*, 699 F.3d 1317, 1324 n.12 (Fed. Cir. 2012) (patent obvious where “[prior art patent] solved similar problems in a similar way.”); *see also In re PepperBall Techs.*, Inc., 469 F. App’x 878, 882–83 (Fed. Cir. 2012). The ’213 patent’s purported problem was that “[m]ethods are needed for rationalizing the selection of sites for substitution in preparing [humanized] antibodies” and claimed their invention could provide methods “for the preparation of antibodies that are less antigenic in humans…but have desired antigen binding.” Ex. 1001 at 3:53–55, 4:24–35. Queen 1990, Kurrle and others had already described exactly this process—they set forth why one would desire to humanize and provided detailed roadmaps on how to achieve it. Any problems identified in the ’213 specification had already been solved and addressed by the prior art. Ex. 1003 ¶¶350–52.

3. No Nexus Between Commercial Success of Genentech Drugs and the Challenged Claims

The Board has explained that "evidence of commercial success is 'only significant if there is a nexus between the claimed invention and the commercial success.'" IPR2014-00652 Final Written Decision at 35, citing *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311–12 (Fed. Cir. 2006). Further:

> [t]o establish a nexus between a claimed invention and the commercial success of a product, there must be "proof that the sales [of the allegedly successful product] were a direct result of the unique characteristics of the claimed invention—as opposed to other economic and commercial factors unrelated to the quality of the patented subject matter."

Id. at 35–36.

Any commercial success of drugs Genentech sells is not a direct result of the Challenged Claims. Indeed, important features of these drugs are not recited in the Challenged Claims, only three of which include more than a single residue substitution. As an example, Genentech's marketed drug Herceptin® has heavy chain residue substitutions at seven positions: 71H, 73H, 78H, 93H, 55L, 66L, and 102L. None of the Challenged Claims recite substitutions at these seven positions. In fact, positions 55L and 102L do not even appear in the '213 patent. Genentech will be unable to show that the claimed features resulted in the commercial success of Herceptin®.

Moreover, any alleged commercial success of Genentech's drugs is not commensurate with the full scope of the Challenged Claims because they are not limited to any particular antibody or even any particular class of antibodies. Ex. 1003 ¶353. Even claim 30—which recites that the antibody binds $p185^{HER2}$—is exceptionally broad and not limited to any specific anti-$p185^{HER2}$ antibodies.

IX. CONCLUSION

Pfizer respectfully requests IPR of the Challenged Claims.

Date: May 24, 2017

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CERTIFICATE OF COMPLIANCE

This Petition complies with the type-volume limitations as mandated in 37 C.F.R § 42.24, totaling 13,888 words. Counsel has relied upon the word count feature provided by Microsoft Word.

/Amanda Hollis/
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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 6,407,213, along will all exhibits and other supporting documents, were served on May 24, 2017, via FedEx Overnight delivery directed to the assignee for the patent and correspondence address of record as follows:

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