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BEFORE THE PATENT TRIAL AND APPEAL BOARD

.

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.
Petitioner,
v.

GENENTECH, INC.
Patent Owner.

IPR2017-02031
U.S. Patent No. 6,407,213

Title: METHOD FOR MAKING HUMANIZED ANTIBODIES

PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 6,407,213 B1

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1001	U.S. Patent No. 6,407,213, *Method for making humanized antibodies* (filed Jul. 17, 1993) (issued June 18, 2002)
1002	File History for U.S. Patent No. 6,407,213 (9 volumes)
1003	Declaration of Dr. Geoffrey Hale, Ph.D. in Support of Petition for *Inter Partes* Review of Patent No. 6,407,213
1003A	*Curriculum Vitae* of Dr. Geoffrey Hale, Ph.D.
1003B	Materials Reviewed by Dr. Geoffrey Hale, Ph.D.
1003C	Exhibits A-R of Dr. Geoffrey Hale, Ph.D.
1004	Intentionally left blank
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1123	U.S. Patent No. 5,889,157 *HumanizedB3 Antibody Fragments, Fusion Proteins, and Uses Thereof* (humanization of monoclonal antibodies to Lewis -related carbohydrate antigen) (Filed October 28, 1994) (Issued March 30, 1999)
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I. INTRODUCTION

Pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42, Boehringer Ingelheim Pharmaceuticals, Inc. ("Boehringer") petitions for *Inter Partes* Review ("IPR") of claims 1, 2, 4, 25, 29, 62-64, 66, 67, 69, 71-73, 75-78, and 80-81 of U.S. Patent No. 6,407,213 to Carter, titled "Method for Making Humanized Antibodies" ("the '213 patent," Ex._1001). With this Petition is a Power of Attorney under 37 C.F.R. §42.10(b); and under 37 C.F.R. §42.103, the §42.15(a) fee. The Commissioner is authorized to charge all fees due to Attorney Deposit Account 506989.

The challenged claims are unpatentable because they would have been anticipated by or obvious from prior art that disclosed humanized antibodies, including the disclosures in EP0403156 ("Kurrle") [Ex._1071], PCT Application No. WO 90/07861 to Queen ("Queen 1990") [Ex._1050], and Jones [Ex._1033]. The challenged claims are also obvious in view of Chothia & Lesk [Ex._1062].

II. MANDATORY NOTICES

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

The real parties-in-interest for Petitioner are: Boehringer Ingelheim GmbH, Boehringer Ingelheim Corporate Center GmbH; Boehringer Ingelheim Pharma GmbH & Co. KG; Boehringer Ingelheim International GmbH; Boehringer Ingelheim USA Corporation; and Boehringer Ingelheim Pharmaceuticals, Inc.

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

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 also aware of two current IPR proceedings for the ’213 patent, both filed by third-party Pfizer, Inc.: IPR2017-01488 and IPR2017-01489. The present IPR petitions offer different arguments from the previously-filed IPR petitions.

Petitioner is not aware of any other judicial or administrative matters that would affect, or be affected by, a decision in this proceeding.

C. Identification of Counsel (37 C.F.R. § 42.8(b)(3)) and Service Information (37 C.F.R. § 42.8(b)(4))

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III. GROUNDS FOR STANDING AND PROCEDURAL STATEMENT

Pursuant to 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.

IV. IDENTIFICATION OF CHALLENGE AND STATEMENT OF THE PRECISE RELIEF REQUESTED

Petitioner requests IPR and cancellation of claims 1, 2, 4, 25, 29, 62-64, 66, 67, 69, 71-73, 75-78, and 80-81 of the '213 patent under pre-AIA 35 U.S.C. §§ 102 and 103, as Petitioner's detailed statement of the reasons for the relief requested sets forth below. Under 37 C.F.R. § 42.6(c), Petitioner provides exhibit copies, and the Declaration of Dr. Geoffrey Hale, Ph.D. (Ex._1003).

Dr. Geoffrey Hale received his Ph.D. in Biochemistry at the University of Cambridge in the U.K. in 1977. In 1986 Dr. Hale collaborated with Professor Waldmann and Sir Gregory Winter to select Campath-1G, an antibody Dr. Hale had developed, as the first therapeutic antibody to be humanized. Ex._1003 at ¶3. His work resulted in numerous publications and patents in his field. Ex._1003A.

The challenged claims generally involve humanized antibodies and humanized antibody variable domains. Ex._1003 at ¶¶36-56. The claims are unpatentable as follows:

Ground	Claims and Basis
1	Claims 1-2, 25, 29, 63, 66, 71, 75-76, 78, 80-81, anticipated by Kurrle
2	Claims 1-2, 4, 29, 62-64, 80-81, anticipated by Queen 1990
3	Claims 1-2, 4, 25, 29, 62-64, 66-67, 69, 71-72, 75-76, 78, 80-81 as obvious over Queen 1990 and Kurrle
4	Claims 1-2, 4, 25, 29, 62, 64, 66, 69, 71, 73, 75-78, 80 and 81, anticipated by Jones
5	Claims 73 and 77 as obvious over Queen 1990 and Kurrle, and also in view of Chothia & Lesk
6	Claim 63 is anticipated by Jones, or optionally obvious over Jones in view of Riechmann

V. STATEMENT OF REASONS FOR THE RELIEF REQUESTED

An IPR petition 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.

A. Summary of the Argument

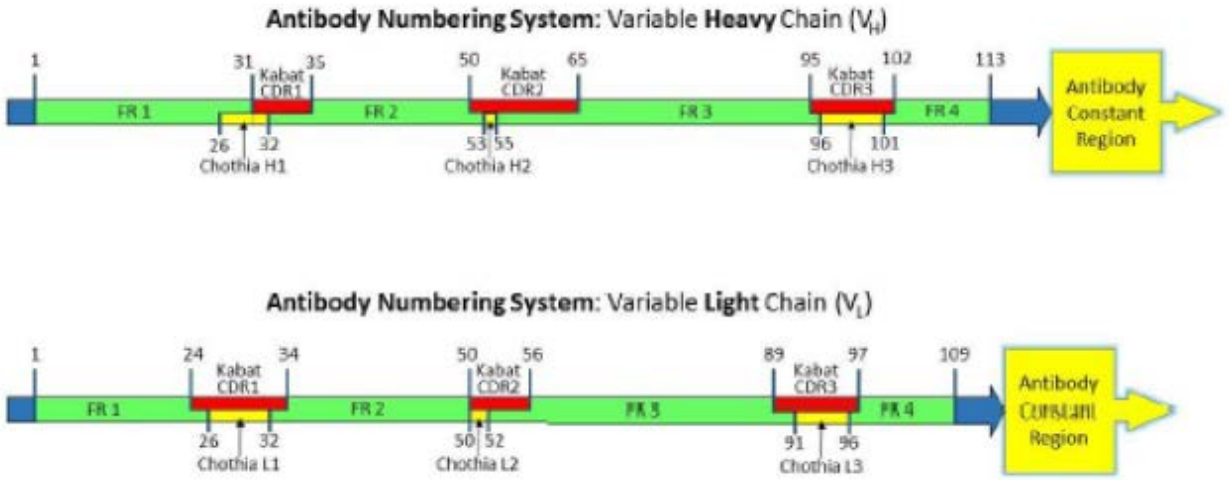
In 1975, *Nature* published a groundbreaking study manufacturing "predefined specific antibodies by means of permanent tissue culture cell lines." Ex._1022 at 1. Mouse monoclonal antibodies exhibited therapeutic and diagnostic promise, but use in patients elicited a human anti-mouse-antibody (HAMA) immunogenicity response. Ex._1003 at ¶¶63-65.

To neutralize the HAMA response, mouse antibodies were first re-engineered to make them "more human" by replacing parts of the mouse antibody with human counterparts. First generation (early-1980s) versions replaced the mouse antibody's constant regions with corresponding human antibody residues. Ex._1003 at ¶¶82-84. While "chimeric" antibodies retained the mouse's affinity and specificity, patients still experienced HAMA responses. Next, scientists replaced mouse variable domain framework regions (FR) flanking the complementarity determining regions (CDR) with human sequences ("CDR grafting"). Ex._1003 at ¶85; *see also* Ex_1033 (Jones).

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 switching select residues in the human FRs back to the mouse residues. Ex._1003 at ¶¶85-105. These techniques were well-known and well mapped-out prior to the earliest priority date (June 14, 1991) of the '213 patent. *Id.* at 1107. 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**;**76H**. 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 ¶¶144-164.

Queen 1990 established a humanization roadmap with four specific yet universal criteria for producing humanized antibodies from non-human monoclonal antibodies. This included substituting human residues for the mouse monoclonal antibody residue in the FRs "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 [Ex._1003 at ¶¶66-84, 137-138; 139-141]:



These defined FR/CDR border positions would have readily allowed a POSA, given Queen 1990's instruction to substitute CDR-adjacent FR residues, to identify at least claimed residues **36H** and **98L** *(see* claims

1;2;4;29;62;65;64;80;81). Queen 1990 thus anticipates at least claims 1;2;4;29;62;64;80;81 of the '213 patent. Ex._1003 at ¶¶165-191.

Moreover, all challenged claims—whether, *e.g.*, they broadly or more specifically list residues or properties, or particular antibodies to humanize—are obvious given the prior art, including Queen 1990; Kurrle; and others. Ex._1003 at ¶¶192-227. The prior art taught the importance of specific claimed residues and their predicted contribution to antigen binding, including **78H**. Ex._1003 at ¶¶100, 108-115. The inclusion of these specific modifications in the challenged claims was not a patentable advance. Given Queen 1990 and Kurrle, alone or in combination with other references as detailed below, the challenged '213 patent claims would have been obvious.

Finally, the claims of the '213 patent are drafted so broadly as to encompass humanized antibodies formed by simple CDR-grafting as taught at least by Jones, so long as the humanized variable domains vary from the consensus framework regions at the sites recited in the claims. For example, Claim 1 is directed to a humanized antibody variable domain "comprising a Framework Region (FR) amino acid substitution at a site selected from the group consisting of: 4L;3SL;43L;44L;SSL;62L;6SL;66L;67L;6SL;69L;73L;SSL;9SL;2H;4H;36H;39H; 43H;4SH;69H;70H;74H;92H, utilizing the numbering system set forth in Kabat." Although claim 1 does not specify that the substitutions must be made to a

consensus sequence, Claim 4 depends from claim 1 and further requires that "the human antibody variable domain is a consensus human variable domain." Because claim 1 requires substitutions in the variable domain, claim 4 must also require substitutions in the variable domain. Claim 4 therefore encompasses humanized antibody variable domains where only *some* of the residues in the sequence are "consensus" residues, and where other, non-consensus residues are "substitutions" in the consensus sequence. A prior art antibody that anticipates claim 4 also anticipates claim 1.

However, for a prior art antibody to anticipate claim 4, the non-consensus residues need not have been intentionally "substituted." The claims of the '213 patent are directed to products, not processes. *See, e.g.*, '213 patent claim 1, directed to "[a] humanized antibody variable domain." Whether an amino acid is present in a sequence because it occurs there naturally or is deliberately inserted through a step of "substitution" does not affect the final amino acid sequence or structure. Ex._1003 at ¶221. Therefore, the requirement for "substitution" in the amino acid sequence is not a structural limitation, but a process limitation of a product-by-process claim that should be disregarded in the patentability analysis. *See, e.g., Purdue Pharma L.P. v. Epic Pharma, LLC*, 811 F.3d 1345, 1353-54 (Fed. Cir. 2016) (finding that "derived from 8α[ ]" was a process limitation in a product-by-process claim and should be disregarded in the patentability analysis). Thus, a

prior art antibody prepared by a different process, but with the same sequence (and thus structure/function) as an antibody prepared according to the claims of the ’213 patent, would anticipate those claims. *See id*. at 1354; *see also In re Thorpe*, 777 F.2d 695, 697 (Fed.Cir.1985) (“If the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.”). Because Jones discloses such a prior art antibody, and as explained in further detail below, Jones anticipates claims 1-2;4;25;29;62-64;66;6971;73;75-78;80-81.

B. ’213 Patent—Background

1. The ’213 Patent

The ’213 patent issued June 18, 2002 from a continuation-in-part of an earlier-abandoned U.S. Appl. 07/715,272 (filed June 14, 1991). For purposes of this IPR only, Petitioner will assume that the ’213 patent claims are entitled to a priority date of June 14, 1991, the ’213’s earliest possible priority date.

The ’213 patent issued with 82 claims. Ex._1001 at 85:44-90:32. Claims 1, 30, 62-64, 66, 79 and 80 are independent claims, and all claim an antibody comprising a “non-human . . . CDR” and a “Framework Region [FR] amino acid substitution” reverting substituted human framework residues back to, *e.g.,* mouse, at “a site selected from the group consisting of” certain recited residues. **Claim 1** chooses from 14 FR light chain residues

(4L;38L;43L;44L;58L;62L;65L;66L;67L;68L;69L;73L;85L;98L); and 10 heavy chain residues (2H;4H;36H;39H;43H;45H;69H;70H;74H;92H) under Kabat's numbering system. **Claims 30**, **62** and **63** add 4 FR residues to claim 1's list (46L;75H;76H;78H). Claim 30's antibody "binds $p185^{HER2}$ and comprises a humanized antibody variable domain"; and 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.

Claim 66 offers a different list of 5 FR residues: 24H;73H;76H;78H;93H. **Claim 79** lists 4 FR substitutions at heavy chain positions: 71H;73H;78H;93H. **Claim 80** claims the residues of claim 1 plus the 5 residues from claim 66, and adds that the FR amino acid substitution: "(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 64's "humanized variant of a non-human parent antibody" includes "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 [CDRs] thereof comprise non-human antibody amino acid residues, and further comprises a [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."

The dependent claims recite specific residues (claims 12;25;42;60;71-77; claims 75-77 further add a substitution at residue 71H); that the substituted humanized antibody residue is "found at the corresponding location of the non-human antibody from which the non-human CDR amino acid residues are obtained" (claims 2;31;67;81); that the human antibody variable domain is a "consensus" domain (claims 4;33;69); or an antibody comprising the claimed humanized variable of claims 1 or 66 (claim 29 and claim 78, respectively).

The patent specification's humanization concepts were neither new nor unknown. The patent acknowledges the well-known principle that function depends on 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 past "molecular modeling" had "increase[d] the antigen binding affinity of a humanized antibody." *Id.* at 3:44-48. The '213 patent applies the same cloning and analysis tools and techniques that Kurrle [Ex._1071], Queen 1990 [Ex._1050], and Jones [Ex._1033] described, including site-directed mutagenesis, molecular modeling, and antibody functionality analysis.

2. Brief Overview of the '213 Patent's Prosecution History and Related PTO Proceedings

'206 Application Prosecution. The '213 patent issued from Application No. 08/146,206 ("'206 application"). During prosecution, the PTO rejected the pending claims for anticipation, obviousness, lack of written description, lack of enablement, indefiniteness and non-statutory obviousness-type-double-patenting. The PTO cited Queen 1989 [Ex._1034] and Kabat 1987 [Ex._1052], asserted in the concurrently-filed petition.

The examiner also raised Queen Patents 5,530,101 ("the '101 patent") and 5,693,762 ("the '762 patent") as § 102(e) references. Among other things, the examiner pointed out that the '101 patent disclosed antibody species with a number of claimed amino acid substitutions, including at recited position 73H. *See*, *e.g.*, Ex._1002 at 739-740. However, Genentech ultimately provided an affidavit signed by inventors Carter and Presta, swearing behind the September 1990 priority date of the '762 and '101 patents. *Id*. at 793, 802-807. They provided pages from a laboratory notebook disclosing proposed sequences for a humanized 4D5 antibody, relying on consensus sequences and at least one substitution at site 73H. *Id*.

The claims were then allowed.

Interference with Application No. 11/284,261. Applicants for Application No. 11/284,261 ("Adair") requested an interference with the '213 patent, regarding claims to humanized antibodies with non-human substitutions at specific variable domain framework positions. The Board declared the interference,

Declaration of Interference at 4 [Ex._1095], but the Board determined that Adair's claim in interference was barred under 35 U.S.C. § 135(b)(1). Decision on Motions at 9-10 [Ex._1095 at 1588-89], aff'd *Adair v. Carter,* 101 U.S.P.Q.2d 1625, 1630 (Fed. Cir. 2012). Ex._1095.

C. Level of Ordinary Skill in the Art

The invention's field involves humanizing non-human antibodies. A POSA[1] would have held a Ph.D. or equivalent in chemistry, biological chemistry, structural biology or a closely related field, or an M.D. with practical academic or industrial experience in the production of recombinant proteins. *See*, *e.g.*, Ex._1003 at ¶¶24-26. Such experience could include, *e.g.*, 3-D computer modeling of immunoglobulin structures, antibody domain and sequence manipulation and swapping, CDR grafting and framework substitution in humanizing antibodies, construction and expression of recombinant antibodies, antibody binding (specificity and affinity) testing, and immunogenicity testing. *Id.* Such person may have consulted with one or more other experienced professionals to develop a humanized monoclonal antibody for therapeutic use, to select non-human

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

monoclonal antibodies (such as a mouse monoclonal antibody) for humanization, and subsequent testing of the humanized antibody and its intermediates. *Id.*

D. Claim Construction

In an IPR, patent claims are given their "broadest reasonable construction in light of the specification of the patent." 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs. LLC v. Lee,* 136 S. Ct. 2131, 2142 (2016). For purposes of this IPR only, Petitioner adopts the following constructions of each respective term.[2]

"***A Humanized Antibody Variable Domain" (Claims 1, 62 and 80), or "A Humanized Antibody" (Claim 63), "A Humanized Variant of a Non-Human Parent Antibody" (Claim 64) or "A Humanized Antibody Heavy Chain Variable Domain" (Claim 64)***. The independent claims each contain a variation of the preamble phrase, "A Humanized Antibody" set forth above.[3] A POSA would understand "a humanized antibody" to include an antibody or antibody fragment

[2] Boehringer does not concede that the claims can be construed to achieve reasonable certainty. Boehringer explicitly does not waive any argument or invalidity position under 35 U.S.C. § 112, or any other invalidity position not presented herein.

[3] For purposes of the present petition only, Petitioner will assume that the claim preambles are limiting.

that has been made more human-like. A POSA would also understand that none of the claims relate to a specific antibody or antibody fragment.

"***And Further Comprising a Framework Region (FR) Amino Acid Substitution at a Site Selected From the Group Consisting Of***". Independent claims 1;62;63;66;80 of the '213 patent 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 group are functionally equivalent"). As none of the claims are limited to a specific antibody, and all Markush Group members are functional equivalents of each other, the broadest reasonable interpretation to a POSA would be that any of the recited residues can be equally substituted for any given antibody.

The term "Framework Region (FR) substitution" is not expressly defined by the '213 patent. A POSA would understand this term to mean that the amino acid residue at a given site within the framework region has been replaced by a different amino acid residue.

"***Numbering System Set Forth in Kabat***". The independent claims at issue include the limitation "utilizing the numbering system set forth in Kabat." The '213 patent specifically ties its numbering system to "Kabat, E.A. *et al.*,

Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, Md.) (1987) and (1991)". *See* Ex._1001 at 10:45-49. As noted above, the Kabat 1987 [Ex._1052] and Kabat 1991 [Ex._1055] data derive 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 FRs in each antibody chain variable domain. The broadest reasonable construction, "utilizing the numbering system set forth in Kabat," encompasses the Kabat 1987 and Kabat 1991 designations,[4] including the amino acid residue positions set forth in Kabat, but also including the boundary designations for CDR and FR structures.

"Consensus Human Variable Domain" (Claims 4, 62, 69) or "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" (Claim 64). Claims 4, 62, and 69 recite that the human variable domain ("HVD" comprise a "consensus" HVD. The '213

[4] Dr. Hale notes there are no significant differences between the Kabat 1987 and Kabat 1991 numbering systems, including CDR and FR boundary designations. Ex._1003 at n.5. However, the priority document (U.S. Patent Application No. 07/715,272) only relies on Kabat 1987, and not Kabat 1991. *Id.*

patent defines a "consensus" sequence as "an amino acid sequence which comprises the most frequently occurring amino acid residues at each location in all human immunoglobulins of any particular subclass or subunit structure." Ex._1001 at 11:33-39. Using similar language, Claim 64 recites that the HVD "comprises 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."

A POSA reading the claims, however, would understand that a "consensus" HVD or the HVD as required in claim 64 must have at least one amino acid residue that is *not* "the most frequently occurring amino acid residue[] at each location," because the claims require substitutions within the framework regions. Claim 4, for example, depends from claim 1, which requires at least one substitution from a site selected from a Markush group of 24 different sites. Claim 1, however, does not limit the substitutions to the Markush group, and does not limit the substitutions to only one. Therefore, because the claims require that at least one of the residues in a sequence be different from the consensus—and in fact allows for multiple differences from the consensus— a HVD comprises a "consensus" sequence so long as *some* of the residues are consensus residues.

E. Patents and Printed Publications Relied On In This Petition

Petitioner relies on the following patents and printed publications:

1. EP 0403156 ("Kurrle") [Ex._1071]

Kurrle, published December 19, 1990, detailed the humanization of a mouse monoclonal antibody (BMA 031) against the human alpha/beta T-cell receptor. Ex._1071 at Abstract. Kurrle provided guidance to a POSA regarding 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 determining regions *and selected framework amino acids necessary for antigen binding* are maintained murine. The remaining framework regions are converted to human sequences.") (Emphasis added).

Kurrle taught that 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."

Kurrle [Ex._1071] at 8:27-29. Kurrle taught such "differences within 4 amino acids" 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 8:38-46.

Applying one or more such criteria, 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 Tables 6A and 6B.[5] Using their roadmap, Kurrle made several FR substitutions in the light and heavy chain, including at positions **4L**;**69H**;**71H**;**73H**;**76H**. *See* Ex._1003C at 4-7 (Hale Exhibit B), ¶¶144-60. The '213 patent claims the same 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 Queen 1989's [Ex._1034] methodology, providing four explicit criteria for humanizing non-human antibodies. Queen 1990 Criterion I relates to the choice of the acceptor human framework:

[5] Dr. Hale notes that Kurrle did not use the Kabat numbering convention in Tables 6A and 6B for the antibody heavy chain. Ex._1003 at n.4. To follow '213 patent's numerical convention of the Kabat," Dr. Hale included a list of the amino acid sequences in Table 6A (heavy chain) with the Kabat 1987 numbering system [Ex._1052] in Ex._1003C at 4-7 as Hale Exhibit B.

> **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....

Ex._1050 at 14:17-32.

Also like Queen 1989, Queen 1990 teaches that 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 donor amino acid rather than the acceptor may be selected....

Id. at 15:21-37. The prior art thus taught maintaining highly conserved residues was important to minimize immunogenicity. Ex._1003 at ¶¶114;119.

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

> **Criterion III**: In the positions immediately adjacent to one or more of the 3 CDR's in the primary sequence of the humanized immunoglobulin chain, the [mouse] donor amino acid(s) rather than 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, to distort the donor CDR's and reduce affinity. Moreover, the adjacent amino acids may interact directly with the antigen (Amit *et al., Science*, 233, 747-53 (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 16:1-12. Kabat and Chothia identified the CDR boundaries, 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, ;**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;102H. '213 patent claims include **36H**; **98L**. Kabat 1987 [Ex._1052]; Ex._1003 at ¶¶165-175.

Queen 1990 further limited the molecular modeling criteria Queen 1989 established, calling for pinpointing framework residues that possess an atom within about 3Å of a CDR atom, thus likely to make a CDR contact:

> **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 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.

Id. at 16:14-31 (citations omitted). Queen 1990 further teaches deriving these "contact" residues from known antibody structures. *Id.* Such framework residues are more likely to influence how CDRs interact with the antigen.

3. Jones [Ex._1033]

Jones, May 1986, disclosed the development of a humanized antibody by substituting the CDRs from the heavy chain of a mouse variable domain that binds to the NP-cap hapten for the CDRs of the human myeloma protein NEWM. Ex._1033 at 522, 523. Jones therefore created a variable domain with a human

framework region but murine hypervariable region. The result, HuV_{NP}, was then linked to a human constant ε region and expressed in a mouse myeloma cell line that secreted a murine light chain to create a full IgE antibody, HuV_{NP}-IgE. *Id*. at 523. Jones further determined that this new humanized antibody had lost the antigenic determinants associated with the murine variable region, suggesting that this method of designing antibodies could lead to reduced immunogenicity compared to the parent mouse antibody. *Id*. at 525.

According to Kabat numbering, Jones's humanized variable domain comprises a human consensus sequence with amino acid differences (*i.e.*, substitutions) at the following sites: 24H;43H;69H;70H;71H;73H;78H. Ex._1003 at 132; Ex._1003C at 779; *see also* Ex._1033 at Figure 2. At least residues 43H;70H;71H are the same as the murine residue at those locations. *Id*.

4. Chothia & Lesk [Ex._1062]

Chothia & Lesk also established certain residues 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 4] summarized in Table 4 (reproduced below):

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] ($Å^2$)	Position	Residues in known structures	A.S.A.[a] ($Å^2$)
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 7, 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 at ¶¶139-41, narrowing the list of substitutable residues significantly. Such residues—including claimed residues

4L;**62L**;**73L**;**4H**;**36H**;**69H78H**;**92H**—constitute potential substitution candidates under Kurrle and Queen 1990. *Id.*

5. Riechmann [Ex._1069]

Riechmann, March 1988, taught the humanization of a non-human antibody by "transplanting only the antigen binding site, rather than the entire variable domain, from a rodent antibody." Ex. 1069 at 323. Riechmann chose to humanize the rat CAMPATH-1 antibody, which was useful in treating problems of immunosuppression, a chronic disorder, but was "limited by the anti-globulin response which can occur within two weeks of the initiation of treatment." *Id*. at 3. The rat CAMPATH-1 hypervariable regions (*i.e*. CDRs) were mounted onto human heavy chain (NEW) and light chain (REI) framework regions. *Id*. The reshaped HVDs were then assembled with human IgG constant domains. *Id*. at 3, 4.

Riechmann discloses that this humanized antibody would be useful for "an extended course of treatment." *Id*. at 5.

F. The Prior Art Anticipates or Renders Obvious the Challenged Claims

1. Detailed Instructions for Humanizing Antibodies Were Widely Available Before the '213 Patent Filing

Before the '213 patent's filing date, multiple research institutions—including Genzyme Corp. [Ex._1071], Protein Design Labs [Ex._1050], the Medical Research Council [Ex._1069], and the National Institutes of Health,—

published details on humanizing antibodies to avoid the immunogenic reactions observed with non-human monoclonal antibody therapeutics. *See* Ex._1071 at 3:8-12; Ex._1050 at Abstract; Ex._1003 at ¶88. 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* Ex._1050 at 5:3033; Ex._1073 at 9:12-19; Ex._1003 at ¶¶82-85.

Queen 1990 detailed the importance of preserving certain mouse framework positions in the resulting humanized antibody to maintain CDR conformation and antigen binding. Ex._1050 at 16:2, 14-15. The prior art thus provided detailed pathways to humanize antibodies for therapeutic use which would "be substantially non-immunogenic and retain substantially the same affinity as the donor immunoglobulin to the antigen." *See id.* at Abstract; Ex._1003 at ¶¶77-105.

Kurrle used similar logic, replacing several human FR sites with mouse residues within the variable region of the light and heavy chains. Ex._1071 at Tables 6A and 6B; Ex._1003 at ¶¶106-109.

Broadly drafted, the claims of the '213 patent are not limited to sequences wherein specific amino acid residues are deliberately replaced. A prior art antibody with both consensus residues and non-consensus residues at sites recited in the claims would anticipate the challenged claims, even though no residues were intentionally substituted, as long as it had the same sequence as an antibody

prepared according to the ’213 patent. Thus, prior art such as Jones, which taught humanizing antibodies through simple CDR grafting, would anticipate the claims of the ’213 patent. *See* Ex._1003 at 228-251; *see also* Ex._1003C at 779 (Hale Exhibit Q).

Simply put, many scientific research groups were making “humanized antibodies” prior to the ’213 patent’s earliest filing date and publishing detailed instructions for doing the same. The prior art demonstrates that each challenged claim was both anticipated and obvious.

G. Ground 1: Claims 1;2;4;25;29;62;63;66;69;71;75;76;78;80;81 Are Unpatentable as Anticipated by Kurrle

As a preliminary matter, Patent Owner may try to argue that Kurrle does not qualify as prior art. During prosecution, Genentech submitted an affidavit signed by the inventors, swearing behind the September 1990 priority date of the ’101 and ’762 patents. Ex._1002 at 793, 802-807. This affidavit provided pages from a laboratory notebook disclosing proposed sequences for a humanized 4D5 antibody, relying on consensus sequences and at least one substitution at site 73H. *Id*..

However, Boehringer does not concede that this affidavit, disclosing a single species, is sufficient to antedate Kurrle. At the outset, it is “well settled that a single species can rarely, if ever, afford sufficient support for a generic claim.” *In re Clarke*, 356 F.2d 987, 992 (C.C.P.A. 1966). While “in an appropriate case a single species could be sufficient to antedate indirectly a different species of a

reference," there must be evidence that a POSA would have considered the two species to have common properties that define a genus. *Id*. at 992-993; *see also id*. at 993 n. 6.

Independent claim 1 recites twenty-four different sites where FR residues may be substituted, and does not limit substitutions to the sites recited. Given twenty possible amino acids for each of the twenty-four locations, claim 1 therefore covers at least 20^{24}, or over a nonillion compositions. The inventors have not identified a common property that defines all the possible antibodies or antibody fragments that could fall within its scope. Indeed, it was well known that the function of an antibody depends on its three-dimensional structure, which depends on its amino acid sequence; thus, changing the amino acid sequence "may adversely affect its activity." Ex._1073 at 5. Because claim 1 does not limit the type of amino acids that may be substituted at the recited locations, antibodies with substitutions at the same sites, but with residues differing substantially in charge or size, could possess completely different properties.

Kurrle describes at least one species of antibody falling within the scope of claim 1 that is distinct from the humanized 4D5 antibody relied upon in Genentech's affidavit, and there is no evidence in the affidavit that a POSA would have expected such different antibodies to have similar properties. Therefore, for

at least this reason, the affidavit submitted by Genentech during prosecution is insufficient to antedate Kurrle.[6]

1. Independent Claim 1 is Anticipated by Kurrle

Independent claim 1 of the '213 patent recites "[a] humanized antibody variable domain comprising," the elements (1) "non-human [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: [the claimed sites], 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." Ex._1071 at Abstract; Ex._1003 at ¶¶106-109. Kurrle also disclosed "non-human [CDR] amino acid residues which bind an antigen" and "a [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.*" Ex._1071 at 3:9-12 (emphasis added); Ex._1003 at ¶145.

[6] Boehringer has not seen any other evidence that Genentech may use to antedate Kurrle. To the extent Genentech submits new evidence, Boehringer reserves the right to argue its insufficiency.

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._1003C at 4-7 (Hale Exhibit B), ¶¶144-47. The '213 patent does not provide any evidence that the particular residues recited in the claim are more important or critical to the claimed invention than others recited in the prior art. Claim 1 is anticipated.

2. Kurrle Anticipates Dependent Claims 2;4;25;29

Claim 2: Claim 2 depends on claim 1, 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." This is precisely what Kurrle did. *See* Ex._1071 at 8:45-47 ("In one position (#93) 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 as taught by Kurrle. *See* Ex._1003 at ¶148. Claim 2 is also anticipated by Kurrle.

Claim 4: Claim 4 depends on claim 1, and further recites "wherein the human antibody variable domain is a consensus human variable domain." The '213 patent defines a "consensus" sequence as "an amino acid sequence which comprises the most frequently occurring amino acid residues at each location in all

human immunoglobulins of any particular subclass or subunit structure." Ex._1001 at 11:33-39. However, claim 1, and therefore claim 4, requires amino acid substitutions at certain locations within the HVD. Claim 1 further does not limit the number of substitutions that may be made in the human antibody variable domain, so long as there is a Framework Region (FR) amino acid substitution at one of the sites recited in claim 1. This is in contrast to language in claim 3, for example, that requires "no human Framework Region (FR) residue other than those set forth in the group has been substituted."

Therefore, a "consensus" sequence as recited in claim 4 does not require that *every* amino acid in the human antibody variable domain be "the most frequently occurring amino acid residue[] at each location in all human immunoglobulins of any particular subclass or subunit structure," because claim 1 requires that some of the amino acids in the variable domain be substitutions. In other words, any HVD with at least *some* consensus residues would fall within the scope of claim 4 so long as at least one residue at a site recited in claim 1 was not a consensus residue.

Claim 1 also does not limit the substituted residues to "the residue found at the corresponding location of the non-human antibody from which the non-human CDR amino acid residues are obtained"—instead, that limitation is found in claim 2. Therefore, a human antibody variable domain with an amino acid residue at a given site that is different from the human consensus sequence at that site, but is

not the corresponding non-human amino acid residue, would also meet the requirements of claim 4.

Kurrle created a "civilized" antibody by searching for a human antibody that was most homologous to the murine BMA 031 antibody. Ex._1071 at 8:16-18. As Dr. Hale explains, the residues in the consensus sequence are by definition the ones most commonly found in the natural human antibody variable regions. *Id*. Ex._1003 at ¶157; *see also* Ex._1071 at Tables 6A and 6B. Thus, the humanized antibodies disclosed by Kurrle comprise both consensus and non-consensus residues. *Id*. The non-consensus residues in the humanized antibodies disclosed by Kurrle were not all deliberately substituted. For the purposes of patentability, it is irrelevant that the prior art sequence disclosed by Kurrle was not prepared by a process of deliberate substitutions at every non-consensus site, so long as the prior art sequence would be the same product as a product falling within the scope of the claim. *See, e.g., In re Thorpe*, 777 F.2d 695, 698 (Fed. Cir. 1985) ("The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.")

The antibody disclosed by Kurrle comprises a "consensus" HVD with substitutions consisting of non-consensus residues. Claim 4 is anticipated by Kurrle.

Claim 25: 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 (§V.G.1), Kurrle anticipates claim 25. Ex._1003 at ¶149.

Claim 29: Claim 29 also depends on claim 1, and recites "[a]n antibody comprising the humanized variable domain of claim 1." Kurrle's explicit goal was to create 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 3:9-12; *see also* 2:2-4; Ex._1003 at ¶150. Kurrle anticipates Claim 29.

3. Independent Claim 62 is Anticipated by Kurrle

Claim 62 shares claim 1's FR substitutable residues list, including residues 4L and 69H, but adds residues 46L; 75H;76H;78H. As discussed above for claim 1, Kurrle substituted several corresponding murine amino acids for human framework residues under Kabat's numbering system, including **4L** and **69H**, as found in claim 62.

Claim 62 also differs from claim 1 by adding the phrase, "incorporated into a consensus human variable domain." As with claim 4, Kurrle meets this limitation as well. Kurrle anticipates claim 62 of the '213 patent.

4. Independent Claim 63 is Anticipated by Kurrle

Claim 63 of the '213 patent 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* §V.G.2, *supra.* 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 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…."); Ex._1003 at ¶¶151-53.

This is, in fact an explicit goal of all antibody humanization projects. *See* Ex._1071 at 3:8-12 ("A further refinement involves humanization of the variable regions ... [T]he resulting mAb of the present invention is thus essentially a human antibody with a much lower immunogenicity in patients."); Ex._1003 at ¶¶152-53. Because this is simply a statement of the intended result of the claimed

composition, this should not be a limitation of the claims. *Bristol-Myers Squibb Co. v. BenVenue Labs, Inc.*, 246 F.3d 1368, 1375-76 (Fed. Cir. 2001). Nonetheless, one of ordinary skill in the art would thus know that Kurrle's humanized antibodies would also "lack immunogenicity compared to a non-human parent antibody upon repeated administration …" . Claim 63 is anticipated.

5. Independent Claim 66 and Dependent Claims 69;71;72;75;76;78 are Anticipated by Kurrle

Independent claim 66 shares elements with claims 1 and 63, which are met as demonstrated above. *See* §§V.G.1 & 4, *supra;* Ex._1003 at ¶¶154-55. Claim 66's substitutable amino acid residues are "selected from the group consisting of: 24H;73H;76H;78H;93H," under Kabat's numbering system. As Kurrle substituted residues **73H** and **76H**, Ex._1003C at 4-7 (Hale Exhibit B) and Ex._1003 at ¶¶154-55, it anticipates claim 66.

Dependent claim 69 further recites that "the human antibody variable domain is a consensus human variable domain." As explained *supra* for claim 4, Kurrle meets this limitation and anticipates claim 69.

Dependent claims 71, 72, 75 and 76 recite "wherein the residue at site 73H has been substituted" (claim 71), " site 76H has" (claim 72), "which further comprises an amino acid substitution at site 71H" (claim 75), and "substitutions at sites 71H and 73H" (claim 76). Kurrle disclosed the substitution of amino acid residues **71H**, **73H** and **76H** in their humanized anti-T-cell receptor monoclonal

antibody. *See* Ex._1071 at Table 6B; Ex._1003C at 4-7 (Hale Exhibit B) and Ex._1003 at ¶156. Accordingly, and as for claims 1 and 63, *see* §§V.G.1 & 3, *supra;* Ex._1003 at ¶¶144-47, 154-56, Kurrle anticipates dependent claims 71, 72, 75 and 76.

Dependent claim 78, which depends on claim 66, recites "[a]n antibody comprising the humanized variable domain of claim 66." The goal of humanization methods, including Kurrle, was to create a therapeutic antibody comprising a humanized variable domain: "The resulting mAb of the present invention is thus essentially a human antibody with a much lower immunogenicity in patients." *See* Ex._1071 at 3:11-12; *see also id*. at 3:26-28. Claim 78 is anticipated by Kurrle.

6. Independent Claim 80 and Dependent Claim 81 Are Anticipated by Kurrle

Claim 80: Independent claim 80 recites "[a] humanized antibody variable domain comprising non-human [CDR] amino acid residues which bind an antigen incorporated into a human antibody variable domain, and further comprising a [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 VL-VH interface by affecting the proximity or orientation of the V_L and V_H regions with respect to one another . . . ." Claim 80 then recites a list of substitutable amino acid residues that differ from claim 1 by adding amino acid

residues 73H;76H;78H;93H to the list. As with claims 1 and 63, residues **4L** and **69H**, and additional residues **73H** and **76H** are substituted in Kurrle. §§V.G.1 & 3, *supra*.

The additional recited elements, which are noted functions of the substituted residues, add nothing new to the claim. *See* claim 63, §V.G.3; Ex._1003 at ¶¶161-62; *see also Atlas Powder,* 190 F.3d at 1347. Even if the inherency of these functions were discounted (they should not be), Kurrle explicitly teaches interaction of the framework residues with the CDR as a reason for substitutability. *See* Ex._1071 at 8:28-29 and 32-40 (use of a "simplified computer model" to determine whether or not FR residues were close enough to CDRs to influence binding); Ex._1003 at ¶¶106-109. 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 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 disclosed in and anticipated by Kurrle. *See* §V.G.2, *supra;* Ex._1071 at Tables 6A and 6B; Ex._1003 at ¶¶161-164.

H. Ground 2: Claims 1;2;4;29;62;63;64;80;81 are Anticipated by Queen 1990

1. Independent Claim 1 is Anticipated by Queen 1990[7]

"A humanized antibody variable domain," is disclosed in Queen 1990. Queen's stated goal was creating "a humanized antibody variable domain" by not only swapping CDRs, but also manipulating the framework region of the variable domain, as recited by '213 claim 1. Queen explicitly provides for "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...." Ex._1050 at Abstract; Ex._1003 at ¶166. Queen 1990 provides a detailed roadmap with specific criteria used in designing humanized immunoglobulins. Ex._1050 at 14:9-15; Ex._1003 at ¶¶165-175. 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***

[7] Boehringer has not seen any evidence that Genentech may use to antedate Queen 1990. To the extent Genentech submits new evidence, Boehringer reserves the right to argue its insufficiency.

immunoglobulin." Ex._1050 at Abstract. The POSA can readily envision such locations. *See* Ex._1003 at ¶¶170-72.

> 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 primary sequence of 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.

Ex._1050 at 16:1-12 (citations omitted); Ex._1003 at ¶170.

Boehringer's expert, Dr. Hale, 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 at ¶171. Using the numbering system set forth by Kabat 1987,[8] the "immediately adjacent" framework residues to CDRs

[8] While Dr. Hale uses the Kabat 1987 reference for designating the amino acid positions according to the Kabat numbering system, there were "no meaningful

as taught by Queen 1990 and recited in claim 1 include **98L** and **36H**. *See* Ex._1003C at 8-9 (Hale Exhibit C) and Ex._1003 at ¶¶165-75; § V.E.2, *supra*.

Thus, Queen 1990's explicit teaching to substitute CDR-adjacent framework region amino acid positions would inevitably include substitutions at the claimed amino acid residues of **98L** and **36H**. The '213 patent does not provide any evidence that the particular residues recited in the claim are more important or critical to the claimed invention than others recited in the prior art. Queen 1990 anticipates claim 1.

2. Queen 1990 Anticipates Dependent Claims 2, 4 and 29

Claim 2: 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* Ex._1050 at 7:36-8:1 ("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"); Ex._1003 at ¶176. Queen 1990 anticipates claim 2.

Claim 4: Claim 4 depends on claim 1, and recites "wherein the human antibody variable domain is a consensus human variable domain." Queen 1990

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differences in the Kabat numbering system, including the CDR boundaries, between Kabat 1987 and Kabat 1991." Ex._1003 at n.5.

expressly teaches this by disclosing in Criterion I that "[a]s acceptor,... use ***a consensus framework*** from many human antibodies." *See* Ex._1050 at 14:17-20 (Criterion I); Ex._1003 at ¶¶117, 177. Queen 1990 anticipates claim 4.

Claim 29: Claim 29 depends on claim 1, and recites "[a]n antibody comprising the humanized variable domain of claim 1." As Dr. Hale explains, the goal of antibody humanization programs was to create a humanized variable domain. See, e.g., Ex._1050 at 6:21-25 ("mouse complementarity determining regions, with or without additional naturally-associated mouse amino acid residues, can be used to produce human-like antibodies . . . ."); Ex._1003 at ¶178. A POSA would thus recognize that Queen's aim was to create therapeutic-quality antibodies with a HVD to maintain a high level of binding and affinity. Ex._1003 at ¶178. Queen 1990 anticipates claim 29.

3. Independent Claim 62 is Anticipated by Queen 1990

Claim 62 shares claim 1's FR substitutable residues list, including residues 98L and 36H, but adds residues 46L;75H;76H;78H. As discussed above for claim 1, *see* §V.H.1, *supra*, Queen 1990 discloses residues **98L** and **36H** as also inevitably requiring substitution.

Claim 62 also differs from claim 1 by adding the phrase, "incorporated into a consensus human variable domain." Ex._1003 at ¶179. Queen 1990 also disclosed in Criterion I that "[a]s acceptor,... use ***a consensus framework*** from

many human antibodies." *See* Ex._1050 at 14:17-20; Ex._1003 at ¶180; §V.H.2, *supra*. Queen 1990 thus anticipates claim 62 of the '213 patent.

4. Independent Claim 63 is Anticipated by Queen 1990

Claim 63 differs from claim 62 by further describing the claimed humanized antibody as lacking "immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient."

As explained above, this is a non-patentable distinction. *See* §V.G.3, citing to *Atlas Powder*, 190 F.3d 1342; Ex._1003 at ¶182. As simply a statement of the intended result of the claimed composition, this should not be a limitation of the claims. *Bristol-Myers Squibb*, 246 F.3d at 1375-76. Nonetheless, Queen 1990 explicitly taught this goal: "When combined into an intact antibody, the humanized immunoglobulins of the present invention *will be substantially non-immunogenic* in humans..." Ex._1050 at Abstract; Ex._1003 at ¶182-83. Claim 63 is also anticipated by Queen 1990.

5. Independent Claim 64 is Anticipated by Queen 1990

Claim 64, described above, is also anticipated by Queen 1990. 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* §§V.H.2 & 3, *supra;* Ex._1003 at ¶¶184-

86; Ex._1050 at 14:17-20 ("As acceptor, ... use ***a consensus framework*** from many human antibodies.").

While the remaining limitations are merely stated functions of the humanized antibody, *see* §V.G.3, *supra,* Queen 1990 also disclosed, from claim 64, at least noncovalently binding antigen and interaction with a CDR in Criterion III:

> Immediately adjacent... 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. Moreover, 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.

Ex._1050 at 16:1-12 (emphasis added); Ex._1003 at ¶186. Because Queen 1990 teaches one to substitute "immediately adjacent" residues **98L** and **36H**, *see* §V.H.1 *supra,* and because Queen 1990 teaches that 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 at ¶¶184-86.

6. Claims 80 and 81 are Anticipated by Queen 1990

Claim 80: 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* §§V.H.1 & 5, *supra;* Ex._1003C at 89 (Hale Exhibit C) and Ex._1003 at ¶¶1887-90 (citing Ex._1050 at 16:4-8). 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." Ex._1050 at 16:10-12; Ex._1003 at ¶188.

Moreover, Criterion IV in Queen 1990 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." Ex._1050 at 16:15-19; Ex._1003 at ¶189. Given that, Queen 1990 anticipates Claim 80.

Claim 81: Claim 81 (which depends 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* Ex._1050 at 7:36-8:1; Ex._1003 at ¶191. Claim 81 is also anticipated by Queen 1990.

I. Ground 3: Claims 1;2;4;25;29;62-64;66-67;69;71-72;75-76;78;80;81 Are Unpatentable As Obvious over Queen 1990 and Kurrle

1. Claim 1 is Obvious Over Queen 1990 and Kurrle

Queen 1990 disclosed to a POSA a detailed pathway for humanizing non-human monoclonal antibodies, with the expectation that the antibodies "will be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen…" Ex._1050 at Abstract. The criteria for this pathway in Queen 1990 are set out above. *See* §V.E.2, *supra*.

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..." Ex._1050 at 8:21-26; Ex._1003 at ¶196. Queen 1990 thus provided "the explicit motivation to follow these steps to obtain a monoclonal antibody that can be used in human therapeutics." Ex._1003 at ¶196.

Kurrle employed a similarly detailed 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; *see* Ex._1071 at 8:16-18), accounting for the adjacent residue rules of Queen 1990 (Criterion III of Queen 1990; *see* Ex._1071 at 8:25-31), substituting CDR-contact

residues using computer models based on solved structures (Criterion IV of Queen 1990; *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; *see* Ex._1071 at 8:36-40). Ex._1003 at ¶¶106-109, 197.

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* §§V.E.1 & G.1, *supra;* Ex._1003C at 4-7 (Hale Exhibit B), Ex._1003 at ¶¶144-47, 198.

A POSA seeking to humanize antibodies would have sought to improve on the successes of prior work in the field, including Kurrle and Queen 1990, published less than six months apart. Exs. 1071 at 1; 1050 at 1. A POSA would have been especially motivated to combine the teachings of Queen 1990 and Kurrle because of the similarity in the approaches implemented in these references. Ex._1003 at ¶¶198-199.

The combination of Queen 1990 and Kurrle thus 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, and targeted the very species residues satisfying the claim 1

genus. Claim 1 is obvious over Queen 1990 in view of Kurrle. Ex._1003 at ¶¶195-199.

2. Claims 2, 25 and 29 are Obvious Over Queen 1990 and Kurrle

Claim 2: Claim 2 is also taught by Queen 1990 and Kurrle. As discussed, this is a basic step in humanization, followed by many in the field, including Queen (Ex._1050 at 7:36-8:1) and Kurrle (Ex._1071 at 8:28-29). *See* §V.G.2 *supra;* Ex._1003 at ¶200. Claim 2 is obvious over Queen 1990 and Kurrle.

Claim 25: Claim 25 depends on claim 1, and further recites "wherein the residue at site 69H has been substituted." Residue 69H was substituted in Kurrle's humanized anti-T-cell receptor antibody. *See* §§V.G.1 & 2, *supra;* Ex._1003 at ¶201. Accordingly, claim 25 is also obvious over Queen 1990 and Kurrle.

Claim 29: Claim 29 depends on claim 1, and further recites "[a]n antibody comprising the humanized variable domain of claim 1." The explicit goals of Queen 1990 and Kurrle was to create antibodies comprising a humanized variable domain: "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." Ex._1050 (Queen 1990) at 8:21-26; *see also* Ex._1071 (Kurrle) at 3:26-28 and 2:2-4; Ex._1003 at ¶202. Claim 29 is also obvious over Queen 1990 in view of Kurrle.

3. Claim 4 is Obvious Over Queen 1990 and Kurrle

Claim 4, which depends from claim 1, recites: "wherein the human antibody variable domain is a consensus human variable domain." Queen 1990 teaches the use of a consensus HVD as the human acceptor framework antibody, *see* Ex._1050 at 14:17-20 ("As acceptor ... use a consensus framework from many human antibodies."), which would have motivated a POSA to use the human "acceptor" framework together with the humanization methods of Kurrle. Ex._1003 at ¶¶117, 203. Claim 4 is also obvious over Queen 1990 and Kurrle.

4. Claim 62 is Obvious Over Queen 1990 and Kurrle

Claim 62 differs from claim 1 by adding that the HVD is a "consensus" HVD. *See* §§V.B.1 & I.1 *supra.* Queen 1990 discloses the use of a consensus HVD in Criterion I of its humanization roadmap. Ex._1050 at 14:17-20 ("As acceptor,... use ***a consensus framework*** from many human antibodies."); Ex._1003 at ¶¶204-205. 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; §H.1) and **4L**, **69H** and **76H** (Ex._1071; §G.1). Ex._1003 at ¶205. Claim 62, as for claims 1 and 4 (see §§V.I.1 & 2, *supra)* of the '213 patent is obvious over Queen 1990 and Kurrle.

5. Claim 63 is Obvious Over Queen 1990 and Kurrle

Claim 63 is similar to claim 62 (incorporating the CDRs and substituted FR residues of claim 1), and adds that the claimed humanized antibody "lacks immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient to treat a chronic disease in that patient." As simply a statement of the intended result of the claimed composition, this should not be a limitation of the claims. *Bristol-Myers Squibb*, 246 F.3d at 1375-76. Nonetheless, as discussed above, this is the stated goal of all humanization projects, including that of Queen 1990 and Kurrle. *See* Ex._1050 at Abstract; Ex._1071 at 3:11-12; Ex._1003 at ¶¶206-209. Claim 63 is also obvious over Queen 1990 and Kurrle.

6. Claim 64 is Obvious Over Queen 1990 and Kurrle

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* §§V.H.2 & 5, *supra;* Ex._1050 at 14:17-20 ("As acceptor, . . . use ***a consensus framework*** from many human antibodies."); Ex._1003 at ¶¶210-13. Both Queen 1990 and Kurrle also taught humanized antibodies containing a non-human CDR and substituted FR residues. *See, e.g*., Ex._1071 (Kurrle); Ex._1003 at ¶214.

While the remaining limitations are merely stated functions of the humanized antibody, *see* §§V.G.3, & H.5 *supra*, both Queen 1990 and Kurrle

disclosed that certain framework residues were important because of their proximity to neighboring CDRs: "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* Ex._1050 at 16:1-12 (emphasis added); *see also* Ex._1071 at 8:27-29; Ex._1003 at ¶214. 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 is Obvious Over Queen 1990 and Kurrle

Both Queen 1990 and Kurrle disclose the claimed "humanized antibody heavy chain variable domain comprising non-human [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* §§V.I.1 & 4, *supra*. Claim 66 further requires the framework substitution of one or more residues, e.g., 24H;73H;76H;78H;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." Ex._1071 at 3:11-12; Ex._1003 at ¶¶14-215.

Both Queen 1990 and Kurrle provide the motivation and a reasonable expectation of success to make "a humanized antibody variable domain" as

claimed in claim 66. Ex._1003 at ¶215. Claim 66 is obvious over Queen 1990 in view of Kurrle.

8. Claims 67, 71, 72, 75, 76 and 78 are Obvious Over Queen 1990 and Kurrle

Claim Language	**Prior Art**
67. "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.,* Ex._1050 at 7:36-8:1 (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"); Ex._1003 at ¶225.
71. "wherein the residue at site 73H has been substituted" **72.** "wherein the residue at site 76H has been substituted" 75. "which further comprises an amino acid substitution at site 71H"	Kurrle substituted the murine amino acid residues at claimed positions **71H**, **73H** and **76H**. Ex._1003 at ¶226. The '213 patent does not provide any evidence that the particular residues recited in the claims are more important

76. "which further comprises amino acid substitutions at sites 71H and 73H"	or critical to the claimed invention than others recited in the prior art.
78. "comprising the humanized variable domain of claim 66."	The goal of humanization methods, 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* Ex._1050 at 8:21-26; Ex._1071 at 3:26-28; Ex._1003 at ¶229.
69. "the human antibody variable domain is a consensus human variable domain."	Queen 1990 explicitly teaches using "[a]s acceptor . . . a consensus framework from many human antibodies." Ex._1050 at 14:17-20; Ex._1003 at ¶230.

9. Claims 80 and 81 are Obvious Over Queen 1990 and Kurrle

Claim 80: Claim 80 claims the same "humanized antibody variable domain" as 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 VL-VH interface ..." Ex._1003 at ¶¶161-164,187-91, 224-227.

Both Queen 1990 and Kurrle explicitly teach interaction of the framework residues with the CDR as a reason for substitutability. *See* Ex._1050 at 16:4-8; Ex._1071 at 8:28-29 and 32-40; Ex._1003 at ¶¶225-226. For the same reasons as claims 1 and 64 above, *see* §§V.I.1 & 6 *supra*, including the disclosure of framework region substitutions at positions **98L** and **36H** as provided by Queen 1990 (§§V.H.1 & I.1 *supra)*, and **4L**, **69H**, **73H** and **76H** (§§V.G.1, G.4 & I.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 §§ V.G.1 & H.1), claim 80 of the '213 patent is obvious over Queen 1990 and Kurrle.

Claim 81: Claim 81 depends on claim 80, adding "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* Ex._1050 at 7:36-8:1; Ex._1071 at 8:28-31; Ex._1003 at ¶227. Claim 81 is obvious over Queen 1990 and Kurrle.

J. Ground 4: Claims 1;2;4;25;29;62;64;66;69;71;73;75-78;80;81 Are Unpatentable As Anticipated by Jones

1. Independent Claim 1 is Anticipated by Jones

Jones disclosed a "humanized antibody variable domain" because it taught "constructing human monoclonal antibodies from the corresponding mouse monoclonal antibodies." Ex._1033 at Abstract; Ex._1003 at ¶¶229. Jones also disclosed that the humanized antibody variable domain comprises "non-human [CDR] amino acid residues which bind an antigen," because Jones substituted the CDRs from a murine variable domain that binds the NP-cap hapten into an HVD. Ex._1033 at Abstract; Ex._1003 at ¶ 230.

Jones also disclosed an antibody "comprising a Framework Region (FR) amino acid substitution 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;92H, utilizing…Kabat." As discussed above at §V.A, this claiming structure yields a product-by-process claim. *See Purdue Pharma*, 811 F.3d at 1353. (Fed. Cir. 2016). The *Purdue* claim, as the court noted, is directed to the "end product," not a method for creating that product. *Id*. However, because the "derived from 8α[ ]" limitation could not be a structural limitation, it had to be a process limitation. *Id*. Once the Federal Circuit determined that this was a

process limitation, the court concluded that it could be disregarded in a patentability analysis, because "[i]n determining validity of a product-by-process claim, the focus is on the product and not the process of making it." *Id*. at 1354.

Claim 1 of the '213 patent presents the same situation as in *Purdue*. As Dr. Hale explains, the *source* of the amino acid at a particular position in an HVD—whether it occurs there naturally or is deliberately substituted—has no effect on the structure or function of the HVD. Ex._1003 at ¶ 231. Just like the limitation analyzed in *Purdue*, claim 1's requirement for an amino acid "substitution" is a process limitation that does not affect the structure or function of a humanized variable domain falling within its scope. As a process limitation, "substitution" can be disregarded in a patentability analysis. Therefore, a prior art antibody prepared without intentional substitutions, but with the same sequence (and thus structure and function) as an antibody prepared according to the claims of the '213 patent, would anticipate those claims. *See Purdue,* 811 F.3d at 1354; *see also In re Thorpe,* 777 F.2d 695, 697 (Fed.Cir.1985) ("If the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.").

Jones discloses such a prior art antibody. As explained in § V.E.3, Jones prepared a humanized antibody through simple CDR grafting. Starting with the human NEWM myeloma protein, Jones substituted the CDRs from the heavy-

chain variable region of mouse antibody B1-8, which binds the NP-cap hapten, for the CDRs of the human NEWM protein. Ex._1033 at 522. Jones did not perform any further substitutions, and concluded that "binding affinity and specificity… can be conferred on a human antibody by grafting in the CDRs from an appropriate mouse antibody." *Id*. at 524.

Thus, Jones did not start with an artificially constructed consensus sequence, and Jones did not intentionally substitute amino acids within the framework region of the NEWM protein. However, as Dr. Hale explains, framework residues are known to be highly conserved and are therefore already the most frequently occurring residues at each location. Ex._1003 at ¶77. Dr. Hale compared the sequence of the NEWM protein with the consensus sequence HUV_HIII (as disclosed in '213 patent Fig. 1B). Ex._1003C at 779 (Hale Exhibit Q). As can be seen in this comparison, there are both consensus and non-consensus residues in the humanized HuV_{NP} variable domain. However, as explained above and as discussed for claim 4 in § V.G.2, any differences from the consensus sequence can be considered a "substitution" of the consensus residue for a non-consensus residue, whether or not it was deliberately replaced. Thus, the sequence of the HuV_{NP} variable domain disclosed by Jones is the same as the sequence of a human consensus variable domain comprising substitutions at least at framework region sites 43H;69H;70H, according to Kabat and as recited in claim 1. Ex._1003 at

¶¶228-232; *see also* Ex._1003C at 779 (Hale Exhibit Q). Because the variable domain disclosed by Jones could have been prepared by substituting a consensus HVD according to the substitutions recited by claim 1, Jones anticipates claim 1.

2. Jones Anticipates Dependent Claims 2, 4, 25 and 29

Claim	**Prior Art**
2. "wherein the substituted residue is the residue found at the corresponding location of the non-human antibody from which the nonhuman CDR amino acid residues are obtained."	As Dr. Hale demonstrates in Ex._1003C at 779 (Hale Exhibit Q),at least residues 43H and 71H in the variable domain disclosed by Jones are the same as the corresponding murine residue at those locations. Ex._1003 at ¶132; *see also* Ex._1033 at Fig. 2.
4. "wherein the human antibody variable domain is a consensus human variable domain."	For the same reasons Kurrle discloses the "consensus" HVD required by claim 4, and as discussed above for claim 1, Jones also discloses the "consensus" HVD.
25. "wherein the residue at site 69H has been substituted."	Because framework residue **69H** is not the same as the human consensus sequence as it is in Jones's HuV_{NP}-IgE

	antibody, it meets the "substitution" requirement according to the analysis provided above for claim 1. Ex._1003 at ¶234.
29. "[a]n antibody comprising the humanized variable domain of claim 1.	Jones assembled the humanized Hu-V_{NP} variable domain with a human ε constant region, creating a full humanized IgE antibody comprising a humanized variable domain. Ex._1033 at 523; *see also* Ex._1003 at ¶129.

3. Independent Claim 62 is Anticipated by Jones

Claim 62 shares claim 1's FR substitutable residues list, including residues 4L and 69H, but adds residues 46L;75H;76H; 78H. As discussed above, Jones substituted several corresponding murine amino acids for human framework residues under Kabat's numbering system, including **43H**, **70H** and **71H**, as found in claim 62.

Claim 62 also differs from claim 1 by adding the phrase, "incorporated into a consensus human variable domain." Ex._1003 at ¶242. As explained above for claim 4, Jones meets this limitation as well. Jones thus anticipates claim 62 of the '213 patent.

4. Independent Claim 64 is Anticipated by Jones

As explained for claims 1, 4 and 29, Jones 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* §§V.J.1 & 2, *supra*.

The '213 patent specifically teaches that "[r]esidues involved with the [V_L-V_H] interface include… 43H." Ex._1001 at 55:61-62. As Dr. Hale explains, the variable domain disclosed by Jones includes a substituted FR residue at 43H. Ex._1003 at ¶ 232; Ex._1003C at 779 (Hale Exhibit Q). Because Jones discloses an antibody with a substituted residue that "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," Jones anticipates claim 64.

5. Independent Claim 66 and Dependent Claims 69, 71, 73, and 75-78 are Anticipated by Jones

Independent claim 66 shares elements with claims 1 and 63, which are met as demonstrated above. *See* §§V.J.1 & 4, *supra*. Claim 66's substitutable amino

acid residues are "selected from the group consisting of: 24H, 73H, 76H, 78H, and 93H," under Kabat. As Jones substituted residues **24H, 73H,** and **78H**, Ex._1003C at 779 (Hale Exhibit Q) and Ex._1003 at ¶¶232, it anticipates claim 66.

Dependent claim 69 further recites that "the human antibody variable domain is a consensus human variable domain." As explained *supra* for claim 4, Jones meets this limitation. Accordingly, Jones anticipates claim 69.

Dependent claim 71 further recites "wherein the residue at site 73H has been substituted." Dependent claim 73 recites "wherein the residue at site 78H has been substituted." Dependent claim 75 recites "which further comprises an amino acid substitution at site 71H." Dependent claim 76 recites "which further comprises amino acid substitutions at sites 71H and 73H." Dependent claim 77 recites "which further comprises amino acid substitutions at sites 71H, 73H and 78H."

Jones disclosed the substitution of amino acid residues at least at 24H, 71H, 73H, and 78H. *See* Ex._1033 at Figure 2; Ex._1003C at 779 (Hale Exhibit Q) and Ex._1003 at ¶232. Accordingly, and in view of the discussion for claims 1 and 63, *see* §§V.J.1 & 4, *supra;* Jones anticipates dependent claims 71, 73, and 75-77.

Claim 78, which depends on claim 66, recites an antibody "comprising the humanized variable domain of claim 66." Jones assembled the humanized variable domain, HuV_{NP}, with a human constant ε region to create a full IgE antibody, HuV_{NP}-IgE. Ex._1033 at 523. Jones therefore anticipates Claim 78.

6. Independent Claim 80 and Dependent Claim 81 Are Anticipated by Jones

Claim 80: As explained for claims 1 and 63, at least residues 24H;43H;69H;70H;73H;78H are substituted in Jones. §§V.J.1 & 4, *supra*. The additional recited elements, which are noted functions of the substituted residues, do not add anything new to the claim. *See* Ex._1003 at ¶¶245-246; *see also Atlas Powder,* 190 F.3d at 1347. Jones 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." This is taught by Jones. *See* §V.J.2, *supra;* Ex._1033 at Figure 2; Ex._1003 at ¶¶247. Claim 81 is thus anticipated by Jones.

K. Ground 5: Claims 73 and 77 are Obvious Over Queen 1990 and Kurrle, In View of 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 light of Queen 1990 and Kurrle. *See* §V.8. A POSA would have been motivated to identify which residues had been identified as being essential for interchain reactions. Ex._1003 at ¶220. Residue 78H was already known as being important for maintaining antibody conformation, and thus antigen

binding and specificity, as identified by Chothia & Lesk and Queen 1990. *See* Ex._1062 at Abstract; Ex._1003 at ¶220. Chothia & Lesk found that "[t]he major determinants of the tertiary structure of the framework are the residues buried within and between the [VL and VH] domains," including residue **78H** specifically. Ex._1062 at 903; Table 4; Ex._1003 at ¶¶221-222. 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 and colleagues, Ex._1062, for residues "critically affecting the conformation of particular CDRs and thus their contribution to antigen binding.").

Thus, the field, including the '213 patent inventors, already recognized the importance of framework residues, such as **78H**, that are important to maintain antigen binding. Ex._1003 at ¶221. In view of the importance of **78H**, it would have been obvious for a POSA to include **78H** as a substitutable residue. Ex._1003 at ¶222; *see also* ¶200. Claim 73 is obvious over Queen 1990, Kurrle and Chothia & Lesk.

Adding residue **78H** to the combination of residues **71H** and **73H** does not extend patentability. Ex._1003 at ¶234. These residues were substituted (**71H** and **73H**) in Kurrle, or would have been substituted (**78H**) if necessary. Ex._1003 at ¶234. Claim 77 is also obvious over Queen 1990, Kurrle and Chothia & Lesk.

L. Ground 6: Claim 63 Is Anticipated by Jones or Obvious Over Jones In View of Riechmann

Claim 63 shares elements with claim 1, but also recites "[a] humanized antibody 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."

This merely states the goal of all antibody humanization projects. Jones specifically analyzes the antigenicity of the HuVNP-IgE antibody, finding that it has lost the antigenic determinants associated with the corresponding murine domain. Ex. 1033 at 525. This is consistent with an antibody that "lacks immunogenicity compared to a non-human parent antibody." Jones therefore anticipates claim 63.

However, if claim 63 is construed so that "upon repeated administration to a human patient in order to treat a chronic disease in that patient" is a claim limitation, Jones optionally in view of Riechmann would render claim 63 obvious. Riechmann, like Jones, substituted the CDRs of a human antibody variable domain with the CDRs of a non-human antibody—in Riechmann's case, the rat CAMPATH-1 antibody. Ex. 1069 at 323,325. This humanized antibody was developed for the purpose of "repeated administration to a human patient in order to treat a chronic disease in that patient"—here, the treatment of leukemia, lymphoma, or immune disorders. Ex. 1069 at 325,327.

Because Jones teaches that simply substituting CDRs from a murine antibody into a human antibody can reduce antigenicity, and because the goal of all humanization projects was to decrease immunogenicity upon repeated administration to a human patient in order to treat chronic disorders, a POSA would have been motivated to apply Jones' teaching to a therapeutic application such as Riechmann. Ex. 1003 at 250. Taken together, a POSA would have found it obvious to develop a therapeutic antibody with the substitutions as recited in claim 1 (and disclosed by Jones and Riechmann), resulting in a composition that satisfies claim 63.

M. Secondary Considerations Cannot Preclude Obviousness.

Patent Owner may attempt to assert secondary considerations of nonobviousness, despite no showing of such in the patent. Such evidence is "insufficient" where, as here, there is a "strong [case] of obviousness." *See 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*, 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."). Nor can Patent Owner show that secondary considerations are commensurate with claim scope, given the breadth of

the challenged claims. *See, e.g.*, *Ex Parte Takeshi Shimono,* Appeal 2013-003410 (P.T.A.B. Apr. 29, 2015). And secondary considerations are irrelevant to the anticipation arguments set out above. Boehringer nonetheless preliminarily addresses potential Patent Owner theories below.

1. The Compositions Recited in the '213 Patent Produced No Relevant Unexpected Results.

The '213 patent makes no claim that the claimed compositions achieve any unexpected result. To the contrary, the '213 patent recognizes that residues important for maintaining CDR conformation and binding were well known prior to June 1991. *See* Ex._1001 at 2:63-3:8; Ex._1003 at ¶¶342-43. Given the extensive prior art, successful antibody humanization was readily achievable, not surprising, or unexpected. Ex._1003 at ¶¶342-43. More specifically, successfully humanizing an antibody using a consensus sequence would have been expected. Ex._1003 at ¶342. As Dr. Hale explains, the residues in the consensus sequence are by definition the ones most commonly found in natural human antibody variable regions. *Id*. Thus, a POSA would have expected the consensus sequence to be effective across a wide variety of antibodies.

During prosecution, Genentech argued:

> 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…

Ex._1002 at 540.

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."

Additionally, the data allegedly showing enhanced (allegedly 3-times more) target binding does not show unexpected improvement. Ex._1003 at ¶343. As Dr. Hale explains, the data provided in the '213 patent and provided to the PTO during prosecution is scientifically insufficient to establish any difference in binding at all. *Id.* Furthermore, no challenged claim requires an in improvement in binding affinity. 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. Indeed, Queen 1990 taught that an increase in affinity would have been expected. Ex._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."). Panka 1988 also disclosed framework changes that increase binding affinity, and stated that "[t]he finding that a framework mutation can alter binding to antigen is not unexpected. Ex._1135 at 3083.

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. The scope of the challenged claims include antibodies other than antibody 4D5. Therefore, any need that this antibody filled is not commensurate in scope with the challenged claims.

Further, Patent Owner cannot show the purported invention solved the problem the specification identified. *See, e.g., Norgren Inc. v. ITC*, 699 F.3d 1317 (Fed. Cir. 2012) (claims obvious where "[prior art patent] solved similar problems in a similar way"); *see also In re PepperBall Techs., Inc.*, 469 F. App'x 878, 88283 (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 asserts that the 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 and 4:24-35. Queen 1990, Kurrle and others had already described this process—they set forth why one would desire to

humanize and provided a detailed roadmap on how to do it. Any problems identified in the '213 specification had already been explicitly addressed and solved by the prior art. Ex._1003 at ¶¶342-346.

3. No nexus/commercial success to Herceptin.

Any commercial success experienced with Herceptin[9] does not provide any indicia of nonobviousness of the challenged claims of the '213 patent. *First,* any alleged commercial success of Herceptin has no nexus to the challenged claims because none of the heavy chain residues cited in claim 1 are modified in Herceptin. *Second,* any alleged success is not commensurate in scope with the challenged claims because they are not limited to any particular antibody or class of antibodies. Ex._1003 at ¶346. Therefore, even if Patent Owner can identify one embodiment in its evidence of objective indicia, they will be unable to "demonstrate that untested embodiments falling within the claimed range will behave in the same manner." *Id.* at 4.

Respectfully submitted,

Dated: August 31, 2017

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[9] While Boehringer presumes that Patent Owner will attempt to rely on Herceptin, Boehringer does not concede that Herceptin provides support for any asserted secondary considerations or is even covered by the challenged claims.

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CERTIFICATE OF WORD COUNT

The undersigned certifies that the attached Petition for *Inter Partes* Review of U.S. Patent No. 6,407,213 contains 13,937 words (as calculated by the word processing system used to prepare this Petition), excluding the parts of the Petition exempted by 37 C.F.R. §42.24(a)(1).

Dated: August 31, 2017

/Ira J. Levy/
Ira J. Levy
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Counsel for Petitioner

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105, I certify that I caused to be served a true and correct copy of the foregoing: **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 6,407,213** and the exhibits cited therein by *Federal Express Next Business Day Delivery* on this day, August 31, 2017 on the Patent Owner's correspondence address of record for the subject patent as follows:

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