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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-02031
Patent 6,407,213 B1

Before SHERIDAN K. SNEDDEN, ZHENYU YANG, and ROBERT A. POLLOCK, *Administrative Patent Judges*.

POLLOCK, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Boehringer Ingelheim Pharmaceuticals, Inc. ("Petitioner" or "Boehringer") filed a Petition for an *inter partes* review of claims 1, 2, 4, 25, 29, 62–64, 66, 67, 71, 69, 71–73, 75–78, 80, and 81 of U.S. Patent No. 6,407,213 B1 ("the '213 patent," Ex. 1001). Paper 2 ("Pet."). Genentech, Inc. ("Patent Owner") timely filed a Preliminary Response. Paper 11 ("Prelim. Resp.").

Our authority to institute an *inter partes* review is derived ultimately from 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted unless the information presented in the Petition shows "there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." Upon consideration of the Petition and Preliminary Response, we determine that Petitioner has shown a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim. Accordingly, and for the reasons set forth below, we institute *inter partes* review of claims 1, 2, 4, 25, 29, 62–64, 66, 69, 71, 73, 75–78, 80, and 81 of the '213 patent. As also discussed below, we decline to institute *inter partes* review of claims 67 and 72 of the '213 patent.

A. Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability (Pet. 4):

Ground	Claim(s)	Basis	Reference(s)
1	1, 2, 25, 29, 63, 66, 71, 75, 76, 78, 80, and 81	§ 102	Kurrle[1]

[1] Kurrle, et al., European Patent Application Publication No. 0403156, published December 19, 1990. Ex. 1071.

Ground	Claim(s)	Basis	Reference(s)
2	1, 2, 4, 29, 62–64, 80, and 81	§ 102	Queen 1990[2]
3	1, 2, 4, 25, 29, 62–64, 66, 67, 69, 71, 72, 75, 76, 78, 80, and 81	§ 103	Kurrle and Queen 1990
4	1, 2, 4, 25, 29, 62, 64, 66, 69, 71, 73, 75–78, 80, and 81	§ 102	Jones[3]
5	73 and 77	§ 103	Kurrle, Queen 1990, and Chothia & Lesk[4]
6	63	§ 103	Jones and Riechmann[5]

In support of its patentability challenges, Petitioner relies on the Declaration of Geoffrey Hale, PhD. Ex. 1003.

B. The '213 Patent and Relevant Background

The '213 patent relates to "methods for the preparation and use of variant antibodies and finds application particularly in the fields of immunology and cancer diagnosis and therapy." Ex. 1001, 1:12–14.

A naturally occurring antibody (immunoglobulin) comprises two heavy chains and two light chains. *Id.* at 1:18–20. Each heavy chain has a variable domain (V_H) and a number of constant domains. *Id.* at 1:21–23. Each light chain has a variable domain (V_L) and a constant domain. *Id.* at

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[2] Queen, et al., International Publication No. WO 90/07861, published July 26, 1990. Ex. 1050.
[3] Jones et al., *Replacing the complementarity-determining regions in a human antibody with those from a mouse*, 321 Nature 522–525 (1986). Ex. 1033.
[4] Chothia and Lesk, *Canonical Structures for the Hypervariable Regions of Immunoglobulins*, 196 J. MOL. BIOL. 901–17 (1987). Ex. 1062.
[5] Riechmann et al., Reshaping human antibodies for therapy, 332 Nature 323–327 (1988). Ex. 1069.

1:23–24. The variable domains are involved directly in binding the antibody to the antigen. *Id.* at 1:36–38. Each variable domain "comprises four framework (FR) regions, whose sequences are somewhat conserved, connected by three hyper-variable or complementarity determining regions (CDRs)." *Id.* at 1:40–43. "The constant domains are not involved directly in binding the antibody to an antigen, but are involved in various effector functions." *Id.* at 1:33–34.

Before the '213 patent, monoclonal antibodies targeting a specific antigen, obtained from animals, such as mice, had been shown to be antigenic in human clinical use. *Id.* at 1:51–53. One object of the invention is "to provide methods for the preparation of antibodies which are less antigenic in humans than non-human antibodies but have desired antigen binding and other characteristics and activities." *Id.* at 4:24–28. In accordance with this goal, the Specification states that embodiments within the scope of the claims have "low immunogenicity," or are designed to "minimize the potential immunogenicity of the resulting humanized antibody in the clinic." *Id.* at 52:54–58, 61:56–61.

The '213 patent recognizes efforts to construct chimeric antibodies and humanized antibodies in the prior art. *Id.* at 1:59–2:52. According to the '213 patent, chimeric antibodies are "antibodies in which an animal antigen-binding variable domain is coupled to a human constant domain" (*id.* at 1:60–62), whereas "humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies" (*id.* at 2:32–35).

The ’213 patent also acknowledges the following as known in the prior art:

1. In certain cases, in order to transfer high antigen binding affinity, it is necessary to not only substitute CDRs, but also replace one or several FR residues from rodent antibodies for the human CDRs in human frameworks. *Id.* at 2:53–61.
2. “For a given antibody[,] a small number of FR residues are anticipated to be important for antigen binding” because they either directly contact antigen or “critically affect[] the conformation of particular CDRs and thus their contribution to antigen binding.” *Id.* at 2:62–3:8.
3. In a few instances, a variable domain “may contain glycosylation sites, and that this glycosylation may improve or abolish antigen binding.” *Id.* at 3:9–12.
4. The function of an antibody is dependent on its three-dimensional structure, and amino acid substitutions can change the three-dimensional structure of an antibody. *Id.* at 3:40–43.
5. “[T]he antigen binding affinity of a humanized antibody can be increased by mutagenesis based upon molecular modelling. *Id.* at 3:44–46.

Despite such knowledge in the field, according to the ’213 patent, at the time of its invention, humanizing an antibody with retention of high affinity for antigen and other desired biological activities was difficult to achieve using then available procedures. *Id.* at 3:50–52. The ’213 patent purportedly provides methods for rationalizing the selection of sites for substitution in preparing humanized antibodies and thereby increasing the efficiency of antibody humanization. *Id.* at 3:53–55. In one embodiment, this involves:

> a. obtaining the amino acid sequences of at least a portion of an import antibody variable domain and of a consensus variable domain;

> b. identifying Complementarity Determining Region (CDR) amino acid sequences in the import and the human variable domain sequences;
>
> c. substituting an import CDR amino acid sequence for the corresponding human CDR amino acid sequence;
>
> d. aligning the amino acid sequences o(a Framework Region (FR) of the import antibody and the corresponding FR of the consensus antibody;
>
> e. identifying import antibody FR residues in the aligned FR sequences that are non-homologous to the corresponding consensus antibody residues;
>
> f. determining if the non-homologous import amino acid residue is reasonably expected to have at least one of the following effects: l. non-covalently binds antigen directly, 2. interacts with a CDR; or 3. participates in the V_L-V_H interface; and
>
> g. for any non-homologous import antibody amino acid residue which is reasonably expected to have at least one of these effects, substituting that residue for the corresponding amino acid residue in the consensus antibody FR sequence.

Id. at 4:43–5:5. Figures 1A and 1B of the '213 patent show alignments of light and heavy chain variable regions of mouse antibody muMAb4D5 with human antibody huMAb4D5, along with their resulting consensus sequences (HUV_{Lk}I and HUV_HIII, respectively). *See id.* at 6:57–7:8 (numbering according to Kabat).[6]

[6] Elvin A. Kabat, et al., *Sequences of Proteins of Immunological Interest* 1–23 (1987) (4th Ed.) (NIH, Bethesda, Md.). Ex. 1552. *See also* Ex. 1001, 10:45–56 (indicating that the Kabat numbering scheme for antibodies "assign[s] a residue number to each amino acid in a listed sequence").

C. Illustrative Claims

Among the challenged claims, claims 1, 30, 62–64, 66, 79, and 80 are independent. Claim 1 is illustrative and is reproduced below:

> 1. A humanized antibody variable domain comprising non-human Complementarity Determining Region (CDR) amino acid residues which bind an antigen incorporated into a human antibody variable domain, and further comprising a Framework Region (FR) amino acid substitution at a site selected from the group consisting of: 4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, and 92H, utilizing the numbering system set forth in Kabat.

Depending from claim 1, claim 4 limits the humanized antibody variable domain of claim 1 to "a consensus human variable domain."

D. Related Proceedings

1. District Court Proceedings

According to Petitioner, the '213 Patent is at issue in *Genentech, Inc. v. Amgen Inc.*, No. 1-17-cv-01407 (D. Del.); *Amgen Inc. v. Genentech, Inc.*, and *Genentech, Inc. v. Amgen Inc.*, No. 1-17-cv-01471 (D. Del.). Paper 16, 1. No. 2-17-cv-07349 (C.D. Cal.). Paper 10. Patent Owner further identifies *Celltrion, Inc. v. Genentech, Inc.*, No. 18-cv-00274 (N.D. Cal.) and *Genentech, Inc. v. Celltrion, Inc.*, No. 18-cv-00095 (D. Del.). Paper 18.

2. Inter Partes Reviews

On August 31, 2017, Petitioner filed both the instant Petition and IPR20117-02032 against claims of the '213 Patent. Although these are the first petitions filed by Petitioner Boehringer, a total of eight petitions with related and overlapping grounds have now been filed against the '213 patent.

On August 30, 2016, Mylan Pharmaceuticals Inc., filed IPR2016–01693 and IPR2016–01694. Patent Owner filed Preliminary Responses in each of these cases on December 16, 2016. On March 10, 2017, we terminated the Mylan cases in response to the parties' Joint Motion to Terminate.

On May 8, 2017, Celltrion, Inc. filed IPR2017-01373 and IPR2017-01374. Patent Owner filed Preliminary Responses on September 6, 2017, and we instituted *inter partes* reviews on December 1, 2017. The Celltrion IPRs are currently pending.

On May 25, 2017, Pfizer, Inc. filed IPR2017-01488 and IPR2017-01489. Patent Owner filed Preliminary Responses on September 5 and 6, 2017, respectively, and we instituted *inter partes* reviews on December 1, 2017. The Pfizer IPRs are currently pending.

On September 29, 2017, Samsung Bioepis Co. Ltd, filed IPR2017-02139 and IPR2017-02140, along with motions for joinder to IPR2017-01488 and IPR2017-01489, respectively. On February 22, 2018, we instituted the *inter partes* review and granted Bioepis' motions for joinder.

II. ANALYSIS

Patent Owner requests that we exercise our discretion under 35 U.S.C § 325(d) to deny institution with respect to Grounds 1–3 and 5 because "Boehringer copied Grounds 1-3 and 5 of this Petition from IPR2017-01374 (Celltrion) and IPR2017-01488 (Pfizer), and copied Grounds 1-5 of IPR2017-02032 from IPR2017-01373 (Celltrion) and IPR2017-01489 (Pfizer)— without seeking joinder with those earlier-filed proceedings." Prelim. Resp. 1. According to Patent Owner, "This redundancy would waste the Board's and Patent Owner's resources, and also

would unfairly allow Boehringer to preview the parties' arguments before having to address them itself." *Id.* at 2. With respect to Grounds 4 and 6, Patent Owner further contends that we should deny institution under § 325(d) "because the PTO has already found the challenged '213 claims patentable over both cited references" (Jones and Riechmann). *Id.* We address Patent Owner's arguments below.

A. Section 325(d)

Institution of an *inter partes* review is discretionary. *See Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1367 (Fed. Cir. 2016) (explaining that under § 314(a), "the PTO is permitted, but never compelled, to institute an IPR proceeding"). Accordingly, our rules provide that "the Board may authorize the review to proceed" or "deny some or all grounds for unpatentability for some or all of the challenged claims." 37 C.F.R. § 42.108(a), (b). Our discretionary determination of whether to institute review is guided, in part, by 35 U.S.C. § 325(d), which states, in relevant part:

> (d) MULTIPLE PROCEEDINGS -- . . . In determining whether to institute or order a proceeding under this chapter, chapter 30, or chapter 31, the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office.

35 U.S.C. § 325(d).

Our discretion under § 325(d) involves a balance between several competing interests. *See Neil Ziegman, N.P.Z., Inc. v. Stephens*, Case IPR2015-01860, slip op. at 12–13 (PTAB Feb. 24, 2016) (Paper 11) ("While petitioners may have sound reasons for raising art or arguments similar to those previously considered by the Office, the Board weighs petitioners'

desires to be heard against the interests of patent owners, who seek to avoid harassment and enjoy quiet title to their rights.") (citing H. Rep. No. 112-98, pt. 1, at 48 (2011)). "On the one hand, there are the interests in conserving the resources of the Office and granting patent owners repose on issues and prior art that have been considered previously." *Fox Factory, Inc. v. SRAM, LLC*, Case IPR2016-01876, slip op. 7 (PTAB Apr. 3, 2017) (Paper 8). "On the other hand, there are the interests of giving petitioners the opportunity to be heard and correcting any errors by the Office in allowing a patent—in the case of an *inter partes* review—over prior art patents and printed publications." *Id*.; *see also, Cultec, Inc. v. Stormtech LLC, Case IPR2017-00777 (PTAB Aug. 22, 2017) (Paper 7)* (denying institution under § 325(d) where reference was applied throughout prosecution).

B. Grounds 1–3 and 5

Patent Owner requests that we exercise our discretion under 35 U.S.C § 325(d) to deny institution with respect to Grounds 1–5 because "Boehringer copied Grounds 1–3 and 5 of this Petition from IPR2017-01374 (Celltrion) and IPR2017-01488 (Pfizer), and copied Grounds 1–5 of IPR2017-02032 from IPR2017-01373 (Celltrion) and IPR2017-01489 (Pfizer)—without seeking joinder with those earlier-filed proceedings." Prelim. Resp. 1. Consistent with that assertion, the following charts illustrate that each claim in Grounds 1–3, and 5 of the instant Petition was previously challenged in the original Mylan Petition, as well as in the

presently pending cases (differences from the instant Petition are underlined.).[7]

Petition	Ground	Claim(s)	Basis	Reference(s)
This Petition	1	**1, 2, 25, 29, 63, 66, 71, 75, 76, 78, 80, and 81**	§ 102	Kurrle
IPR2016-01693 (Mylan)	1	**1, 2, 25, 29, 63, 66, 71, 75, 76, 78, 80, and 81**	§ 102	Kurrle
IPR2017-01374 (Celltrion)	1	1, 2, 25, 29, 63, 66, 71, 75, 76, 78, 80, and 81	§ 102	Kurrle
IPR2017-01488 (Pfizer) Joined with IPR2017-02139 (Bioepis)	1	1, 2, 25, 29, 63, 66, 67, 71, 72, 75, 76, 78, 80, and 81	§ 102	Kurrle

Petition	Ground	Claim(s)	Basis	Reference(s)
This Petition	2	1, 2, 4, 29, 62–64, 80, and 81	§ 102	Queen 1990
IPR2016-01693 (Mylan)	2	1, 2, 4, 29, 62–64, 80, and 81	§ 102	Queen 1990
IPR2017-01374 (Celltrion)	2	1, 2, 4, 29, 62–64, 80, and 81	§ 102	Queen 1990
IPR2017-01488 (Pfizer) Joined with IPR2017-02139 (Bioepis)	2	1, 2, 4, 29, 62–64, 80, and 81	§ 102	Queen 1990

[7] According to Petitioner, "[t]he present IPR petition[] offer[s] different arguments from the previously-filed IPR petitions." Pet. 2. Insofar as Petitioner does not elaborate on this statement, and the grounds referenced in the above tables are the same as set forth in the prior IPRs. Accordingly, we presume that Petitioner refers to Grounds 4 and 6.

Petition	Ground	Claim(s)	Basis	Reference(s)
This Petition	3	1, 2, 4, 25, 29, 62–64, 66, 67, 69, 71, 72, 75, 76, 78, 80, and 81	§ 103	Kurrle and Queen 1990
IPR2016-01693 (Mylan)	3	1, 2, 4, 25, 29, 62–64, 65, 66, 67, 69, 71, 72, 75, 76, 78, 80, and 81	§ 103	Kurrle and Queen 1990
IPR2017-01374 (Celltrion)	3	1, 2, 4, 25, 29, 62–64, 66, 67, 69, 71, 72, 75, 76, 78, 80, and 81	§ 103	Kurrle and Queen 1990
IPR2017-01488 (Pfizer) Joined with IPR2017-02139 (Bioepis)	3	1, 2, 4, 25, 29, 62–64, 66, 67, 69, 71, 72, 75, 76, 78, 80, and 81	§ 103	Kurrle and Queen 1990

Petition	Ground	Claim(s)	Basis	Reference(s)
This Petition	5	73 and 77	§ 103	Kurrle, Queen 1990, and Chothia & Lesk
IPR2016-01693 (Mylan)	5	73, 74, 77, and 79	§ 103	Kurrle, Queen 1990, and Chothia & Lesk
IPR2017-01374 (Celltrion)	5	65, 73, 74, 77, and 79	§ 103	Kurrle, Queen 1990, and Chothia & Lesk
IPR2017-01488 (Pfizer) Joined with IPR2017-02139 (Bioepis)	5	73 and 77	§ 103	Kurrle, Queen 1990, and Chothia & Lesk

According to Patent Owner, "[t]his redundancy would waste the Board's and Patent Owner's resources, and also would unfairly allow Boehringer to

preview the parties' arguments before having to address them itself." *Id.* at 2. We find Patent Owner's argument persuasive.

In determining whether to institute an *inter partes* review, we "may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d). As Patent Owner correctly points out, Grounds 1–3 and 5 asserted in the Petition "are essentially identical to those already instituted in" IPR2017-01374 and IPR2017-01488. Prelim. Resp. 12–13. Petitioner filed this Petition before we issued the decisions instituting *inter partes* reviews in IPR2017-01374 and IPR2017-01488. Thus, Petitioner could have sought to join the pending IPRs. It did not do so and the time for requesting joinder has expired. *See* 37 C.F.R. § 42.122. As such, we exercise our discretion under § 325(d) and deny the Petition with respect to Grounds 1–3 and 5.

C. Grounds 4 and 6

Petitioner challenges claims 1, 2, 4, 25, 29, 62, 64, 66, 69, 71, 73, 75–78, 80, and 81 as anticipated by Jones (Ground 4), and further challenges claim 63 as obvious over Jones in view of Riechmann (Ground 6). Pet. 54–64. Patent Owner does not respond on the merits, but argues that we should deny institution of Grounds 4 and 6 under § 325(d) "because the PTO has already found the challenged '213 claims patentable over both cited references." Prelim. Resp. 2, 15–16. We address, in turn, Patent Owner's § 325(d) argument and the merits of Petitioner's challenge.

1. Analysis under §325(d)

The inventors first raised Jones and Riechmann in the Background section of the Specification as illustrating prior efforts to "substitut[e] . . .

rodent CDRs or CDR sequences for the corresponding segments of a human antibody." Ex. 1001, 2:20–26. According to the inventors, Jones shows that, in some cases, "substituting CDRs from rodent antibodies for the human CDRs in human frameworks is sufficient to transfer high antigen binding affinity," whereas Riechmann found it "necessary to additionally replace one . . . framework region (FR) residue[]." *Id.* at 2:53–61.

Jones and Riechmann were also raised in the prosecution leading to the issuance of the '213 patent. In addressing a rejection under 35 USC § 112, first paragraph, Applicants pointed to Jones and Riechmann as among fifteen references exemplifying "potential candidates for humanization . . . . provided in the background section of the application." Ex. 1002, 370; *see id.* at 252, 384–390 (Examiner's rejection). Although the prosecution history contains only this passing reference to Jones, Riechmann was repeatedly cited by the Examiner as part of multiple obviousness rejections involving two or more other references. *Id.* at 253–254, 386–388, 415–418. According to the Examiner, Riechmann taught "a method of reshaping human antibodies for therapy by CDR grafting" that involved "altering the sequence of the antibody to restore packing or to increase binding affinity." *Id.* at 253. Applicants expressly addressed the teachings of Riechmann in traversing the rejections. *See id.* at 372–374, 430–435. The Examiner withdrew the rejections involving Riechmann without further comment. *See id.* at 508–511.

In contrast to the Examiner's focus on Riechmann in setting forth the above rejections, Petitioner's arguments supporting Grounds 4 and 6 focus on Jones as the sole or primary reference. *See* Pet. 54–64. And, as discussed in more detail below, Petitioner broadly interprets the instant

claims as encompassing the CDR-grafted antibodies disclosed in Jones without further amino acid substitution—a construction, Petitioner contends, was apparently not contemplated by the Examiner. *See id.* Petitioner's arguments with respect to Jones, therefore, differ substantially from positions taken by the Examiner during prosecution. Petitioner also relies on the testimony and analysis of Dr. Hale as evidence of unpatentability not available during prosecution. *See, e.g.*, Ex. 1003 ¶¶ 228–232; Ex. 1003C, 779.

Given the limited discussion of Jones in the intrinsic record, and in light of Petitioner's new arguments and evidence, we decline to exercise our discretion to deny institution with respect to these grounds under 35 U.S.C § 325(d).

2. Analysis on the Merits

To anticipate a claim under 35 U.S.C. § 102, "a single prior art reference must expressly or inherently disclose each claim limitation." *Finisar Corp. v. DirecTV Group, Inc.*, 523 F.3d 1323, 1334 (Fed. Cir. 2008). That "single reference must describe the claimed invention with sufficient precision and detail to establish that the subject matter existed in the prior art." *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d 1116, 1120 (Fed. Cir. 2002).

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which that subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). In analyzing the obviousness of a combination of prior art elements,

it can be important to identify a reason that would have prompted one of skill in the art "to combine . . . known elements in the fashion claimed by the patent at issue." *Id.* at 418.

A precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *Id.* Rather, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (internal quotations and citations omitted).

3. Person of Ordinary Skill in the Art

According to Petitioner, a person of ordinary skill in the art

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

Pet. 13–14 (internal citations to Ex. 1003 ¶¶ 24–26 omitted). Patent Owner does not address the level of skill in the art in its Preliminary Response, but has done so in the Pfizer and Celltrion IPRs, which address the same claims of the '213 patent. *See* IPR2017-01488, Paper 6 at 18; IPR2017-01374, Paper 7 at 17–18. Although Petitioner's proposed definition is somewhat more detailed than that previously argued by Patent Owner, at this stage of the proceeding, any differences would not affect the outcome. Accordingly, for purposes of this Decision, and in the interest of consistency, we adopt Patent Owner's proposed definition that "[a] person of ordinary skill for the '213 patent would have had a Ph.D. or equivalent in chemistry, biochemistry, structural biology, or a closely related field, and experience with antibody structural characterization, engineering, and/or biological testing, or an M.D. with practical academic or industrial experience in antibody development," as we have previously done in the Pfizer and Celltrion IPRs. *See* IPR2017-01488, Paper 27 at 8; IPR2017-01374, Paper 15 at 10–11.

We further note that the prior art itself demonstrates this level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown" (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp*., 755 F.2d 158, 163 (Fed. Cir. 1985)).

4. Overview of Jones (Ex. 1033)

Jones "grafted the CDRs from the V_H domain of the mouse monoclonal antibody B1-8 into the V_H domain of the human myeloma

protein NEWM." Ex. 1033, 523. The resulting antibody variable domain, HUV_{NP}, was subsequently grafted to a human ε constant region and co-expressed with human λ light chains to form the humanized IgE antibody, HUV_{NP}-IgE. *Id.* at 523; see Ex. 1003 ¶¶ 128–130. HUV_{NP}-IgE retained the binding specificity of the mouse B1-8 CDRs. Ex. 1033, 524 & Table 1; Ex. 1003 ¶ 131. Figure 2a of the reference compares the human and mouse framework and variable regions of NEWM and B1-8. Ex. 1033, 524. The amino acid sequence of the hybrid HUV_{NP} antibody variable domain of HUV_{NP}-IgE is set forth in Figure 2b. *Id*. According to Jones, HUV_{NP}-IgE lost antigenic determinants associated with the parent mouse antibody. *Id.* at 525 & Fig. 3.

5. Overview of Riechmann (Ex. 1069)

In order to reduce the antigenicity of therapeutically administered non-human antibodies, Riechmann "attempted to build rodent antigen binding sites directly into human antibodies by transplanting only the antigen binding site, rather than the entire variable domain, from a rodent antibody." Ex. 1069, 323. In particular, Riechmann substituted the CDRs of a human antibody variable domain with the CDRs of rat antibody directed against the human lymphocyte/monocyte antigen CAMPATH-1. *Id.* at 325.

Anti-CAMPATH-1 antibodies "have important applications in problems of immunosuppression: for example control of graft-versus-host disease in bone marrow transplantation; management of organ rejection; the prevention of marrow rejection; and the treatment of various lymphoid malignancies." *Id*. Riechmann proposes that the CDR-grafted "human antibody with specificity for the CAMPATH-1 antigen should permit a full analysis of the in vivo potency and immunogenicity of an anti-lymphocyte

antibody with wide therapeutic potential. Even if anti-idiotypic responses are eventually observed, considerable therapeutic benefit could be derived from an extended course of treatment." *Id.* at 327.

6. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016) (upholding the use of the broadest reasonable interpretation standard). Under that standard, we presume that a claim term carries its "ordinary and customary meaning," which "is the meaning that the term would have to a person of ordinary skill in the art in question" at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007); *see also Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016) ("Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history."). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). Limitations, however, may not be read from the specification into the claims (*In re Van Geuns*, 988 F.2d 1181, 1184 (Fed. Cir. 1993)), nor may the Board "construe claims during [an *inter partes* review] so broadly that its constructions are unreasonable under general claim construction principles" (*Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015) (overruled on other grounds by *Aqua Products, Inc. v. Matal*, 872 F.3d 1290 (Fed. Cir. 2017))).

Claim 1 of the '231 patent recites "[a] humanized antibody variable domain . . . 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, and 92H." Depending from claim 1, claim 4 limits the humanized antibody variable domain of claim 1 to "a consensus human variable domain."[8]

Petitioner reasons that "[b]ecause claim 1 requires substitutions in the variable domain, claim 4 must also require substitutions in the variable domain" such that the claims "encompass[] 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." Pet. 7–8.

Petitioner further argues "substitution," and the related term "substituted," do not require the intentional replacement of amino acids in a human consensus variable domain. *See id.* at 8–9. Rather, Petitioner argues, as used in the challenged claims, these terms invoke product-by-process limitations, which should be disregarded in the patentability analysis. *Id.* at 8 (citing, e.g., *Purdue Pharma L.P. v. Epic Pharma, LLC*, 811 F.3d 1345, 1353–54 (Fed. Cir. 2016). Taken together, Petitioner argues that "any

[8] Although we focus our analysis on claim 4 as it depends from claim 1, similar usages are found throughout the challenged claims. Claim 64, for example, recites "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 . . . compris[ing] a Framework Region (FR) substitution where the substituted FR residue" evidences one or more recited physical properties.

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." *Id.* at 56.

We do not find Petitioner's unopposed argument unreasonable on the current record. Accordingly, for the purpose of this Decision, we construe the claim term "substitution" and variants thereof, as referring to the amino acid sequence of an antibody variable domain, irrespective of the process by which that sequence was derived. We further construe claim 4 as encompassing humanized variable domains where only some of the residues in the sequence are amino acids of a consensus human variable domain.

In section II(D)(5), below, we discuss the weight accorded the preamble to claim 63. No other claim term requires express construction for purposes of this decision. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) (instructing that claim terms need only be construed to the extent necessary to resolve the controversy).

1. Analysis of Ground 4

Applying the above construction of "substitution," Petitioner relies on the testimony of Dr. Hale in arguing that 1, 2, 4, 25, 29, 62, 64, 66, 69, 71, 73, 75–78, 80, and 81 are anticipated by Jones. Pet. 54–63. For the purpose of this Decision, we focus on claim 1.

As set forth in the Petition, Dr. Hale compared the sequence of Jones' NEWM protein (containing the HUV_{NP} hybrid heavy chain variable domain) with the consensus sequence HUV_{H}III disclosed in figure 1B of the '213 patent. Pet. 56 (citing Ex. 1003C, 779). According to Petitioner, and assuming that "any differences from the consensus sequence can be considered a 'substitution' of the consensus residue for a non-consensus

residue," Dr. Hale's comparison shows that "the sequence of the HuV_{NP} variable domain disclosed in Jones is the same as the sequence of a human consensus variable domain comprising substitutions at least at framework region sites 43H;69H;70H." *Id.* at 56–57 (citing Ex. 1003 ¶¶ 228–32; Ex. 1003C, 779). As we understand Petitioner's argument, claim 1 is anticipated because Jones discloses a variable domain having the same structure as that disclosed in claim 1, irrespective of how it was prepared. *See id.* at 57 ("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.)". Petitioner further contends that Jones discloses corresponding substitutions of murine amino acids for human framework residues as set forth in the remaining challenged claims. *Id.* at 57–63.

On the present record, we determine that Petitioner has shown a reasonable likelihood that it would prevail in showing the unpatentability of at least claim 1 of the '231 patent. Accordingly, we institute *inter partes* review of claims 1, 2, 4, 25, 29, 62, 64, 66, 69, 71, 73, 75–78, 80, and 81 as anticipated by Jones.

2. Analysis of Ground 6

With respect to Ground 6, Petitioner further challenges claim 63 as obvious in view of Jones and Reichmann. Pet. 63–64. Claim 63 recites a humanized antibody comprising amino acid substitutions at the same sites as set forth in claim 1. As with Ground 4, Petitioner relies on Dr. Hale's comparison to show that Jones discloses a subset of those amino acid substitutions. *See id.* at 63. Addressing claim 63's recitation of "[a] humanized antibody which lacks immunogenicity compared to a non-human

parent antibody upon repeated administration to a human patient," Petitioner reasonably argues that "[t]his merely states the goal of all antibody humanization projects." *Id.*; *see* Ex. 1033, 525 (indicating that HUV_{NP}-IgE lost undesirable antigenic determinants associated with the parent mouse antibody).

Petitioner relies on Riechmann only to the extent we construe the preamble as limiting. *Id.* at 63. In particular, Petitioner argues that Riechmann discloses a humanized antibody developed as a therapeutic for treating leukemia, lymphoma and immune disorders, which is, thus, for "repeated administration to a human patient in order to treat a chronic disease in that patient" as recited in the preamble.[9] *Id.*

At this stage of the proceeding, neither party has taken a position as to whether the preamble is limiting. However, as in the present case, where the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states the purpose or intended use of the invention, and not a distinct definition of any claimed limitation, the preamble is not considered limiting and is of no significance to claim construction. *See Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999). For the purpose of this Decision, we accord no patentable weight to the preamble of claim 63. The parties are invited to address the issue of whether the preamble limits the scope of claim 63 in the Patent Owner Response and Petitioner's Reply.

[9] With respect to 35 U.S.C § 325(d), Patent Owner does not argue, nor do we discern, that Applicant's relied on Riechmann for this purpose.

As discussed above, Petitioner has shown a reasonable likelihood that it would prevail in showing the unpatentability of claim 1 of the '231 patent for anticipation, which, absent the preamble, is substantially similar to claim 63. Because anticipation is the epitome of obviousness, Petitioner has also shown a reasonable likelihood that it would prevail in showing the unpatentability of claim 63 for obviousness over Jones or Jones in view of Riechmann.[10] *See In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002) (quoting *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983)). Further, to the extent the preamble of claim 63 is limiting, Petitioner presents a reasoned and presently unopposed argument that Riechmann teaches or suggests "repeated administration to a human patient in order to treat a chronic disease in that patient," as set forth in the preamble. *See* Pet. 63–64.

Accordingly, we institute *inter partes* review of claim 63 in view of Jones and in view of Jones and Riechmann.

III. ORDER

Accordingly, it is

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review is hereby instituted on the following grounds:

1. claims 1, 2, 4, 25, 29, 62, 64, 66, 69, 71, 73, 75–78, 80, and 81, as anticipated by Jones,
2. claim 63, as obvious over Jones, and

[10] Patent Owner does not raise secondary consideration evidence in the Preliminary Response. To the extent such evidence is raised in the Patent Owner Response, we will consider the parties' arguments and evidence on the fully developed record.

3. claim 63, as obvious over Jones in view of Riechmann.

FURTHER ORDERED that no other ground of unpatentability is authorized in this *inter partes* review.

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(a), *inter partes* review of the '213 patent is hereby instituted commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial.

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