

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BICARA THERAPEUTICS, INC.,
Petitioner

v.

THE JOHNS HOPKINS UNIVERSITY,
Patent Owner

CASE: PGR2026-00025

Patent No. 12,295,968

PATENT OWNER'S PRELIMINARY RESPONSE

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Patent Trial and Appeal Board
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<i>Allstate Ins. Co. v. Plambeck</i> , 66 F. Supp. 3d 782 (N.D. Tex. 2014)	11
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<i>Amgen Inc. v. Sanofi</i> , 598 U.S. 594 (2023).....	<i>passim</i>
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<i>Karim v. Jobson,</i> Interference No. 105,376, 2007 WL 5211664 (B.P.A.I. Feb. 28, 2007)	23
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Other Authorities

MPEP § 2103 (9th ed. Rev. 1, Jan. 2024).....	23
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INDEX OF EXHIBITS

Exhibit No.	Description
2001	<i>History</i> , BIOCON, https://www.biocon.com/docs/SHP-Website-2025.pdf [https://perma.cc/WR8S-LW4Y] (downloaded on Mar. 17, 2026).
2002	<i>General information about company</i> , BIOCON, https://archive.biocon.com/biocon_aboutus_history.asp [https://perma.cc/VAR5-T45A] (downloaded on Mar. 17, 2026).
2003	Gloria Haraito, <i>Strong Wall Street Debut Shows Potential of Indian Billionaire-Backed Bicara's Cancer Drugs</i> , FORBES (Sept. 21, 2024), https://www.forbes.com/sites/gloriaharaito/2024/09/21/strong-wall-street-debut-shows-potential-of-indian-billionaire-backed-bicaras-cancer-drugs/ (downloaded on Mar. 17, 2026).
2004	Bicara Therapeutics Inc., Amendment No. 3 to Registration Statement (Form S-1/A) (Sept. 11, 2024), https://ir.bicara.com/static-files/e47a411a-9c71-4d3a-af2a-925c015486f4 [https://perma.cc/VE8Y-S2QD] (downloaded on Mar. 17, 2026).
2005	Machine-generated transcript of UNBOXING BENGALURU, <i>From Garage Startup to India's Pharma Giant ft. Kiran Mazumdar-Shaw FCTC Ep. 1 Pt. 1</i> (YOUTUBE, Oct. 8, 2024), https://www.youtube.com/watch?v=fKVfUfX825w (last visited on Mar. 17, 2026).
2006	Amirah Al Idrus, <i>Bicara Debuts with \$40M from Biocon to Bankroll Bifunctional Antibodies</i> , FIERCE BIOTECH (Mar. 15, 2021), https://www.fiercebiotech.com/biotech/bicara-debuts-40m-from-biocon-to-bankroll-bifunctional-antibodies (downloaded on Mar. 17, 2026).
2007	Bicara Therapeutics, Inc., Proxy Statement (Form DEF 14A) (Apr. 25, 2025), https://ir.bicara.com/static-files/fd7b4b0e-c56d-4387-9fbf-043196a22590 [https://perma.cc/Q9CT-5F5Q] (downloaded on Mar. 17, 2026).
2008	Bicara Therapeutics Inc., Quarterly Report (Form 10-Q) (Nov. 10, 2025), https://ir.bicara.com/static-files/0e5f262d-98b6-43c6-84e9-54586e258753 [https://perma.cc/6YHG-NHHG] (downloaded on Mar. 17, 2026).
2009	<i>Shareholder</i> , BLACK'S LAW DICTIONARY (12th ed. 2024) (downloaded on Mar. 17, 2026).
2010	<i>Non-Final Rejection</i> dated Dec. 3, 2024 in Appl. No. 18/883,719.

Exhibit No.	Description
2011	<i>Examiner Interview Summary Record</i> dated Dec. 23, 2024 in Appl. No. 18/883,719.
2012	Johns Hopkins University, <i>JOHNS HOPKINS UNIVERSITY FACT BOOK</i> (May 2023), https://web.archive.org/web/20250428011824/https://www.jhu.edu/assets/uploads/2018/12/johnshopkinsfactbook.pdf (downloaded on Mar. 17, 2026).
2013	Econsult Solutions, Inc., <i>QUANTIFYING THE ECONOMIC FOOTPRINT AND CATALYTIC ROLE OF JOHNS HOPKINS</i> (Oct. 10, 2025), https://gce.jhu.edu/wp-content/uploads/2025/10/Johns-Hopkins-Impact-Report-2025-10-10-Final.pdf (downloaded on Mar. 17, 2026).
2014	<i>Johns Hopkins University - University Profile</i> , https://research.com/university/johns-hopkins-university (downloaded on Mar. 18, 2026).
2015	<i>Research.com</i> , https://www.linkedin.com/company/research-com [https://perma.cc/C8MU-Q7XY] (downloaded on Mar. 18, 2026).
2016	Johns Hopkins University, <i>Intellectual Property Policy</i> , https://www.jhu.edu/assets/uploads/2014/09/intellectual_property_policy.pdf (downloaded on Mar. 18, 2026).
2017	Johns Hopkins Med., <i>Johns Hopkins Researchers Invent New Technology for Cancer Immunotherapy</i> , (Mar. 1, 2018), https://www.hopkinsmedicine.org/news/newsroom/news-releases/2018/03/johns-hopkins-researchers-invent-new-technology-for-cancer-immunotherapy (downloaded on Mar. 18, 2026).
2018	<i>Y-Trap, Inc. v. Biocon Ltd.</i> , No. 24-12678-GAO, Amended Answer, Dkt. 120 (Nov. 11, 2025).
2019	Bicara Therapeutics Inc., Annual Report (Form 10-K) (Mar. 30, 2026), https://ir.bicara.com/static-files/e0668c54-a117-474a-a534-e903979a75ef [https://perma.cc/VCJ5-C2SQ] (downloaded on Apr. 6, 2026).
2020	<i>Y-Trap, Inc. v. Biocon Ltd.</i> , No. 24-12678-GAO, First Amended Complaint, Dkt. No. 58 (Jan. 31, 2025).
2021	Gwendolyn Wu, <i>Two Antibody Startups File for IPOs Amid Summer Slump</i> , <i>BIOPHARMA DIVE</i> (Aug. 23, 2024), https://www.biopharmadive.com/news/bicara-zenas-ipo-summer-biotech/725104/ [https://perma.cc/Q4ZG-QPN6] (downloaded on Apr. 15, 2026).

Exhibit No.	Description
2022	Rowan Walrath, <i>Indian Biopharma Spinout Raises Second Nine-Figure Round This Year</i> , BOS. BUS. J. (Dec. 12, 2023), https://www.bizjournals.com/boston/news/2023/12/12/bicara-series-c-nine-figure-round.html (downloaded on Apr. 16, 2026).
2023	Excerpts of <i>Y-Trap 2026 Company Profile: Valuation, Funding & Investors</i> , https://pitchbook.com/profiles/company/185290-93 (downloaded on Apr. 16, 2026).
2024	<i>Grantome: Search</i> , https://grantome.com/search?q=@author%20%20Atul%20Bedi [https://perma.cc/37VW-FMRF] (downloaded on Apr. 17, 2026).
2025	John Mendelsohn et al., <i>CCR 20th Anniversary Commentary: A Chimeric Antibody, C225, Inhibits EGFR Activation and Tumor Growth</i> , 21(2) Clinical Cancer Rsch. 227 (Jan. 15, 2015), https://aacrjournals.org/clincancerres/article-pdf/21/2/227/2026982/227.pdf [https://perma.cc/2MUD-886Y].
2026	Letter from Karen D. Weiss, Ctr. for Drug Evaluation & Rsch., to Lily Lee, ImClone Sys. Inc., BLA Approval, STN BL 125084/0 (Cetuximab) (Feb. 12, 2004), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2004/125084ltr.pdf .
2027	U.S. Food & Drug Admin., FDA-Approved Labeling for ERBITUX™ (Cetuximab), BLA STN 125084 (approved Feb. 12, 2004), https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/125084lbl.pdf .
2028	Feng He et al., <i>High Throughput Thermostability Screening of Monoclonal Antibody Formulations</i> , 99(4) J. Pharm. Sci. 1707 (Apr. 2010), https://jpharmsci.org/article/S0022-3549(16)30499-3/abstract .
2029	Gavin C. Barnard et al., <i>High-throughput Screening and Selection of Yeast Cell Lines Expressing Monoclonal Antibodies</i> , 37(9) J. Indus. Microbiology & Biotech. 961 (Sept. 1, 2010), https://academic.oup.com/jimb/article-pdf/37/9/961/34736419/jimb0961.pdf [https://perma.cc/H7JE-THPU].
2030	Neil I. Goldstein et al., <i>Biological Efficacy of a Chimeric Antibody to the Epidermal Growth Factor Receptor in a Human Tumor Xenograft Model</i> , 1(11) Clinical Cancer Rsch. 1311 (Nov. 1, 1995), https://aacrjournals.org/clincancerres/article-pdf/1/11/1311/1950051/1311.pdf [https://perma.cc/3RZV-YN78].

Exhibit No.	Description
2031	Kristian M. Müller et al., <i>The First Constant Domain (C_H1 and C_L) of an Antibody Used as Heterodimerization Domain for Bispecific Miniantibodies</i> , 422 FEBS LETTERS 259 (Jan. 30, 1998), https://plueckthun.bioc.uzh.ch/wp-content/uploads/Publications/APpub0137.pdf [https://perma.cc/P2H7-MXK2].
2032	Bryan A. Garner, <i>Garner's Modern English Usage</i> (4th ed. 2016).
2033	GenScript, <i>Biology Terms Dictionary</i> , https://www.genscript.com/biology-glossary/17561/scfv-fc (downloaded May 18, 2026).
2034	Creative Biolabs, <i>scFv-CH1/CL</i> , https://www.creative-biolabs.com/bsab/category/scfv-ch1-cl-1505.htm (downloaded May 18, 2026) [https://perma.cc/HJU8-A4AB].
2035	Daniela Röthlisberger et al., <i>Domain Interactions in the Fab Fragment: A Comparative Evaluation of the Single-chain Fv and Fab Format Engineered with Variable Domains of Different Stability</i> , 347 J. MOL. BIOL. 773 (Apr. 8, 2005), https://plueckthun.bioc.uzh.ch/wp-content/uploads/Publications/APpub0255.pdf [https://perma.cc/KXG3-ZDY9].

I. INTRODUCTION

The Johns Hopkins University (“JHU” or “Patent Owner”) submits this preliminary response to the post grant review of U.S. Patent No. 12,295,968 (“the ’968 patent”, EX1001), filed by Petitioner Bicara Therapeutics, Inc. (“Bicara” or “Petitioner”).

The Board should deny institution because the ’968 patent is ineligible for Post-Grant Review proceedings because it has an effective filing date prior to March 16, 2013. In particular, the ’968 patent has a clear, unbroken priority chain to PCT/US2011/027317 (“the ’317 PCT Application”), filed on March 4, 2011. Further, because the ’968 patent specification fully complies with 35 U.S.C. § 112 for all claims of the ’968 patent and is virtually identical to the ’317 PCT Application specification, the challenged claims are entitled to priority as of the ’317 PCT Application filing date, March 4, 2011.

II. OVERVIEW OF THE ’968 PATENT

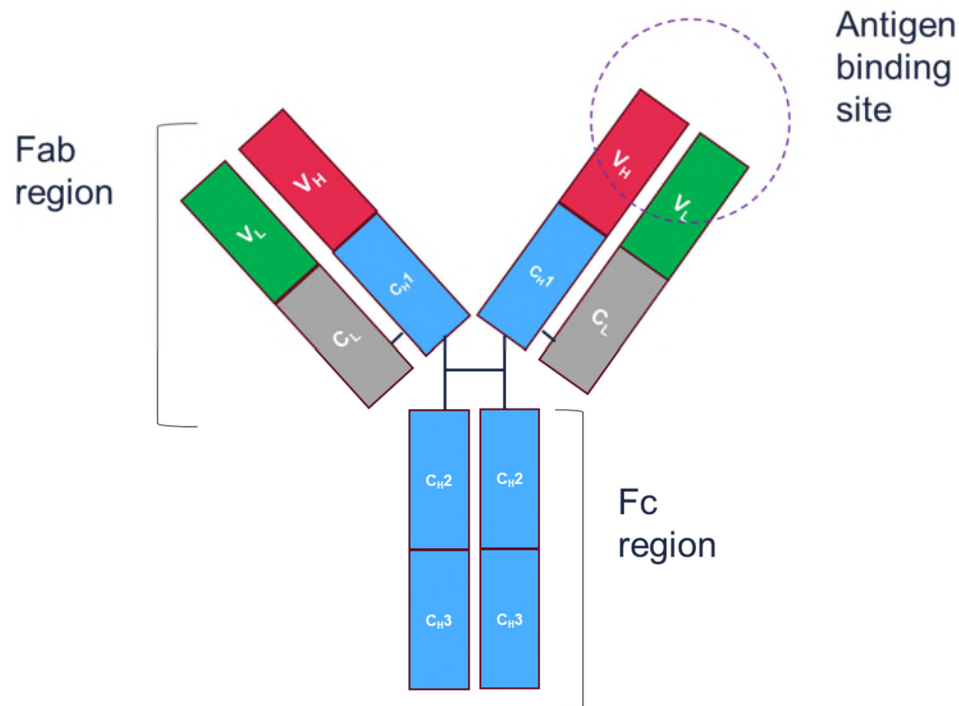
The ’968 patent is directed to the discovery of revolutionary cancer immunotherapies, including the use of novel fusion proteins—*i.e.*, proteins with multiple moieties fused together—and their use in cancer immunotherapy. EX1001 at 2:12-15. These fusion proteins counteract tumor-induced immune tolerance and enhance the antitumor efficacy of chemotherapy by activating T cell-mediated adaptive antitumor immunity against resistant or disseminated cancer cells.

EX1001 at 2:26-31. The claimed fusion proteins harness the proven clinical efficacy of anti-epidermal growth factor receptor (“anti-EGFR”) antibodies (*i.e.*, cetuximab) with a transforming growth factor beta receptor II (“TGF β RII”) that boosts the immune system’s response to cancer cells. EX1001 at 21:18-26.

III. OVERVIEW OF ANTIBODY STRUCTURE AND ANTIBODY FRAGMENTS

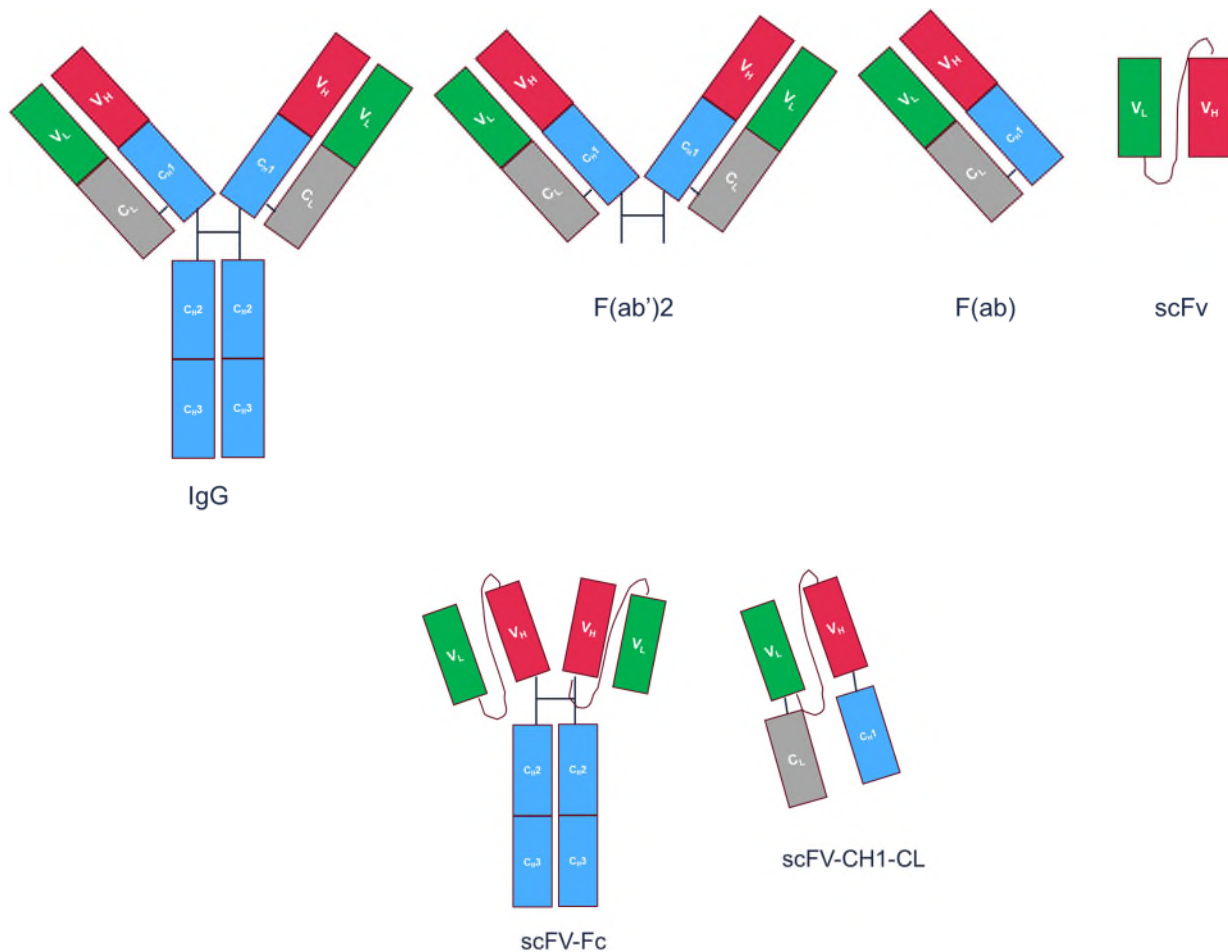
A. Antibody Structure.

An antibody (“Ab”) is a large protein belonging to the immunoglobulin superfamily, which is used by the immune system to identify and neutralize antigens. Antibodies are Y-shaped proteins composed of four polypeptide chains—two identical heavy (“H”) chains and two identical light (“L”) chains—linked by disulfide bonds. The structure consists of two **fragment antigen-binding (“Fab”) regions** (arms) for binding to a target (a region or “antigen” on, *e.g.*, a cancer cell or a virus) and a **Fragment crystallizable (“Fc region”)** (stem) that provokes a desirable response from the body’s immune system. The arms are connected to the stem by a flexible structure known as the hinge region.



Each antibody has two heavy and two light chains. Each heavy and light chain contains a variable region (V_L and V_H) and a constant region. The antibody variable region (“V-region”) is the antigen-binding tip of the antibody and contains Complementarity Determining Regions (“CDRs”) (CDR1-3) on each chain. These CDRs provide unique specificity and high-affinity binding to specific antigens. The constant regions (C_L, C_{H1}, C_{H2}, C_{H3}) are the relatively invariant portion of the heavy and light chain and determines the class of the antibody (immunoglobulin G (“IgG”), immunoglobulin M (“IgM”), etc.). The constant region can interact with immune cells to mediate effector functions and bind to Fc receptors.

Antibody fragments: Antibody fragments are smaller, engineered, or enzymatic-derived portions of antibodies that retain the specific antigen-binding capabilities of the full-length antibody. Common types include Fab, F(ab')₂, and single chain fragment variable (“scFv”), which offer better tissue penetration and lower immunogenicity for diagnostics, imaging, and therapies.



F(ab')₂ fragments are produced by proteolytic digestion that retains an antibody's disulfide bonds within the hinge region. The resulting product is a mini-

Y with both Fab regions still attached to one another. Fab' fragments are produced by mild reduction of F(ab')₂ fragments, which reduces the hinge region disulfide bonds, resulting in two independent Fab fragments with small tails of the hinge region. Fab fragments are produced by proteolytic digestion above the hinge-region, which results in two independent Fab fragments. scFv fragments are composed of the variable domains of the heavy and light chains of an antibody but also include certain molecules which include the constant regions of antibodies, such as scFv-Fc and scFv-C_H1-CLfc. For an scFv-Fc fusion, the scFv is directly linked to the hinge and Fc domains of an antibody (typically IgG1). This format extends the in vivo half-life of an scFv from a few hours to several days and restores bivalent binding. scFv-C_H1-C_L fusions retain the constant heavy 1 (C_H1) and constant light (C_L) domains of a natural Fab fragment providing increased structural stability, better manufacturability, and helps prevent spontaneous aggregation.

IV. PERSON OF ORDINARY SKILL IN THE ART (POSITA) AND CLAIM CONSTRUCTION

A. Person of Ordinary Skill in the Art.

Petitioner proposes a high level of ordinary skill in the art, namely a POSITA “for the challenged claims as of the earliest effective filing date would have held a Ph.D. or equivalent (for example, 4 to 5 years of work experience) in

biochemistry, molecular biology, immunology, or a closely related field,” including experience with “antibody domain and sequence manipulation, construction, expression, and purification of recombinant” and “experience in the medicinal, pharmaceutical, or biotech industry.” Pet. at 16-17.

Solely for purposes of Patent Owner’s Preliminary Response, Patent Owner does not dispute the preceding proposal for a POSITA. Therefore, at this stage, the Board has discretion to adopt or reject Petitioner’s proposal for a POSITA. *See, e.g., Phison Elecs. Corp. v. Vervain, LLC*, PGR2024-00047, Paper 9 at 15 (P.T.A.B. Mar. 17, 2025); *DynaEnergetics US, Inc. v. GEODynamics, Inc.*, PGR2018-00065, Paper 8 at 9 (P.T.A.B. Nov. 15, 2018); *Allergan, Inc. v. BTL Healthcare Techs. A.S.*, PGR2021-00020, Paper 16 at 9 (P.T.A.B. June 16, 2021).

B. Claim Construction.

Here, Petitioner proposes claim constructions for two terms: “scFv” and the term “or” as it appears in the longer limitation “the antibody fragment comprises a light chain domain or a variable heavy chain domain” should be construed as “the antibody fragment comprises either a light chain domain or a variable heavy chain domain, but not both.” Pet. at 20-21. As discussed below, each of Petitioner’s proffered constructions should be rejected because both improperly narrow the plain meaning of these claims. There are “*only two exceptions*” to the heavy presumption that claim terms are construed according to their plain-and-ordinary

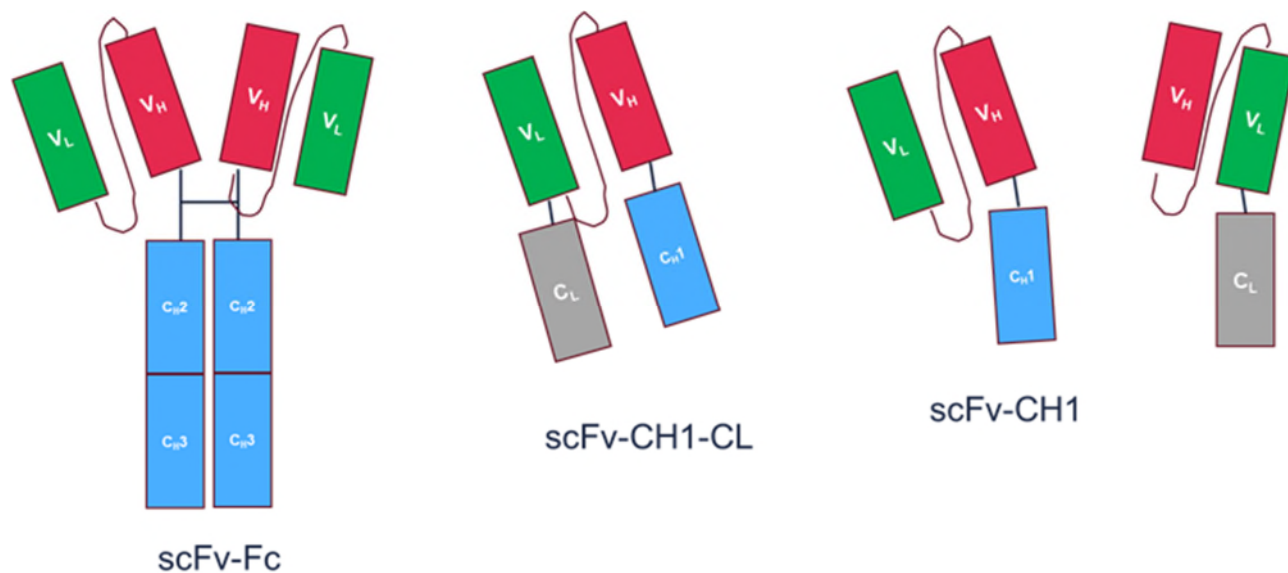
meaning: (1) when the patentee acts as his or her own lexicographer; or (2) when the patentee disavows the full scope of the claim term either in the specification or during prosecution. *Thorner v. Sony Comput. Ent. Am. LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012). The standards for finding either lexicography or disavowal “are exacting.” *Hill-Rom Servs., Inc. v. Stryker Corp.*, 755 F.3d 1367, 1371 (Fed. Cir. 2014) (emphasis added). Petitioner fails to identify either lexicography or disavowal that justifies narrowing the plain meaning as reflected in both of its constructions.

1. Petitioner’s construction of “scFv” improperly narrows the plain meaning of claim 2.

Claim 2 of the ’968 patent recites “the targeting moiety comprises an antibody fragment selected from a Fab or scFv.” “Comprising” is an open-ended transition phrase with a well-understood meaning in patent law: “including, but not limited to.” In the context of claim 2, “comprising” means that the targeting moiety includes but is not limited to a Fab or an scFv, *i.e.*, the targeting moiety can include more than just a Fab or scFv.

Targeting moieties in the form of fusion molecules that include an scFv and other components are well-known in the art. One example is an scFv-Fc fusion where the scFv is directly linked to the hinge and Fc domains of an antibody (typically IgG1) which results in increased half-life of the molecule (see below).

See EX2033.¹ Another example is a scFv- C_H1 - C_L fusion where the scFv retains the constant heavy 1 (C_H1) and constant light (C_L) domains of a natural Fab fragment providing increased structural stability (see below). See EX2034. Further, some scFv molecules incorporate the C_H1 or C_L constant regions of the heavy or light chains (see below). EX2031 at 259-260. Muller et al. produced an scFv- C_H1 molecule by fusing an IgG C_H1 domain to an anti-EGFR scFv and an scFv- C_L molecule by fusing the C_L domain of kappa light chain to an anti-CD2 scFv. EX2031 at 259.



¹ The drawings below were created to imitate the style of drawing used in the Petition and elsewhere in this Patent Owner Preliminary Response.

A particularly relevant example is the scFv-C_L fusion shown on the far right above, which includes an entire scFv (*i.e.*, variable regions from a heavy chain and a light chain joined by a peptide bond) in addition to a light chain constant region bound to the scFv. In the context of claim 1, the V_L (variable region of the light chain) and C_L (constant region of the light chain) are SEQ ID NO:71 and the V_H is the amino acids 1-119 of SEQ ID NO:71. The scFv-C_{H1}-C_L example shown above (second from the left) includes everything from the scFv-C_L fusion plus an additional constant region from the heavy chain. Such fusion molecules were known in the art at the time of the '968 patent. EX2035 at 3 (see Fig. 1).

As demonstrated in all of the examples above, targeting moieties that include an scFv as well as additional components (heavy and light chain constant and variable regions) were known in the art at the time of the '968 patent. Thus, the plain meaning of an scFv does not preclude the scFv from comprising one part of a larger targeting moiety as recited in claim 1.

Petitioner identifies no disavowal or lexicography anywhere in the specification or prosecution history that modifies the plain meaning of either “comprising” or “scFv” to justify restricting claim 2 such that the claimed targeting moiety consists of only an scFv when the targeting moiety includes an scFv as asserted in the Petition at 46-47. As a result, Petitioner’s construction must be

rejected. *Thorner v. Sony Computer Ent. Am. LLC*, 669 F.3d 1362, 1367 (Fed. Cir. 2012).

2. Petitioner’s construction of “or” is improperly narrow.

Petitioner construes the term “the antibody fragment comprises a light chain domain or a variable heavy chain domain” as “the antibody fragment comprises either a light chain domain **or** a variable heavy chain domain, but not both.” Pet. at 20 (emphasis added). This construction improperly narrows the plain meaning of “or” in this term. The plain meaning of “or” includes both stated alternatives, because under “the ordinary sense of the word, understood by everyone and universally accommodated by the simple *or*,” the word carries an inclusive sense and is interchangeable with “and/or.” EX2032 at 5; *see Fortin v. Comm’r of Soc. Sec.*, 112 F.4th 411, 422 (6th Cir. 2024) (“But the word ‘or’ can be used in the inclusive sense (A or B, or both) And ‘[t]he meaning of *or* is usually inclusive.’”) (alterations in original) (quoting Bryan A. Garner, *Garner’s Dictionary of Legal Usage* 639 (3d ed. 2011)).

For example, “[w]hen a waiter offers a patron ‘coffee or dessert,’ an ordinary English speaker understands that he can have both coffee *and* dessert if he so chooses.” *Rush v. Kijakazi*, 65 F.4th 114, 120 (4th Cir. 2023); EX2032 at 5 (“If you are offered coffee or tea, . . . you may for whatever reason order both. This is the

ordinary sense of the word, understood by everyone and universally accommodated by the simple *or*.”).

Instead of relying on the “ordinary sense of the word,” Petitioner proffers the unusual meaning of the word that “comes up when the choices are mutually exclusive.” EX2032 at 5. As numerous authorities have noted, the “meaning of *or* is usually inclusive” meaning “A or B, or both,” instead of the “the exclusive sense (A or B, but not both).” *Fortin*, 112 F.4th at 422; *see Texas Standard Oil Co. v. Forest Oil Corp.*, No. CV G-05-490, 2008 WL 11399510, at *4 (S.D. Tex. Jan. 3, 2008) (“Authorities agree that ... *or* has an inclusive sense as well as an exclusive sense ... The meaning of *or* is usually inclusive.”) (alterations and emphases in original) (quoting Bryan A. Garner, *Dictionary of Modern Legal Usage* 624 (2d ed. 1995)).

Petitioner’s argument that the term “or” should be given its exclusive sense, instead of its inclusive sense is misplaced, because “[t]he ordinary meaning of ‘or,’ as used disjunctively, is not to indicate an exclusive alternative—that is, one or the other but not both.” *Allstate Ins. Co. v. Plambeck*, 66 F. Supp. 3d 782, 788 (N.D. Tex. 2014). On the contrary, even when “disjunctive, ‘or’ is also ‘usually inclusive.’” *Lance M. v. Kijakazi*, No. 2:21-CV-628, 2022 WL 3009122, at *12 (E.D. Va. July 13, 2022), *R. & R. adopted*, 2022 WL 3007588 (E.D. Va. July 28, 2022).

The cases that Petitioner cites to “support” its proffered construction for the term “or” are mischaracterized and readily distinguishable. Petitioner’s reliance on *SkinMedica, Inc. v. Histogen Inc.*, 727 F.3d 1187 (Fed. Cir. 2013) is illustrative. *See* Pet. at 22. The list at issue in *SkinMedica* was recited in the specification and included three structures for cell culturing: a one-dimensional structure; a two-dimensional structure; and a three-dimensional structure. *See* 727 F.3d at 1199 (“The cells are cultured in monolayer, beads (*i.e.*, two-dimensions) or, preferably, in three-dimensions.”) (emphasis removed) (quoting U.S. Patent No. 6,372,494 at 7:24-29). That list was relevant because the panel considered whether “two-dimensional, culturing in beads [could] be the three-dimensional culturing required by the claims.” 727 F.3d at 1202.

In view of the patent “clearly differentiat[ing] between cells cultured using beads and those cultured in three-dimensions” and “expressly cho[osing] to define beads as culturing in ‘two-dimensions,’” the *SkinMedica* panel concluded that “culturing in beads cannot be the three-dimensional culturing required by the claims.” 727 F.3d at 1199-1202. In other words, it was apparent from the intrinsic evidence in *SkinMedica* that the list of structural choices was both disjunctive and mutually exclusive, because the specification clearly indicated that a structure cannot be both two-dimensional and three-dimensional. *See id.* at 1202 (“[T]he use of the disjunctive in context of the entire specification and prosecution history in

evidence plainly evinces an intent of the inventors to classify culturing with beads as a non-three-dimensional cell culturing method.”). Petitioner fails to identify any similar intrinsic evidence that would warrant reaching the conclusion reached in *SkinMedica*. Nor does Petitioner’s expert opine on the issue, despite offering opinions on the “scFv” term.

Petitioner has identified neither lexicography nor disavowal that justifies narrowing “or” from its ordinary, inclusive sense to its exclusive sense. Therefore, the Board should reject Petitioner’s proffered construction for the term “or” in claim 3. *See Wasica Fin. GmbH v. Cont’l Auto. Sys., Inc.*, 853 F.3d 1272, 1282 (Fed. Cir. 2017) (“[A]bsent a clear disavowal or alternative lexicography by a patentee, he or she ‘is free to choose a broad term and expect to obtain the full scope of its plain and ordinary meaning.’”) (quoting *Thorner*, 669 F.3d at 1367).

V. THE ’968 PATENT IS INELIGIBLE FOR POST-GRANT REVIEW PROCEEDINGS

A. Background Law.

1. Priority in the PGR context.

“The post-grant review provisions set forth in Section 6(d) of the AIA apply only to patents subject to the first-inventor-to-file provisions of the AIA.” *US Endodontics, LLC v. Gold Standard Instruments, LLC*, PGR2015-00019, Paper 17 at 7 (P.T.A.B. Jan. 29, 2016) (footnote omitted).

A “patent that issues from an application filed after March 16, 2013, that claims priority to an application filed before March 16, 2013, is available for post-grant review ‘if the patent contains ... at least one claim that was not disclosed in compliance with the written description and enablement requirements of § 112(a) in the earlier application for which the benefit of an earlier filing date prior to March 16, 2013 was sought.’” *Id.* at 8 (alteration in original) (footnote omitted) (quoting *Inguran, LLC v. Premium Genetics (UK) Ltd.*, PGR2015-00017, Paper 8 at 11 (P.T.A.B. Dec. 22, 2015)).

Petitioner has the burden on “the issue of entitlement to a claimed priority date [when it] arises in the context of post-grant review eligibility.” *US Endodontics*, PGR2015-00019, Paper 17 at 10-11. Thus, when the challenged patent issued from an application filed after March 16, 2013 and claims priority to an application filed before March 16, 2013, the “Petitioner bears the burden of proving that the challenged claims lack the benefit of the filing date of the earliest application that supports the claims.” *Ecto World, LLC v. Rai Strategic Holdings, Inc.*, PGR2024-00049, Paper 10 at 15 (P.T.A.B. Mar. 10, 2025).

The Board has repeatedly rejected challenges when the petitioner fails to carry its burden to establish that a priority chain is broken due to issues of written description or enablement. *See, e.g., Concert Pharms., Inc. v. Incyte Corp.*, PGR2017-00034, Paper 9 at 10, 13-14 (P.T.A.B. Jan. 11, 2018); *Novartis Pharms.*

Corp. v. Plexxikon Inc., PGR2018-00069, Paper 16 at 22 (P.T.A.B. Jan. 16, 2019);
Ecto World, PGR2024-00049, Paper 10 at 18.

2. The written description requirement.

“The purpose of the adequate written description requirement is to ensure that the inventor had possession of the claimed subject matter at the time the application was filed.” *In re Alton*, 76 F.3d 1168, 1175 (Fed. Cir. 1996). “To satisfy the written-description requirement of §112 ¶ 1, a patent’s specification must ‘reasonably convey[]’ that, as of the filing date, ‘the inventor[s] had possession of the claimed subject matter’—*i.e.*, that they ‘actually invented the invention claimed.’” *Teva Pharms. Int’l GmbH v. Eli Lilly & Co.*, 172 F.4th 1367, 1374 (Fed. Cir. 2026) (alterations in original) (quoting *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc)).

Under *Ariad*, “[t]his test requires an ‘objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art,’ who ‘comes to the patent with the knowledge of what has come before.’” *Teva*, 172 F.4th at 1374 (citation omitted) (first quoting *Ariad*, 598 F.3d at 1351; then quoting *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006)); see *Medtronic, Inc. v. Teleflex Innovations S.a.r.l.*, 69 F.4th 1341, 1354 (Fed. Cir. 2023) (“As the Board acknowledged, written description requires only that a skilled artisan would reasonably conclude, based on the patent’s disclosures and the

knowledge of a person skilled in the art, that the applicant possessed ... [the claimed invention].”).

3. The enablement requirement.

“The enablement requirement ... serves the purpose of ‘ensur[ing] that the invention is communicated to the interested public in a meaningful way.’” *Ex Parte Vaananen*, Appeal No. 2023-002058, 2024 WL 807653, at *2 (P.T.A.B. Feb. 23, 2024) (some alterations in original) (quoting MPEP § 2164 (9th ed. Rev. 1, Jan. 2024)). The Federal Circuit “has repeatedly explained that a patent applicant does not need to include in the specification that which is already known to and available to one of ordinary skill in the art” to comply with the enablement requirement. *Koito Mfg. Co. v. Turn-Key-Tech, LLC*, 381 F.3d 1142, 1156 (Fed. Cir. 2004) (collecting cases); see *Streck, Inc. v. Rsch. & Diagnostic Sys., Inc.*, 665 F.3d 1269, 1288 (Fed. Cir. 2012) (“It is well-established, however, that a specification need not disclose what is well-known in the art.”).

“The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.” *Resmed Corp. v. Cleveland Med. Devices, Inc.*, PGR2024-00012, Paper 7 at 22 (P.T.A.B. June 24, 2024) (quoting *U.S. v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988)); see *Teva*, 172 F.4th at 1380 (“To satisfy the enablement requirement of §112 ¶ 1, a

patent’s specification ‘must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.’”) (quoting *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1380 (Fed. Cir. 2012)).

“The key word is ‘undue,’ not experimentation.” *BASF Corporation v. Ingevity South Carolina, LLC*, PGR2020-00035, Paper 11 at 13 (P.T.A.B. Sept. 10, 2020) (quoting *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)). “[U]ndue experimentation is analyzed by applying the factors set forth in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988).” *Aradigm Corporation v. Insmed Incorporated*, PGR2017-00021, Paper 10 at 9-10 (P.T.A.B. Nov. 15, 2017).²

² *Amgen Inc. v. Sanofi*, 598 U.S. 594 (2023) has not displaced the cited caselaw.

“The Federal Circuit did not ‘interpret *Amgen* to have disturbed [its] prior enablement case law, including *Wands* and its factors.’ *Baxalta Inc. v. Genentech, Inc.*, 81 F.4th 1362, 1367 (Fed. Cir. 2023). The Office ‘continue[s] to use the *Wands* factors to ascertain whether the experimentation required to enable the full scope of the claimed invention is reasonable’ because ‘Federal Circuit precedent applying the *Wands* factors prior to *Amgen* is still informative.’ 89 Fed. Reg. 1,563, 1,565–66 (Jan. 10, 2024).” *Phison Elecs. Corp. v. Vervain, LLC*, PGR2024-00047, Paper 9 at 35-36 (P.T.A.B. Mar. 17, 2025) (alterations in original).

Specifically, the *Wands* “[f]actors for assessing whether a disclosure would require undue experimentation include: ‘(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.’” *Bayer Healthcare LLC v. Baxalta Inc.*, 989 F.3d 964, 981 (Fed. Cir. 2021) (quoting *Wands*, 858 F.2d at 737).

Denial is warranted when a “Petition does not address the *Wands* factors sufficiently so as to show that undue experimentation is required to make or use the claimed invention.” *Minerva Surgical, Inc. v. Hologic, Inc.*, PGR2017-00002, Paper 36 at 34 (P.T.A.B. May 8, 2018); *see, e.g., Merck Sharp & Dohme Corp. v. Wyeth LLC*, PGR2017-00016, Paper 9 at 8 (P.T.A.B. Oct. 20, 2017) (“Petitioner’s failure to adequately address the *Wands* factors supports denial of the Petitions.”); *Lassen Therapeutics 1, Inc. v. Singapore Health Servs. Pte Ltd.*, PGR2019-00053, Paper 10 at 18 (P.T.A.B. Feb. 6, 2020) (“Petitioner’s failure to adequately address the disclosure of these antibodies from Edwards pervades their analysis of the *Wands* factors and results in a failure to sufficiently establish that the claims of the ’603 patent lack enablement.”); *Allergan, Inc. v. BTL Healthcare Techs. A.S.*, PGR2021-00020, Paper 16 at 24 (P.T.A.B. June 16, 2021) (“Absent persuasive

evidence or argument directly and persuasively addressing *Wands* factors 5–7, we are not persuaded that Petitioner has carried its burden to establish that it is more likely than not to prevail in showing that the experimentation required to achieve the claimed result of muscle toning would have been undue.”).

B. The Petition fails to show that the effective filing date of any one of the challenged claims is after the effective date of the AIA.

As the '968 patent claims priority to an application filed before March 16, 2013, Petitioner must “carry its burden to show lack of written description or non-enablement ... to establish that the [challenged] patent is eligible for post-grant review.” *Novartis*, PGR2018-00069, Paper 16 at 22; *see supra* §V.A.1. As discussed below, because Petitioner has failed to carry that burden, this Petition must be denied. *See Novartis*, PGR2018-00069, Paper 16 at 22; *see also supra* §V.A.1.

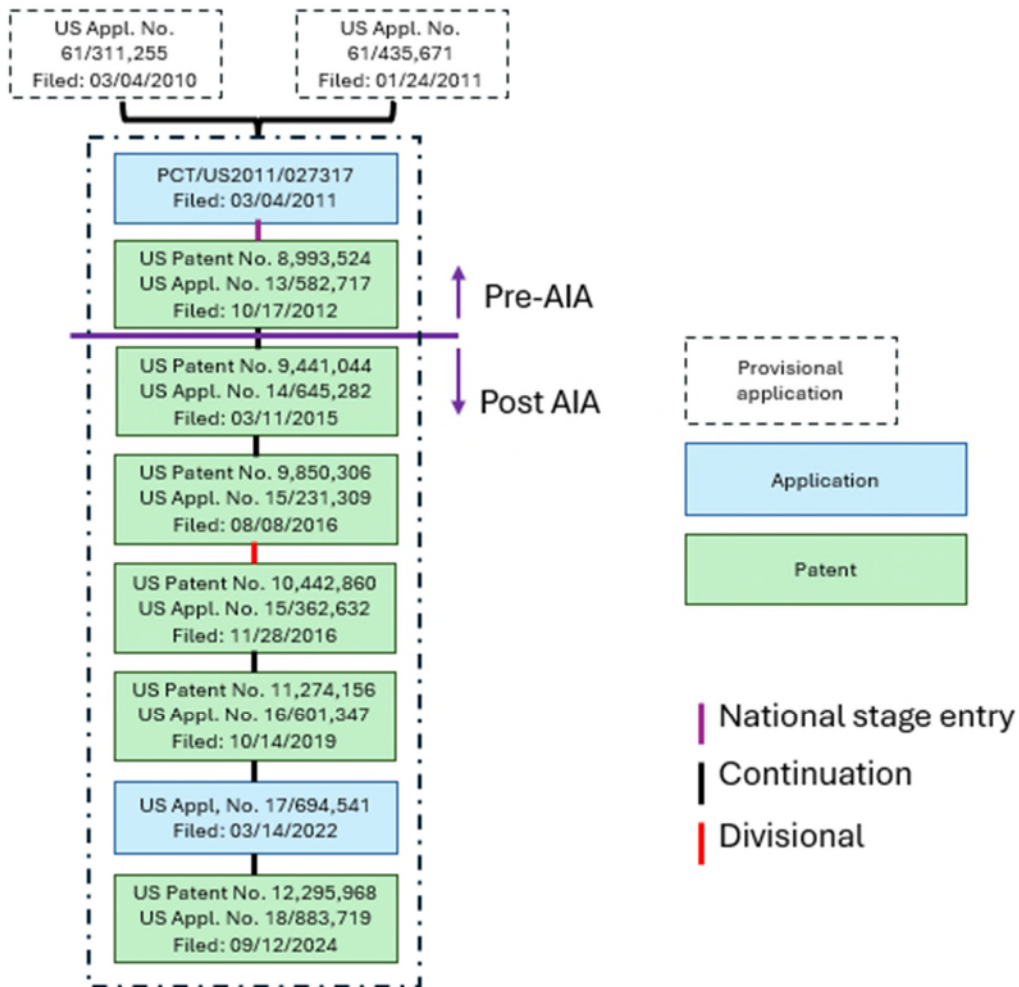
1. The '968 patent is presumptively entitled to a priority date of no later than March 4, 2011.

A patent is presumptively “entitle[d] to a claimed priority date [when it] arises in the context of post-grant review eligibility.” *US Endodontics*, PGR2015-00019, Paper 17 at 10-12. While the parties dispute whether the '968 patent is entitled “to claim priority to two earlier provisional applications,” Pet. at 3, Petitioner agrees that the '968 patent on its face claims priority through a priority

chain tracing back to *at least* the PCT application filed on March 4, 2011.³ Pet. at 5 n.2 (Petitioner representing that “the shared disclosure of the ’968 Patent through the applications and issued patents in its priority chain back to the PCT [] Application [is] highly similar [and] [a]ny differences between the disclosures do not alter” the patentability analysis). And, Petitioner has failed to establish a reasonable likelihood that the ’968 patent is not entitled to claim priority to that PCT application.

As shown below and expressly stated in the patent (EX1001 at (60)), the ’968 patent’s priority chain includes the ’317 PCT application through a series of five U.S. Patents and one U.S. Patent Application:

³ Patent Owner’s Preliminary Response does not address Petitioner’s arguments concerning the provisional applications, because resolution of that issue is unnecessary at this stage. Patent Owner reserves the right to address this issue should the Board institute trial.



Thus, here, the '968 patent is entitled to an effective filing date of at least March 4, 2011, unless Petitioner proves that the priority chain is broken. *See Ecto World*, PGR2024-00049, Paper 10 at 18 (determining challenged patent not eligible for PGR because lack of written description not established in petition).

2. The patent examiner expressly examined the '968 patent under the pre-AIA first to invent provisions.

An “[e]xaminer’s acknowledgement during prosecution that a patent application is entitled to a pre-AIA priority date may be a factor supporting a finding that the patent is ineligible for post grant review.” *Merck*, PGR2017-00016, Paper 9 at 14-15 (parenthetical summary of *Mylan Pharms. Inc. v. Yeda Research & Dev. Co. Ltd.*, PGR2016-00010, Paper 9 at 7 (PTAB Aug. 15, 2016)). As discussed below, like the challenged patent in *Merck*, the '968 patent “was assigned pre-AIA status and examined under pre-AIA first-to-invent provisions,” and this acknowledgement “is consistent with ... Petitioner[’s] fail[ure] to demonstrate adequately that the [challenged] patent is eligible for post grant review.” *Merck*, PGR2017-00016, Paper 9 at 14 (citing to examiner “checking ‘No’ indication in the AIA status box”).

Here, prosecution of the '968 patent was expressly conducted under pre-AIA first to invent provisions. Specifically, in the Office Action that was issued on December 3, 2024, Examiner Bunner stated that the '968 patent was given pre-AIA status and would be examined under pre-AIA provisions:

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

EX1002 at 400. This statement was repeated in the January 29, 2025 Notice of Allowance. EX1002 at 464. A patent examiner is required to, and presumptively does, thoroughly examine “each claim ... for compliance with every statutory requirement for patentability.” MPEP § 2103 (9th ed. Rev. 1, Jan. 2024); *see Karim v. Jobson*, Interference No. 105,376, 2007 WL 5211664, at *5-6 (B.P.A.I. Feb. 28, 2007) (“We are confident that the examiners in the USPTO are deserving of the presumption [to correctly perform their jobs] expressed by the Federal Circuit.”). Thus, this is an acknowledgement by the Office of the validity of the priority claim of the ’968 patent and thus its ineligibility for PGR proceedings. *See Merck*, PGR2017-00016, Paper 9 at 14-15.

3. Petitioner fails to establish a reasonable likelihood that the ’968 patent is not entitled to its presumptive priority date.

As discussed below, Petitioner did not and cannot “carry its burden to show lack of written description or non-enablement ... to establish that the” ’968 patent “is eligible for post-grant review.” *Novartis*, PGR2018-00069, Paper 16 at 22.

a. Petitioner fails to carry its burden to show lack of written description.

The challenged claims are adequately supported by written description. “To satisfy the written-description requirement of §112 ¶ 1, a patent’s specification must ‘reasonably convey[]’ that, as of the filing date, ‘the inventor[s] had possession of the claimed subject matter’—*i.e.*, that they ‘actually invented the

invention claimed.’” *Teva*, 172 F.4th at 1374 (alterations in original) (quoting *Ariad*, 598 F.3d at 1351).

Petitioner cannot carry its burden because a skilled artisan would reasonably conclude, based on the patent’s disclosures and the knowledge of a person skilled in the art, that the applicant possessed the claimed inventions.

Independent claims 1 and 9: Independent claim 1 of the ’968 patent is directed to fusion proteins comprising (a) a targeting moiety comprising amino acids 1-119 of SEQ ID NO:2 and the amino acid sequence of SEQ ID NO:71 and (b) an immunomodulatory moiety comprising an amino acid sequence of the extracellular domain of transforming growth factor-beta receptor II (TGF β RCII) comprising the amino acid sequence of SEQ ID NO:87. The specification provides written description support for the claims. EX1001 at p.102 (Sequence Listing, Seq ID NO:2), p.117-118 (Sequence listing, SEQ ID NO:71), p.120 (Sequence listing, SEQ ID NO:87), Figs. 1B and 3; EX1017 (showing same).

Similarly, independent claim 9 of the ’968 patent is directed to fusion proteins comprising a targeting moiety comprising amino acids 1-119 of SEQ ID NO:2 and the amino acid sequence of SEQ ID NO:71, an immunomodulatory moiety comprising an amino acid sequence of the extracellular domain of transforming growth factor-beta receptor II (TGF- β RCII) comprising the amino acid sequence of SEQ ID NO:87 and a linker of SEQ ID NO:104. The

specification provides written description support for the claims. EX1001 at p.102 (Sequence Listing, SEQ ID NO:2), p.117-118 (Sequence listing, SEQ ID NO:71), p.120 (Sequence listing, SEQ ID NO:87), p.123 (Sequence listing, SEQ ID NO:104), Figs. 1B, 1C, and 3; EX1017 (showing same).

As shown below, with color added, Figures 3, 1B and 1C below, which themselves are blaze marks to an “integrated whole” embodiments encompassed by claims 1 and 9, disclose expressly and emphasizes using additional blaze marks (*e.g.*, underlining, bold, and italics) the specifically claimed sequences for the particular portions of the fusion protein recited in claims 1 and 9 of the '968 patent:

FIG. 3 of the '968 Patent

Fusion proteins comprising Anti-EGFR1 antibody and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ECD).

Anti-EGFR1 heavy chain + TGFβ-RII ECD fusion amino acid sequence (SEQ ID NO: 2):

QVLEQGNHSLWYFEGCLSTCTVSGFELTWYGVHWRQIFQKLEWLVIMSGGNTVYHTPT
LSDFKLEKQVYFQMSLQSDNTAIYVCARALTYGYEFLYMQCTLVTEAASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSVYTVPSSSLGTQ
TYICNVNHRFSNTKVDKRVPEKSCQXHTCPCPAPELLGGPSVTLFPPKPKDTLMISRTPEVTCV
VYDMSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYBVSVLTVLHQDWLNGKEYKCKVSKKAL
PAPIETKISKAKQQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEMESNQCPENNYKTT
PPVLDGGSEFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGSGGGGS TIPPHVQK SVNNDMIVTD NRGAVKFPQL CKFCQVRFST
CDNQKSCMSN CSITSICEKP QEVCAVWRK NDENITLTV CHDPKLPYHD FILEDAASPK
CIMKERRKPG EYFFMCSCSS DECNDNIIFS EYNTSNPD

Anti-EGFR1 light chain amino acid sequence (SEQ ID NO: 71):

DILDTQSPVILSVSPGERVFSFCRASQSIGTNIRWYQORTNGSPRLIRYASESTGGIFSRFSGSG
SGTDETLINSVESEDIADYYCQQNHHPTFGAGTKLELRVAAREVFIFFPSDGLASGTARW
VCLINDYFPREAKVGNKVDNALQSCNSQESVTEQOSKDSITYSLSTLTLSKADYERKRRVYACEVTH
QGLSSPVYAKSINRQD

Underlined: Anti-EGFR antibody variable region
Plain: Anti-EGFR antibody constant region
Italic: Linker
Bold: TGFβRII ectodomain

FIG. 3

CLAIM 1 of the '968 Patent

1. An isolated molecule comprising:
(a) a targeting moiety comprising an antibody or antibody fragment thereof, comprising amino acids 1-119 of SEQ ID NO: 2 and the amino acid sequence of SEQ ID NO: 71, which specifically binds Epidermal Growth Factor Receptor (EGFR); and
(b) an immunomodulatory moiety comprising an amino acid sequence of the extracellular domain of Transforming growth factor-beta receptor II (TGF-βRII) comprising the amino acid sequence of SEQ ID NO: 87.

FIG. 1B of the '968 Patent

(iv) TGF-β R-II containing the extracellular domain that binds TGF-β (SEQ ID NO: 87):

TIPPHVQK SVNNDMIVTD NRGAVKFPQL CKFCQVRFST CDNQKSCMSN CSITSICEKP
QEVCAVWRK NDENITLTV CHDPKLPYHD FILEDAASPK CIMKERRKPG EYFFMCSCSS
DECNDNIIFS EYNTSNPD

FIG. 1B

FIG. 3 of the '968 Patent



CLAIM 9 of the '968 Patent

9. An isolated molecule comprising:
- (a) a targeting moiety comprising an antibody fragment which specifically binds Epidermal Growth Factor Receptor (EGFR) comprising a light chain domain comprising the amino acid sequence of SEQ ID NO: 71 and a variable heavy chain domain comprising amino acids 1-119 of SEQ ID NO: 2;
 - (b) an immunomodulatory moiety comprising an amino acid sequence of the extracellular domain of Transforming growth factor-beta receptor II (TGF- β RII) comprising the amino acid sequence of SEQ ID NO: 87; and
 - (c) a polypeptide linker comprising the amino acid sequence of SEQ ID NO: 104;
- wherein the light chain domain comprising the amino acid sequence of SEQ ID NO: 71 is fused to an N-terminus of the polypeptide linker comprising the amino acid of SEQ ID NO: 104, and wherein the immunomodulatory moiety comprising the amino acid sequence of SEQ ID NO: 87 is fused to a C-terminus of the polypeptide linker comprising the amino acid sequence of SEQ ID NO: 104.

FIG. 1B of the '968 Patent

(iv) TGF- β R-II containing the extracellular domain that binds TGF- β (SEQ ID NO: 87):

TIPFHVQR SYNNDMIYTD NMGAVKFPQL CKPCDVRFT CDNRKSCMSN CSITSTCEKR
DEVCAVVRK NDENIILBTY CHDPKLPYTD FILEDAASK CIMREKKRPG EYFPMSCSS
ECNDNIIFS REYNTSNPD

FIG. 1B

FIG. 1C of the '968 Patent

Linker sequence used in fusion proteins (SEQ ID NO: 104):

GGGGSGGGSGGGGS

FIG. 1C

Amino acids 1-119 of SEQ ID NO:2 are shown annotated in yellow, and originally appear with underlining blaze mark and label “Underlined: Anti-EGFR antibody variable region”. The amino acid sequence of SEQ ID NO:71 is shown annotated in green, and originally appears with the label “anti-EGFR1 light chain amino acid sequence.” The extracellular domain of TGF β -RII is disclosed as part of SEQ ID NO:2 in Figure 3—separately identified as SEQ ID NO:87 in Figure 1B—is shown annotated in blue, and originally appears with bolding blaze marks and label “**Bold: TGF β RII ectodomain.**” The linker sequence is disclosed as part of SEQ ID NO:2 in Figure 3—separately as SEQ ID NO:104 in Figure 1C—is shown annotated in purple, and originally appears with italics blaze marks and label “*Italic: Linker.*” As such, each of the claimed elements is clearly disclosed in the

specification of the '968 patent—which dates back to the March 4, 2011 PCT filing.

Dependent claims 2-8: Dependent claims 2-8 of the '968 patent are similarly supported in the specification. Dependent claims 2-4 and 8 further limit the targeting moiety to an antibody fragment selected from a Fab, scFv, a variable heavy or light chain, a light chain domain comprising SEQ ID NO:71 and a variable heavy chain domain comprising amino acids 1-119 of SEQ ID NO:2. Dependent claims 5-7 further recite that the fusion protein comprises a linker and specify how the linker is fused to the light chain domain and the immunomodulatory moiety. As shown below, each of the dependent claims is fully supported by the specification at least at:

Claim	Element	Disclosure in the '968 patent (EX1001)
2	the targeting moiety comprises an antibody fragment selected from a Fab or scFv	Column 20, lines 43-53 Column 27, lines 38-43 Column 29, lines 24-35 Column 34, lines 40-45 Column 35, lines 56-62
3	antibody fragment comprises a light chain domain or a variable heavy chain domain	Column 34, lines 46-52

Claim	Element	Disclosure in the '968 patent (EX1001)
4	the antibody fragment comprises a light chain domain comprising the amino acid sequence of SEQ ID NO:71	Fig. 3 SEQ ID NO:71
5	further comprising a polypeptide linker comprising the amino acid sequence of SEQ ID NO:104	Column 35, lines 33-40 Fig. 3 Fig. 1C SEQ ID NO:104
6	the light chain domain comprising the amino acid sequence of SEQ ID NO:71 is fused to an N-terminus of the polypeptide linker comprising the amino acid sequence of SEQ ID NO:104	Column 35, lines 48-50
7	wherein the immunomodulatory moiety comprising the amino acid sequence of SEQ ID NO:87 is fused to a C-terminus of the polypeptide linker comprising the amino acid sequence of SEQ ID NO:104	Column 35, lines 48-50

Claim	Element	Disclosure in the '968 patent (EX1001)
8	the variable heavy chain domain comprises amino acids 1-119 of SEQ ID NO:2	Fig. 3 SEQ ID NO:2

Moreover, for each challenged claim, Figure 3 of the '968 patent provides written description support for the entire claimed invention. As shown in the annotated figure above, Figure 3 identifies all of the elements of the claims, both individually and in combination:

- an antibody or antibody fragment comprising amino acids 1-119 of SEQ ID NO:2 (annotated with yellow highlighting; underlined in original) and the amino acids sequence of SEQ ID NO:71 (highlighted in green; labeled “anti-EGFR1 light chain amino acid sequence” in original);
- an immunomodulatory moiety comprising an amino acid sequence of TGFβRII comprising the amino acid sequence of SEQ ID NO:87 (annotated with blue highlighting; bolded in original); and
- a polypeptide linker comprising the amino acid sequence of SEQ ID NO:104 (annotated with purple highlighting; italicized in original).

Therefore, the '968 patent claims had written description support in the '317 PCT application, which was filed before the March 16, 2013 cut-off date for PGR eligibility.

All claims are sufficiently supported in the '317 PCT application: The applications and patents in the '968 patent priority chain share a common specification, therefore support in the '968 patent is necessarily disclosed in the '317 PCT application. Shown below are non-limiting examples of the support for the claims disclosed in the '968 patent and the corresponding support for the claims in the '317 PCT application:

Claim	'317 PCT application (EX1017)	'968 patent (EX1001)
1	Fig. 3 Fig. 1B SEQ ID NO:2 SEQ ID NO:71 SEQ ID NO:87 SEQ ID NO:104	Fig. 3 Fig. 1B SEQ ID NO:2 SEQ ID NO:71 SEQ ID NO:87 SEQ ID NO:104
2	Paragraph [0113] Paragraph [0155] Paragraph [0158]	Column 20, lines 43-53 Column 27, lines 38-43 Column 29, lines 24-35

Claim	'317 PCT application (EX1017)	'968 patent (EX1001)
	Paragraph [0178] Paragraph [0184]	Column 34, lines 40-45 Column 35, lines 56-62
3	Paragraph [0179]	Column 34, lines 46-52
4	Fig. 3 SEQ ID NO:71	Fig. 3 SEQ ID NO:71
5	Paragraph [0182] Fig. 3 Fig. 1C SEQ ID NO:104	Column 35, lines 33-40 Fig. 3 Fig. 1C SEQ ID NO:104
6	Paragraph [0182]	Column 35, lines 48-50
7	Paragraph [0182]	Column 35, lines 48-50
8	Fig. 3 SEQ ID NO:2	Fig. 3 SEQ ID NO:2
9	Fig. 3 Fig. 1B Fig. 1C SEQ ID NO:2 SEQ ID NO:71	Fig. 3 Fig. 1B Fig. 1C SEQ ID NO:2 SEQ ID NO:71

Claim	'317 PCT application (EX1017)	'968 patent (EX1001)
	SEQ ID NO:87	SEQ ID NO:87
	SEQ ID NO:104	SEQ ID NO:104
	Paragraph [0182]	Column 35, lines 48-50

Petitioner’s lack of written description arguments fail as a matter of law: As discussed below, Petitioner’s argument that “all claims lack written description” fails as a matter of law because it is based on misstatements of law, misstatements of fact, and unsupported assertions. Pet. at 26.

First, Petitioner’s primary argument—that the specification fails to provide written description support for the specific targeting moiety of claims 1 and 9 (Pet., 27) overstates the written description requirement and ignores binding precedent. As discussed below, there is no requirement that the specification itself must describe every requirement that is claimed. Instead, “[a]s the Board [has] acknowledged, written description requires only that a skilled artisan would reasonably conclude, *based on the patent’s disclosures and the knowledge of a person skilled in the art*, that the applicant possessed” the claimed invention. *Medtronic*, 69 F.4th at 1354 (emphasis added); see *Shieldmark, Inc. v. Lowe*, PGR2019-00058, Paper 13 at 10 (P.T.A.B. Sept. 4, 2020) (collecting “Federal

Circuit cases holding that the written description inquiry is highly fact specific, and must consider the skill level of the ordinary skilled artisan”).

As the Federal Circuit recently noted, the written description “test requires an ‘objective inquiry into the four corners of the specification *from the perspective of a person of ordinary skill in the art,*’ who ‘comes to the patent with the knowledge of what has come before.’” *Teva*, 172 F.4th at 1374 (emphasis added) (citation omitted) (first quoting *Ariad*, 598 F.3d at 1351; then quoting *Falko-Gunter*, 448 F.3d at 1366). Because this inquiry is from the perspective of a skilled artisan, “the adequate written description requirement [may be] met,” “even if every nuance of the claims is not explicitly described in the specification.” *In re Alton*, 76 F.3d at 1175. In other words, to satisfy the written description requirement, “an applicant is not required to describe in the specification every conceivable and possible future embodiment of his invention.” *Rexnord Corp. v. Laitram Corp.*, 274 F.3d 1336, 1344 (Fed. Cir. 2001) (citing *SRI Int’l v. Matsushita Elec. Corp. of Am.*, 775 F.2d 1107, 1121 (Fed. Cir. 1985) (en banc)).

The Petition alleges that claims 1 and 9 require just parts of the targeting moiety, *i.e.*, a targeting moiety that binds to EGFR and includes antibody fragments comprising amino acids 1-119 of SEQ ID NO:2 and the amino acid sequence of SEQ ID NO:71 and that there is no express disclosure of the claimed targeting moiety. Pet., 28-29. This is incorrect.

The '968 patent provides that the targeting moiety includes an antibody or antibody fragment that binds to EGFR (*i.e.*, an anti-EGFR antibody). EX1001 at 2:43-54; 3:12-17; 20:43-54; 21:18-26; 29:24-35. Additionally, the '968 patent provides specific examples of clinically validated anti-EGFR antibodies, *i.e.*, cetuximab, panitimumab, nimotuzumab, zalutumumab and necitumumab. EX1001 at 29:39-43. As discussed above, Figure 3 of the '968 patent provides the sequence of the heavy and light chains of an anti-EGFR antibody, specifically cetuximab. EX1001 at Fig. 3. Figure 3 additionally points to the variable heavy chain (underlined portion of SEQ ID NO:2, amino acids 1-119) and the light chain (SEQ ID NO:71)—the targeting moiety of claims 1 and 9. EX1001 at Fig. 3.

The Petition states that there is no disclosure of antibody fragments with only a portion of SEQ ID NO:2 and the entirety of SEQ ID NO:71. Pet., 30. However, there is no requirement that the specification itself must describe every embodiment that is claimed. The '968 patent provides written description support for a POSITA to arrive at the targeting moieties of claims 1 and 9, especially from the specific amino acid sequence disclosure in Figure 3 and from the disclosures in the '968 patent regarding antibody fragments as discussed further below. EX1001 at Fig. 3, 29:24-35, 34:23-60.

Second, Petitioner’s primary argument—that a specification always must provide “express disclosure of [each] limitation” or express “blaze marks” for each limitation (Pet. at 26, 30) is plainly wrong.

Petitioner’s proffered requirement that the specification itself must provide “express disclosure of [each] limitation” or express “blaze marks” for each limitation runs afoul of the preceding caselaw, Pet. at 26, and ignores the well-settled rule that “[t]he written description ‘need not include information that is already known and available to the experienced public.’” *Zoltek Corp. v. United States*, 815 F.3d 1302, 1308 (Fed. Cir. 2016) (quoting *Space Sys./Loral, Inc. v. Lockheed Martin Corp.*, 405 F.3d 985, 987 (Fed. Cir. 2005)); see, e.g., *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1368 (Fed. Cir. 2006) (“Indeed, a requirement that patentees recite known DNA structures, if one existed, would serve no goal of the written description requirement.... Indeed, the forced recitation of known sequences in patent disclosures would only add unnecessary bulk to the specification. Accordingly, we hold that where, as in this case, accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences (here ‘essential genes’), satisfaction of the written description requirement does not require either the recitation or incorporation by reference (where permitted) of such genes and sequences.”) (footnote omitted); *Capon v. Eshhar*, 418 F.3d 1349, 1358 (Fed. Cir. 2005) (“The chimeric genes here at issue

are prepared from known DNA sequences of known function. The Board's requirement that these sequences must be analyzed and reported in the specification does not add descriptive substance. The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes.”).

As explained above, the specification discloses both parts of the claimed targeting moiety including the variable region of the heavy chain (amino acids 1-119 of SEQ ID NO:2) and the light chain (SEQ ID NO:71) in Fig. 3. The emphasis of these two portions of the targeting moiety of Fig. 3 *are* blaze marks that clearly indicate the importance of those regions. Petitioner acknowledges the emphasis on these regions of the targeting moiety in Fig. 3 but ascribes no meaning that a POSITA would ascribe to that emphasis, instead arguing that those portions are part of the entire molecule of Fig. 3. That argument ignores the clear disclosures in the specification of fragments as well as a POSITA's knowledge that certain fragments are known to be functional.

Petitioner's argument to the contrary is based on a conclusory allegation that fails for numerous reasons. For example, when alleging that the claimed “targeting moiety” is insufficiently described, Petitioner cites four pages of an expert declaration that the Petition does not adequately discuss. *See* Pet. at 29 (“There is

no express disclosure of such an incomplete targeting moiety required by independent claims 1 and 9 anywhere in the '968 Patent. [EX1003], ¶¶117-22.”). “This practice of citing [an expert] [d]eclaration to support conclusory statements that are not otherwise supported in the Petition [] amounts to incorporation by reference.” *Cisco Sys., Inc. v. C-Cation Techs., LLC*, No. IPR2014-00454, Paper 12 at 9 (P.T.A.B. Aug. 29, 2014) (informative); *see id.* at 9-10 (refusing to consider a petition’s “conclusory paragraph [that] [was] followed by a footnote, citing to ¶¶271-273 of Dr. Roy’s Declaration—one and a half pages indicating the combinations would have been ‘well within the ordinary creativity of a person of ordinary skill in the art’ and providing reasons why one would have combined the teachings of the references”); *3M Co. v. Evergreen Adhesives, Inc.*, No. IPR2018-00576, Paper No. 49 at 8 (P.T.A.B. Feb. 4, 2020) (refusing to consider petitioner’s “explanation that ... was not advanced in the briefing and [was] referenced only through citation to the expert reports”), *aff’d*, 860 F. App’x 724 (Fed. Cir. 2021). Critically, the Petition acknowledges that the specification uses blaze marks of underlining (Pet., 33-34, 88), bold (Pet., 45 n. 11), and italics (not mentioned in the Petition), but fails to explain why those blaze marks are insufficient.

Third, Petitioner’s argument that the '968 patent only discloses full-length antibodies used as the targeting moiety and does not support antibody fragments

ignores numerous disclosures in the specification. Pet. at 34-37. For example, the '968 patent specification provides:

In one aspect, the targeting moiety includes an antibody, **antibody fragment, scFv, or Fc-containing polypeptide** that specifically binds a component of a tumor cell, tumor antigen, tumor vasculature, tumor microenvironment, or tumor-infiltrating immune cell. In one aspect, the targeting moiety specifically binds epidermal growth factor receptor (EGFR1, Erb-B1), HER2/neu (Erb-B2), CD20, Vascular endothelial growth factor (VEGF), insulin-like growth factor receptor (IGF-1R), TRAIL-receptor, epithelial cell adhesion molecule, carcino-embryonic antigen, Prostate-specific membrane antigen, Mucin-1, CD30, CD33, CD40, or a combination thereof.

EX1001 at 29:24-35 (emphasis added). This passage, referring expressly to the inclusion of antibody fragments, directly contradicts Petitioner's assertion that the specification only supports full-length antibodies.

And that is not all. The '968 patent specification includes numerous additional disclosures providing written description support for antibody and specific antibody fragments:

In one embodiment, the targeting moiety or fusion protein is an immunoglobulin. As used herein, the term "immunoglobulin" includes natural or artificial mono- or polyvalent antibodies including, but not limited to, polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, **single**

chain antibodies, Fab fragments. F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The term “antibody,” as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site that immunospecifically binds an antigen. The immunoglobulin ion can be of any type (e.g., IgG, IgE, IgM, IgD, IgA, and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2) or subclass of immunoglobulin molecule.

An antibody as disclosed herein includes an antibody fragment, such as, but not limited to, Fab, Fab' and F(ab')₂, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdfv) and fragments including either a VL or VH domain. In one embodiment, the targeting moiety is an antibody or scFv.

An antigen-binding antibody fragment, including single-chain antibody, may include the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. An antigen-binding fragment can also include any combination of variable region(s) with a hinge region, CH1, CH2, and CH3 domains. Also includes is a Fc fragment, antigen-Fc fusion proteins, and Fc-

targeting moiety. The antibody may be from any animal origin including birds and mammals. In one aspect, the antibody is, or derived from, a human, murine (e.g., mouse and rat), donkey, sheep, rabbit, goat, guinea pig, camel, horse, or chicken. Further, such antibody may be a humanized version of an antibody. The antibody may be monospecific, bispecific, trispecific, or of greater multispecificity.

EX1001 at 34:23-60 (emphases added).

An antibody fragment can include a portion of an intact, antibody, e.g., including the antigen-binding or variable region thereof. Examples of antibody fragments include **Fab, Fab', F(ab')₂, and Fv fragments; Fc fragments or Fc-fusion products; diabodies; linear antibodies; single-chain antibody molecules; and multispecific antibodies formed from antibody fragment(s).**

EX1001 at 35:56-62 (emphasis added).

The term “fragment” refers to any subject polypeptide having an amino acid residue sequence shorter than that of a polypeptide whose amino acid residue sequence is disclosed herein.

EX1001 at 36:62-65.

Furthermore, as discussed above, Figure 3 discloses the entirety of the claimed targeting moiety in a single figure by specifically identifying the heavy and light chain of the claimed EGFR antibody, underlining the variable heavy

chain and variable light chain sequences (*i.e.*, antibody fragments) as well as the claimed sequences of the targeting moiety (*i.e.*, amino acids 1-119 of SEQ ID NO:2 and SEQ ID NO:71). As such, the '968 patent defines a targeting moiety as an antibody or antibody fragment, provides a definition of an antibody and an antibody fragment, examples of antibody fragments (*i.e.*, Fab, Fab' and F(ab')₂, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdfv) and fragments including either a VL or VH domain) and the specific sequence of the claimed targeting moiety. Therefore, the '968 patent provides written description support both generically and specifically for a “targeting moiety” comprising an antibody comprising amino acids 1-119 of SEQ ID NO:2 and the amino acid sequence of SEQ ID NO:71.

Fourth, Petitioner's secondary argument—that purportedly “there is no disclosure of the specific combination of all the limitations as an integrated whole for each claim” (Pet. at 26)—fails for at least the same reasons that its primary argument fails: it is based on misstatements of fact and misstatements of law.

As explained above, for each claim, all claim limitations are disclosed in a single embodiment of the specification or in multiple figures that are evidently and clearly linked together by the specification. As JHU has demonstrated “how each limitation ... is disclosed in combination with all of the other claim limitations,” JHU has sufficiently considered each claim “as an ‘integrated whole’ when

assessing written description.” *Respironics, Inc. v. Zoll Med. Corp.*, No. IPR2013-00322, Paper 46 at 24 (P.T.A.B. Sept. 17, 2014) (quoting *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1349 (Fed. Cir. 2013)), *vacated on other grounds*, 656 F. App’x 531 (Fed. Cir. 2016).⁴

Petitioner’s secondary argument also fails, because Petitioner mischaracterizes the “integrated whole” requirement. Under Petitioner’s incorrect view of *Flash-Control, LLC v. Intel Corp.*, to satisfy the written description requirement, the specification by itself must provide a single embodiment with every claim limitation described in painstaking detail. No. 2020-2141, 2021 WL 2944592, at *4 (Fed. Cir. July 14, 2021) (non-precedential).

⁴ In *Respironics* the patentee had the burden to demonstrate written description, because it was proposing a substitute claim. See IPR2013-00322, Paper 46 at 24 (“Zoll proposes extensive modifications relative to claim 1. Zoll seeks to add hundreds of words to claim 1, more than tripling its length. Yet Zoll offers only a string of citations to the ’003 patent and to the underlying provisional application as evidence showing written description support. So extensive a modification of the claim requires a more detailed showing.”). Here, however, Petitioner has the burden to demonstrate a lack of written description support.

Contrary to Petitioner’s view, “*Ariad* does not require disclosure of a specific example embodying all of the claim limitations.” *First Quality Tissue, LLC v. Irving Consumer Prods. Ltd.*, No. CV 19-428-RGA, 2022 WL 958089, at *8 (D. Del. Mar. 30, 2022). “As *Ariad* itself expressly states, the Federal Circuit has ‘made clear that the written description requirement does not demand either examples or an actual reduction to practice.’” *First Quality Tissue*, 2022 WL 958089, at *8 (quoting *Ariad*, 598 F.3d at 1352). This is consistent with the Federal Circuit precedent discussed above with respect to Petitioner’s primary written description argument.

Additionally, Petitioner’s incorrect view of *Flash-Control* is foreclosed by longstanding precedent that: (a) rejects “the broad proposition ... that in every case where the description of the invention in the specification is narrower than that in the claim there has been a failure to fulfill the description requirement in section 112,” and (b) “explain[s] that, in the context of written description, the fact ‘that a claim may be broader than the specific embodiment disclosed in a specification is in itself of no moment.’” *Bilstad v. Wakalopulos*, 386 F.3d 1116, 1123-24 (Fed. Cir. 2004) (alteration in original) (quoting *In re Smythe*, 480 F.2d 1376, 1382 (C.C.P.A. 1973)); *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1371 (Fed. Cir. 2009) (summarizing *In re Rasmussen*, 650 F.2d 1212, 1215 (C.C.P.A. 1981)). That precedent, adopted by the *en banc* Federal Circuit in *S. Corp. v. United States*,

690 F.2d 1368, 1370 (Fed. Cir. 1982), is “binding precedent ... unless and until overturned *in banc*” and therefore controls over any subsequently issued panel decision. *Newell Companies, Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 765 (Fed. Cir. 1988) (“Where there is direct conflict, the precedential decision is the first.”).

Dependent claims 2-8: Petitioner contends that dependent claims 2-8 lack written description support. Petitioner’s contention that purportedly “there is no disclosure of the specific combination of all the limitations as an integrated whole for each claim” (Pet. at 26)—fails at because it is based on misstatements of fact and misstatements of law.

As explained above, for each claim, all claim limitations are disclosed in a single embodiment of the specification or in multiple figures that are evidently and clearly linked together by the specification. As shown below, specific support for all of the elements of claims 2-8 are found in the ’968 patent.

Claim	Element	Disclosure in the ’968 patent (EX1001)
2	the targeting moiety comprises an antibody fragment selected from a Fab or scFv	Column 20, lines 43-53 Column 27, lines 38-43 Column 29, lines 24-35 Column 34, lines 40-45 Column 35, lines 56-62

Claim	Element	Disclosure in the '968 patent (EX1001)
3	antibody fragment comprises a light chain domain or a variable heavy chain domain	Column 34, lines 46-52
4	the antibody fragment comprises a light chain domain comprising the amino acid sequence of SEQ ID NO:71	Fig. 3 SEQ ID NO:71
5	further comprising a polypeptide linker comprising the amino acid sequence of SEQ ID NO:104	Column 35, lines 33-40 Fig. 3 Fig. 1C SEQ ID NO:104
6	the light chain domain comprising the amino acid sequence of SEQ ID NO:71 is fused to an N-terminus of the polypeptide linker comprising the amino acid sequence of SEQ ID NO:104	Column 35, lines 48-50
7	wherein the immunomodulatory moiety comprising the amino acid sequence of SEQ ID NO:87 is fused to a C-terminus of the	Column 35, lines 48-50

Claim	Element	Disclosure in the '968 patent (EX1001)
	polypeptide linker comprising the amino acid sequence of SEQ ID NO:104	
8	the variable heavy chain domain comprises amino acids 1-119 of SEQ ID NO:2	Fig. 3 SEQ ID NO:2

For all of the foregoing reasons, Petitioner has failed to establish that any claim of the '968 Patent is unpatentable for lack of written description support, and Ground 1 should be denied.

b. Petitioner fails to carry its burden to show lack of enablement.

The Petition fails to demonstrate a reasonable likelihood that the specification does not enable all challenged claims. As discussed earlier, the '968 patent shares a common specification with each of the patents and patent applications in its chain of priority beginning with the '317 PCT application. As discussed below, that specification readily satisfies the enablement requirement of 35 U.S.C. § 112 ¶ 1, at least because “one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.” *Resmed*, PGR2024-00012, Paper 7 at 22 (quoting *Telectronics*, 857 F.2d at 785).

i. Petitioner conflates experimentation and undue experimentation.

Petitioner’s enablement challenge fails because the Petition does not show that “one reasonably skilled in the art could [not] make or use the invention from the disclosures in the patent coupled with information known in the art *without undue experimentation*.” *Resmed*, PGR2024-00012, Paper 7 at 22 (emphasis added) (quoting *Telectronics*, 857 F.2d at 785). As discussed below, Petitioner’s arguments to the contrary are unpersuasive and fail to support Petitioner’s conclusion that a “person of ordinary skill in the art to make and use the full scope of the challenged claims without undue experimentation.” Pet. at 2.

To begin with, Petitioner’s “analysis” ignores that “[t]he key word is ‘undue,’ not experimentation.” *BASF*, PGR2020-00035, Paper 11 at 13 (quoting *Wands*, 858 F.2d at 737). This is exemplified by the Petition’s failure to acknowledge that “[s]ome experimentation, even a considerable amount, is not ‘undue’ if, *e.g.*, it is merely routine, or if the specification provides a reasonable amount of guidance as to the direction in which the experimentation should proceed.” *Kiosoft Techs., LLC v. Payrange Inc.*, PGR2021-00077, Paper 32 at 35 (P.T.A.B. Oct. 26, 2022) (quoting *Wands*, 858 F.2d at 737).

The Petition’s failure to focus on whether required experimentation would rise to the level of undue experimentation is further exemplified by the Petition’s

preoccupation with whether experimentation would be “extensive.” Pet. at 68, 71, 74-75, 77-78, 82, 85. Even putting aside that the Petition overstates the amount of required experimentation, the need for “significant experimentation,” alone does not constitute undue experimentation. *Grünenthal GmbH v. Antecip Bioventures II LLC*, No. PGR2019-00003, Paper 22 at 21 (P.T.A.B. May 5, 2020) (“Even accepting that significant experimentation would be required to determine the appropriate dose of neridronic acid for a given patient, the information advanced in the Petition is insufficient to establish that the experimentation would have been anything other than straightforward, routine, and empirical, for one of skill in the art.”); see *Instrumentation Lab’y Co. v. HemoSonics LLC*, PGR2019-00047, Paper 8 at 26 (P.T.A.B. Oct. 24, 2019) (“[T]he need for ‘multiple iterations, prototypes, and refinements,’ alone does not constitute undue experimentation.”) (quoting and rejecting petitioner’s expert testimony). For example, “‘a considerable amount of [routine] experimentation’ is permitted without rising to the level of undue experimentation under a correct enablement analysis.” *Grünenthal GmbH v. Antecip Bioventures II LLC*, PGR2018-00092, Paper 31 at 41 (P.T.A.B. Dec. 22, 2020) (alteration in original) (quoting *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996)).

Petitioner fails to establish that the breadth of the claims (*Wands*

Factor 8) weighs against enablement: As discussed below, Petitioner’s argument

that the “breadth and diversity” of the challenged claims by itself “supports the lack of enablement” is based on Petitioner misstating law and misstating the scope of the challenged claims. Pet. at 62.

Petitioner argues that the breadth of these claims (*Wands* Factor 8) *per se* weighs against these claims being enabled. See Pet. at 56-62. But Petitioner provides no legal support for that argument, which is plainly wrong. See *Sandoz Inc. v. Boehringer Ingelheim Int’l GmbH*, PGR2022-00037, Paper 13 at 12-13 (P.T.A.B. Feb. 23, 2023) (finding *Wands* Factor 8 did not weigh against enablement for a “moderately broad” claim). Even assuming *arguendo* that the challenged claims are broad, to carry its burden, the Petition must explain *why* the breadth of the challenged claims would require undue experimentation to make and use the claimed invention. See *Viavi Sols. Inc. v. Materion Corp.*, PGR2019-00017, Paper 13 at 26 (P.T.A.B. May 17, 2019) (“Even if we were to accept Petitioner’s contention that the specification fails to disclose explicitly how to make and use the claimed invention to the full breadth of the claims ..., Petitioner fails to provide any evidence, besides Mr. Flasck’s unsupported testimony, that the experimentation required would be undue. Mr. Flasck ... does not explain, even for the one factor he considers (breadth of the claims), why the experimentation needed to make and use the claimed invention would be undue.”). The Petition fails to provide such an explanation, however. See Pet. at 56-62 (merely arguing that claim 1 is broad).

Additionally, Petitioner’s argument regarding the breadth of the challenged claims (*Wands* Factor 8) is flawed, because it overstates the scope of the challenged claims. A patentee “must only enable the *claimed* invention.” *In re Entresto*, 125 F.4th 1090, 1099 (Fed. Cir. 2025) (quoting *Amgen v. Sanofi*, 598 U.S. 594, 610 (2023)); see *Inguran, LLC v. Premium Genetics (UK) Ltd.*, PGR2015-00017, Paper 8 at 18 (P.T.A.B. Dec. 22, 2015) (“Petitioner’s arguments are misplaced because they are not commensurate in scope with the limitations of claim 1.”). As discussed below, Petitioner’s argument that the scope of claims 1 and 9 includes a diverse subgenus of isolated molecules overstates the scope of the claims.

Scope of Independent Claims 1 and 9: Petitioner contends that claim 1 encompasses a substantial subgenus of “isolated molecule[s]” because it is limited to three structural sequences and the functional limitation that the targeting moiety binds to EGFR, and that “[a]ny molecule with these three components . . . and the functional limitation that the targeting moiety specifically bind EGFR is covered.” Pet. at 56. Petitioner then extrapolates this contention into a parade of hypothetical molecular architectures, including “various forms of intact antibodies, fragment antigen-binding (Fab) regions, molecules that include multiple separate peptides, molecules where the various separate peptides are linked by covalent bonds, and molecules where the various separate peptides are variously fused together in

different orientations,” and asserts that “claim 1 is so broad as to allow the components to be associated in essentially any random orientation.” Pet. at 57.

This characterization is misleading. The claims are not defined by function alone—they also require specific amino acid sequences to define each of the targeting moiety and the immunomodulatory moieties. Claim 1 requires “(a) a targeting moiety comprising an antibody or antibody fragment thereof, comprising amino acids 1-119 of SEQ ID NO: 2 and the amino acid sequence of SEQ ID NO: 71, which specifically binds Epidermal Growth Factor Receptor (EGFR); and (b) an immunomodulatory moiety comprising an amino acid sequence of the extracellular domain of Transforming growth factor-beta receptor II (TGF- β RII) comprising the amino acid sequence of SEQ ID NO: 87.” EX1001 at 97:39-49. These are not abstract functional descriptors—rather they structural requirements that constrain the scope of the claims to molecules to contain specific amino acid sequences. A POSITA reading these claims would readily understand that they are directed to a defined and limited number of molecules, not an unbounded genus.

Claim 9 is narrower still, requiring “(a) a targeting moiety comprising an antibody fragment which specifically binds Epidermal Growth Factor Receptor (EGFR) comprising a light chain domain comprising the amino acid sequence of SEQ ID NO: 71 and a variable heavy chain domain comprising amino acids 1-119 of SEQ ID NO: 2; (b) an immunomodulatory moiety comprising an amino acid

sequence of the extracellular domain of Transforming growth factor-beta receptor II (TGF- β RII) comprising the amino acid sequence of SEQ ID NO: 87; and (c) *a polypeptide linker comprising the amino acid sequence of SEQ ID NO: 104*; wherein the light chain domain comprising the amino acid sequence of SEQ ID NO: 71 is fused to an N-terminus of the polypeptide linker comprising the amino acid of SEQ ID NO: 104, and wherein the immunomodulatory moiety comprising the amino acid sequence of SEQ ID NO: 87 is fused to a C-terminus of the polypeptide linker comprising the amino acid sequence of SEQ ID NO: 104.”

EX1001 at 98, 44-64 (emphasis added). This claim specifies four structural components and their precise spatial arrangement, leaving little room for the “random orientation” hypotheticals that Petitioner conjures. Pet. at 57.

Therefore, despite Petitioner’s claims 1 and 9 encompass a substantial subgenus of “isolated molecule[s],” the claims are limited by both functional and structural requirements that limit the number of species encompassed by each claim.

Fusion proteins encompassed by claims 1 and 9: Petitioner reiterates that the ’968 patent broadly defines the terms “targeting moiety” and “immunomodulatory” and discloses a broad genera of what is encompassed by these moieties. Pet. at 61.

In his expert declaration, Dr. Hale calculated that at least 227,332 candidate fusion proteins are disclosed in the '968 patent using the formula⁵:

$$(269 \text{ targets} + 84 \text{ antibodies}) \times 23 \text{ immunomodulators} \times 14 \text{ linkers} \times 2 \text{ orientations} = 227,332$$

EX1003 at 38, n7. However, this calculation includes fusion proteins outside the scope of claim 1. Dr. Hale arrived at this total based on all 269 targets he identified as being disclosed in the '968 patent specification as listed in Appendix B of EX1003 at B3 through B8 as shown below:

Targets		
1-2 microglobulin	ErbB-4(HER4)	mdm-2
4-1BB (CD137)	estrogen receptors (ER)	melanoma ubiquitous mutated 1
4-1BB ligand(4-1BBL)	Ets variant gene 6/acute myeloid leukemia 1 gene ETS (ETC6-AML1) fusion protein	MGAT5
707 alanine praline (707-AP)	FATE	MLA-All
ADAM2	FGFR ligand family	MMA1
adenocarcinomaantigen recognized by T cells 4 (ART-4)	fibroblast growth factor receptor (FGFR) family	MORC
adipophilin	fibroblast growth factor-5 (FGF-5)	mucin 1 (MUC1)
AF15q14	fibronectin (FN)	MUM-1
alpha-actinin-4	FRAME	MuSK receptor family

Targets		
alpha-feta protein (AFP)	FTHL17	Myosin class 1
ANA Ab	GAGE-45 1	NA-88
androgen receptors (AR)	GD2	neo-PAP
angiopoietin 1	GITR/AITR	neuron-specific enolase
ARTC1	GITRL/AITRL	NYFC
AXL receptor family	glucocorticoid-induced tumor necrosis factor receptor family-related gene (GITR)	N-ras (NRAS)
B7 family	glycoprotein 250 (gp250)intestinal carboxyl esterase (iCE)	NXF2 TDRDI
B7-1 (CD50)	GM2	NY-ESO-1
B7-2 (CD86)	GNI-250 Mab	NY-ESO-1/35
B7-DC	GnT-V (aberrant N-acetyl glucosaminyltransferase V)	LAGE-2
B7-H3	gp100/Pmel17 (SILV)	NY-SAR-35
B7-H4	gp100	OAI
B7-H1	GPNMB	OGT
BAGE	HAGE	orHVEM
BAGE-1	HCA661	OS-9
BAGE-2	heat shock protein 70-2 mutated (HSP70-2M)	OX40 (CD134)
Bence-Jones protein	heat shock protein gp96	OX40 ligand (OX40L)
betacatenin (CTNNB1)	Hepatitis B or 20C virus proteins	p53(TP53)
beta-human chorionic gonadotropin	HERV-K-MEL	PAGE-5
BING-4	HGF receptor family: TRK receptor family	PBF
		PD-1 ligand 1 (PD-L1)

Targets		
BORIS	HIV proteins	PD-1 ligand 2 (PD-L2)
B-RAF	HLA-35 A2	PDGFR ligand family
BRDT	HOM-TES-85	platelet derived growth factor receptor (PDGFR) family
breakpoint cluster region-Abelson (Bcr-abl) fusion products	HPV-E7	pml-RARalpha fusion protein
BTLA	HRAS	PRDX5
CAGE	Human papilloma virus (HPV) proteins (HPV-E6)	Programmed Death-1 (PD-1)
calcium-activated chloride 15channel-2 (CLCA2)	human signet ring tumor-2 (HST-2)	prostate specific antigen (PSA)
cancer antigen 125 (CA 125)	human telomerase reverse transcriptase (hTERT)	prostate specific membrane antigen
cancer antigen 15-3 (CA 15-3)	IGF binding proteins (IGFBPs)	prostatic acid 40 phosphatase (PAP)
cancer antigen 19-9(CA 19-9)	IGFR ligand family (IGF-IR)	PSMA
cancer antigen 27-29 (CA27-29)	IL-12 receptor	PTPRK
cancer antigen 72-4 (CA 72-4)	IL-2aR	RAGE-1
cancer-testis (CT) antigens	IL-4 receptor	RBAF600
carcinoembryogenicantigen peptide-1 (CAP-1)	immunoglobulin idiotypes	Receptor activator of nuclear factor-KB (RANK)
carcinoembryonicantigen (CEA)	insulin-like growth factor receptor (IGFR) family	Receptor activator of nuclear factor-

⁵ Patent Owner disagrees that this formula is correct.

Targets		
		KB (RANK) ligand(RANKL) receptor tyrosine kinase-like orphanreceptor (ROR) receptor family
caspase-5 (CASP-5)	interferon inducible protein absent in melanoma 2 (AIM-2)	
caspase-8 (CASP-8)	Interleukin-10 (IL-10)	RET receptor family
CD137L	Interleukin-12 (IL-12)	RNF43
CD152	Interleukin-13 receptor alpha2 chain (IL13Ralpha2)	RU2AS
CD19	Interleukin-4	RYK receptor family
CD20	Interleukin-4 receptor (IL-4R)	SAGE
CD25 (IL-2a receptor)	Interleukin-6 (IL-6)	sargramostim
CD27	Kallikrein 4	SGY-1
CD3	K1AA0205	SIRT2
CD30	KK-LC	SNRPDI
CD33	KLK receptor family	SOX10
CD4	KM-HNI	Sp17
CD40	K-ras (KRAS2)	SPANX
CD40 ligand (CD40L)	LAG-3	SPOL1
CD70	LAGE	squamous cell carcinoma antigen
CDKN2A	LAGE-1	SSX-1
cell division cycle 27 (CDC27)	LDHC	STEAPI
Class I (hematopoietin family) and Class II (interferon/IL-10 family) receptors	leukocyte tyrosinekinase (LTK) receptor family	survivin (BIRC5)
COA-1	LIGHT	SYCP1

Targets		
CPSF	lineage-specific anti-25 gens	SYT-SSX1 or -SSX2 fusion protein
CSAGE	LIPI	telomerase
CTAGE-1	IL-6 receptor	TEX 15
CTL-recognized antigen on melanoma (CAMEL)	LMP2	TGF-a receptor
	low density lipid receptor/GDP-L fucose: beta-Dgalactose 2-alpha-L-fucosyltransferase (LDLR/FUT) fusion protein	
cyclin D 1		TIE receptor family
cyclindependentkinase 4 (CDK4)	MAGE-3	TNF-a
cyclophilin B (Cyp-B)	MAGE-A12	TNFRSF18
Cytokine receptors	MAGE-A2	TPTE
cytotoxic T-lymphocyte antigen-4 (CTLA-4)	MAGE-A3	TPX1
death receptor family	MAGE-A4	TRAIL-receptor
		Transforming growth factor alpha (TGF-a)
dek-can fusion protein	MAGE-A6	Transforming growth factor-beta (TGF-b)
differentiation antigens	MAGE-A9	Transforming growth factor-beta receptor (TGF-bR)
discoidin domain receptor (DDR) family	MAGE-A1 (MAGE-1)	Triosephosphate isomerase
EFTUD-2	MAGE-A11	TRP-1/gp75
EGFR ligand family	MAGE-A10	TRP-2
EGFR1	MAGE-A5	TRP-2-INT2
Elongation factor 2 (ELF2)	MAGE-B2	

Targets		
EMD-72000 (chimeric-EGF antagonist)	MAGE-B5	tumor necrosis factor (TNF) family
		tumor necrosis factor (TNF) receptor superfamily (TNTRSF)
EphA3	MAGE-B6	tumor necrosis factor (TNF) superfamily
ephrin (EPH) receptor family	MAGE-B1	tumor necrosis factor receptor (TNFR) superfamily
 epidermal growth factor receptor (EGFR)	MAGE-C2	tumor necrosis factor-a (TNF-a)
epithelial cell adhesion molecule (Ep-CAM)	MAGEC1	tyrosinase (TYR)
Epstein-Barr virus (EBV) proteins (EBV latent membrane proteins-LMP)	major or minor capsid antigens	vascular endothelial growth factor receptor (VEGFR) family
ErbB-1	mammaglobin-A	VEGF family
ErbB-2 (HER2/neu)	MART-1/Melan-A(MLANA)	Wilms' tumor gene (WT1)
ErbB-3/HER3	MART2	XAGE
ErbB-4/HER4	M-CSF	

However, only the highlighted one of those 269 targets is recited in the challenged claims: EGFR. Dr. Hale's calculation was also based on all 84 antibodies that he identified as being disclosed in the '968 patent as listed in EX1003, B9 as shown below:

Targeting Antibodies and Fusion Proteins			
3622W94 mAb	Certolizumab	Ipilimumab	Panorex
893 (human anti-CD40 mAb)	 cetuximab	Keliximab	Pertuzumab
Abatacept	CP870	lerdelimumab	Ramucirumab
Adalimumab	Daclizumab	LymphoCide	Ranibizumab
Aflibercept	Dalotuzumab	MDX-1106	REGN88
Alemtuzumab	Denosumab	MDX-210	Rituximab
AMG386	Efalizumab	MDX-260 bispecific	SGN-40
ANA Ab	EMD-72000	MDX-447	SMART ABL 364 Ab
antibody to GITR	Epratuzumab	metelimumab	SMART ID10 Ab
anti-CTLA-4 mAb	Etanercept	Muromonab-CD3	SMART M195 Ab
anti-idiotypic mouse mAb	Farletuzumab	Naptumomab	Teplizumab
Atacicept	GC1008	Natalizumab	T1h (anti-CD6 mAb)
Basiliximab	Gemtuzumab ozogamicin	Necitumumab	TNT (chimeric mAb to histone antigens)
BEC2	Girentuximab	nimotuzumab	Tocilizumab
Belatacept	Gliomab-H	NovoMAb-G2	Tositumumab-1131
Belimumab	GNI-250 Mab	Obinutuzumab	trastuzumab
Bevacizumab	Golimumab	Ofatumumab	Tremilimumab
BMS-663513	humanized 13' 1 LYM-1	Oncolym	Ustekinumab
Brentuximab vedotin	Ibritumomab tiuxetan	Otelixizumab	Vedolizumab
Briakinumab	ID11	Ovarex	Zalutumumab
Catumaxomab	Infliximab	panitumumab	Zenapax

Yet only one of these antibodies is within the scope of the challenged claims: cetuximab. Dr. Hale's calculation was also based on 23 immunomodulators he identified as being disclosed in the specification and which he listed in EX1003, B1-B2 as shown below:

Section 1 - List of immunomodulatory moieties, targeting moieties, and targets found in the summary of the '968 patent (EX1001, 2:10-7:17).

Immunomodulatory Moieties	Targeting Moieties	Targets
TGF-beta	antibody	component of a tumor cell
PD-L1	antibody fragment	tumor antigen
PD-L2	scFv	tumor vasculature
RANKL	Fe polypeptide	tumor microenvironment
TGF-beta receptor		tumor-infiltrating cell
PD-1		
RANK		EGFR1
		HER2/neu
TGF-beta RII		CD20
TGF-beta RIib		VEGF
TGF-beta RIIL		IGF-1R
		TRAIL-receptor
		epithelial cell adhesion molecule
		carcino-embryonic antigen
		prostate-specific membrane antigen
		mucin-1
		CD30
		CD33
		CD40
		regulatory T cell
		myeloid suppressor cell
		dendritic cell
		CD4
		CD25
		CTLA-4
		IL-10

Immunomodulatory Moieties	Targeting Moieties	Targets
		TGF-beta receptor
		TGF-beta
		PD-1
		PD-L1
		PD-L2
		RANK
		RANKL

Section 2 - List of immunomodulatory moieties and immunomodulatory targets found in the description of the '968 patent (EX1001, 31:51-32:21).

Immunomodulatory Moieties	Immunomodulatory Targets
4-1BB (CD137)	4-1BB (CD137)
CD40	4-1BB ligand (4-1BBL, CD137L)
GITR; AITR; TNFRSF18	B7-H3
IL-10R	B7-H4
IL-12R	BTLA
OX40 (CD134, TNFR4)	CD27
Programmed Death-1 (PD-1)	CD40
Receptor activator of nuclear factor-KB (RANK)	CD40 ligand (CD40L)
Transforming growth factor beta receptor (TGF-betaRII)	CD70
Transforming growth factor beta receptor (TGF-betaRIib)	GITRL/AITRL
Transforming growth factor beta receptor (TGF-betaRIIL)	GITR; AITR; TNFRSF18
vascular endothelial growth factor receptor (VEGFR1 or VEGFR2)	HVEM
	LIGHT
	OX40 (CD134; TNFR4)
	OX40 ligand (OX40L)
	PD-1 ligand 1 (PD-L1; B7-H1)
	PD-1 ligand 2 (PD-L2; B7-DC)

Yet, only one immunomodulator is recited in the challenged claims: TGFβRII.

When the number of targets, antibodies and immunomodulators corresponding to the claims are used, the formula results in a significantly lower number than alleged by Dr. Hale:

$$(269 \text{ 1 targets} + 84 \text{ 1 antibodies}) \times 23 \text{ 1 immunomodulators} \times 14 \text{ linkers} \times 2 \text{ orientations} = 56$$

The enablement inquiry asks whether the specification enables “the full scope of the invention *as defined by its claims.*” *Amgen v. Sanofi*, 598 U.S. 594, 610 (2023) (emphasis added). When Dr. Hale’s own formula—(targets + antibodies) × immunomodulators × linkers × orientations—is properly applied to challenged claims, the number of molecules that fall within the scope of the claims is only 56. This is magnitudes fewer possible fusion proteins than the purported

227,332 fusion proteins allegedly disclosed in the '968 patent and is not in any sense an “immense” number of “isolated molecule[s]” as alleged by Petitioner. Pet. at 57. The Petition therefore fails to establish that claims 1 and 9 encompass an unreasonable number of species for a POSITA to make and test without undue burden.

ii. *Amgen and Baxalta Are Distinguishable.*

Petitioner relies heavily on *Amgen v. Sanofi*, 598 U.S. 594 (2023), for the proposition that “the specification must enable the full scope of the invention as defined by its claims” (Pet. at 53) and that “[t]he more one claims, the more one must enable.” (Pet. at 54). Petitioner also cites *Baxalta Inc. v. Genentech, Inc.*, 81 F.4th 1362 (Fed. Cir. 2023), for the proposition that there is a “lack of enablement for broad functional claims where specification disclosed 11 working examples of antibodies.” Pet. at 66.

The challenged claims of the '968 patent “present[] a very different factual scenario from *Amgen* [*v. Sanofi*], in which there were potentially millions of embodiments that had not been enabled.” *ESCO Grp. LLC v. Deere & Co.*, No. CV 20-1679-WCB, 2023 WL 4199413, at *17 (D. Del. June 22, 2023) (Bryson, J.). In *Amgen v. Sanofi*, “Amgen s[ought] to monopolize an entire class of things defined by their function—every antibody that both binds to particular areas of the sweet spot of PCSK9 and blocks PCSK9 from binding to LDL receptors.” 598 U.S. at

613. Yet, despite “seek[ing] to claim ‘sovereignty over [an] entire kingdom’ of antibodies,” which included “at least millions of candidates,” “Amgen offer[ed] persons skilled in the art little more than advice to engage in ‘trial and error.’” 598 U.S. at 615 (some alterations in original) (first quoting *Consol. Elec. Light Co v. McKeesport Light Co*, 159 U.S. 465, 476 (1895); then parenthetically quoting district court’s opinion).

The ’968 patent claims are readily distinguishable from the claims at issue in *Amgen* because here, the ’968 patent issued claims contain both structural and functional elements. Claim 1 requires specific amino acid sequences to define the antibody or antibody fragment of the targeting moiety, amino acids 1-119 of SEQ ID NO: 2 and the amino acid sequence of SEQ ID NO: 71, and the amino acid sequence of SEQ ID NO: 87 for the immunomodulatory moiety. EX1001 at 97:39-49. Claim 9 further specifies the linker (SEQ ID NO: 104) and the precise fusion orientation. EX1001 at 98:44-64. A POSITA is not left to screen unknown candidates as the structural and functional identity of every component is defined by sequence and activity.

As demonstrated above, claim 1 encompasses approximately 56 possible fusion proteins using Petitioner’s Expert’s formula when properly applied in view of the express limitations of claim 1. Claim 9 is narrower than claim 1 and therefore encompasses fewer possible fusion proteins. Petitioner argues that:

the common specification leaves the POSA with nothing more than the extensive and random trial-and-error experimentation that is undue under *Amgen*. 598 U.S. 594; *Baxalta*, 81 F.4th at 1367 (“Under *Amgen*, such random trial-and-error discovery, without more, constitutes unreasonable experimentation that falls outside the bounds required by §112(a).”); *Seagen*, 160 /f.4th at 1333 (similar).

Pet. at 71. But unlike *Amgen*, where the court was concerned with claims covering “an entire class” of antibodies identifiable only through “trial and error,” the full scope of claims 1 and 9 is enabled because a POSITA can identify and produce the molecules encompassed within the scope of the claim from the structural limitations and general knowledge in the art.

Similarly, in *Baxalta*, the court found that the specification provided “no disclosures—such as ‘a quality common to every functional embodiment’—that would allow a skilled artisan to predict which antibodies will perform the claimed functions.” Pet. at 71. Here, the ’968 patent claims do not ask a POSITA to discover new antibodies through functional screening, rather the claims require an antibody or antibody fragment defined by specific sequences and that specifically binds EGFR. EX1001 at 98:39-49. The targeting moiety sequences (amino acids 1-119 of SEQ ID NO: 2 and SEQ ID NO: 71) are derived from cetuximab, a well-characterized, FDA approved therapeutic antibody. Petitioner’s own expert, Dr. Hale, acknowledges that cetuximab “was constructed which consisted of the mouse

heavy and light chain variable regions linked to human immunoglobulin constant regions. Goldstein 1995 (EX1055) at p.1311. This is the antibody that became known as cetuximab (trade name Erbitux®).” EX1003 at 22. Dr. Hale further confirms that cetuximab’s EGFR-binding properties were extensively documented, noting that “[e]xtensive in vitro and in vivo experiments have shown that cetuximab inhibits the invasive and metastatic ability of different tumour types” Pet. at 22. A POSITA would thus have had no uncertainty about whether the claimed sequences bind EGFR—that was already established in the art—therefore there is no undue experimentation.

iii. Petitioner fails to establish that the unpredictability and lack of guidance for producing the claimed molecules (*Wands* Factors 2-7) weighs against enablement.

Petitioner argues that the ’968 patent does not provide working examples or clear guidance on how to make the claimed fusion proteins. Pet. at 63. However, the Federal Circuit “has repeatedly made clear, the specification need not include a working example of every possible embodiment to enable the full scope of the claims.” *Bayer Healthcare*, 989 F.3d at 982. “[A]lthough working examples may be desirable, ‘examples are not required to satisfy section 112, first paragraph’ so long as a person skilled in the art can practice the invention without undue experimentation.” *Ex Parte Patterson*, Appeal No. 2024-000852, 2025 WL

2050780, at *5 (P.T.A.B. July 9, 2025) (quoting *In re Strahilevitz*, 668 F.2d 1229, 1232 (C.C.P.A. 1982)); see, e.g., *Grünenthal GmbH v. Antecip Bioventures II LLC*, PGR2018-00092, Paper 25 at 31 (P.T.A.B. Feb. 25, 2020) (“An enabling disclosure need not disclose any working examples or demonstrate that the claimed invention was actually reduced to practice at the time of filing.”) (citing *Alcon Rsch. Ltd. v. Barr Lab’ys, Inc.*, 745 F.3d 1180, 1190 (Fed. Cir. 2014)); *Midwest Indus. Supply, Inc. v. Soilworks, LLC*, PGR2016-00014, Paper 6 at 14 (P.T.A.B. Sept. 7, 2016) (“[E]ven if the working examples do not themselves enable the entire claimed range of synthetic fluids, this does not necessarily show that the claims are not enabled.”); *Therabody, Inc. v. DataFeel Inc.*, PGR2025-00026, Paper 14 at 28 (P.T.A.B. Aug. 21, 2025) (“[R]egarding *Wands* factor 3, the absence of working examples of the claimed treatment device, alone, does not support a determination of non-enablement.”). “While ‘a patentee is not required to provide actual working examples,’ the presence of working examples helps the POSA practice the invention by showing what has worked before.” *Astellas Pharma Inc. v. Zydus, Inc.*, No. 1:20CV1589, 2025 WL 1111447, at *13 (D. Del. Apr. 15, 2025) (quoting *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1310 (Fed. Cir. 2015)).

The specification provides detailed guidance on the structural components and production of fusion proteins. The specification expressly directs the POSITA to these established methods, stating:

A targeting moiety, including an antibody, can be coupled to an immunomodulatory moiety including a polypeptide derived from the extracellular domain of TGF β RII. Crosslinkers or activating agents for such coupling or conjugation are well known in the art.

Alternatively, the fusion proteins of the invention can be synthesized using recombination DNA technology well known in the art where the coding sequences of various portions of the fusion proteins can be linked together at the nucleic acid level. Subsequently the fusion proteins of the invention can be produced using a host cell well known in the art.

EX1001 at 43:40-52. It further discloses that “a targeting moiety comprising an antibody, antibody fragment, or polypeptide is linked or fused to an immunomodulatory moiety consisting of a polypeptide, with a linker or without a linker,” that “a linker is (GGGGS) n (SEQ ID NO: 123) wherein n is 1, 2, 3, 4, 5, 6, 7, or 8,” and that “[i]n various aspects, the immunomodulatory moiety is a polypeptide that is fused to the C-terminus of the Fc region of the heavy chain of a targeting antibody or Fc-containing fusion protein. In another aspect, the immunomodulatory moiety is a polypeptide that is fused to the C-terminus of the light chain of a targeting antibody.” EX1001 at 35:31-50. Accordingly, the specification provides detailed guidance and a roadmap to guide a POSITA to the structural components of the ‘968 claimed fusion proteins and the production of such fusion proteins.

Petitioner argues that “a patentee ‘cannot simply rely on the knowledge of a [POSITA] to serve as a substitute for the missing information in the specification.’” Pet. at 54 (quoting *Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc.*, 928 F.3d 1340, 1348 (Fed. Cir. 2019)). But the law does not require a specification to recite every detail of well-established laboratory techniques. The specification need only enable a POSITA, and a POSITA in this field would have been thoroughly familiar with standard recombinant DNA expression systems, antibody construction and purification methods, and binding assays. However, Petitioner’s expert, Dr. Hale, concedes this fact:

By 2010, the manufacture of conventional recombinant IgG antibodies was a comparatively predictable and routine process. This included (1) transfection of a suitable host cell with a plasmid or viral vector which encoded the antibody, (2) selection of a stable transfectant, (3) culture of the cells, and (4) purification of the antibody from the culture supernatant.

EX1003 at 25-26. Thus, both Petitioner’s expert and the ’968 patent owner are in agreement that a POSITA armed with the ’968 patent specification and routine antibody production methods known in the field well before the first patent application in the ’968 chain of title, could readily generate the claimed fusion proteins.

Petitioner argues that “[o]f the examples of fusion proteins in the ’968 Patent, only one is described as actually having been made—the TGF β RII:Fc fusion protein in Example 1, which bears no relation to the molecules claimed in claim 1. Otherwise, all of the other examples of fusion proteins are prophetic with no evidence in the specification that they were actually made. Even more problematic, the ’968 patent does not disclose how to make any of the fusion proteins.” Pet. at 63. This is incorrect. The specification provides both a working example and express guidance on production methods for the claimed fusion proteins.

First, the specification discloses the production and use of a TGF β RII:Fc fusion protein. The specification describes that “tumor-bearing mice were treated with a soluble chimeric protein comprising the extracellular domain of TGF β RII and the Fc portion of the murine IgG1 heavy chain (TGF β RII:Fc). This fusion protein interferes with the binding of TGF- β to endogenous TGF β RII and functions as a stable TGF- β antagonist. ELISA assays confirmed the ability of TGF β RII:Fc to sequester TGF- β in supernatants of MB49 tumor cells in a concentration-dependent manner.” EX1001 at 40:42-41:8. Petitioner dismisses this example because “[t]he TGF β RII:Fc fusion protein comprises a TGF β RII extracellular domain fused to a Fc portion of a mouse IgG heavy chain” (Pet. at 63) and “does not include an antibody targeting moiety as required by claim 1.” (Pet. at 4). But

this argument overlooks a critical point: TGF β RII:Fc is itself a fusion protein containing an antibody fragment. As Dr. Hale explains, “[a] Fc fusion protein is a non-immunoglobulin protein fused to an intact immunoglobulin Fc fragment without the presence of a targeting fragment and is normally dimeric.” EX1003 at 23. The Fc region is an antibody fragment—it is the constant region fragment of an immunoglobulin heavy chain. Dr. Hale confirms that antibody fragments are “truncated portions of a full-length antibody” and that “papain cleaves on the amino-terminal side of the hinge disulphide bonds to yield Fab and Fc fragments.” EX1003 at 17. The working example thus demonstrates that the inventors successfully produced a fusion protein comprising the TGF β RII extracellular domain (SEQ ID NO: 87) fused to an antibody fragment (Fc), confirming that the immunomodulatory moiety required by all challenged claims can be expressed, properly folded, and retain its TGF- β binding function in a fusion protein context with an antibody fragment. Therefore the ’968 patent provides a working example of producing a fusion protein.

Second, the specification expressly identifies the methods for producing the claimed fusion proteins. The specification states: “A targeting moiety, including an antibody, can be coupled to an immunomodulatory moiety including a polypeptide derived from the extracellular domain of TGF β R2. Crosslinkers or activating agents for such coupling or conjugation are well known in the art. Alternatively,

the fusion proteins of the invention can be synthesized using recombination DNA technology well known in the art where the coding sequences of various portions of the fusion proteins can be linked together at the nucleic acid level. Subsequently the fusion proteins of the invention can be produced using a host cell well known in the art.” EX1001 at 43:40-52. A POSITA would readily make the claimed fusion proteins based on this disclosure combined with general knowledge in the art. Dr. Hale himself concedes, as stated above, that “[b]y 2010, the manufacture of conventional recombinant IgG antibodies was a comparatively predictable and routine process. This included (1) transfection of a suitable host cell with a plasmid or viral vector which encoded the antibody, (2) selection of a stable transfectant, (3) culture of the cells, and (4) purification of the antibody from the culture supernatant.” EX1003. at 25-26. Dr. Hale further acknowledges that “[t]hroughout the 1980s, molecular biology techniques were being developed for cloning and expression of genes and site-directed mutagenesis, enabling the development of the above methods for production of humanized and human antibodies. They also enabled the creation of antibodies which were engineered for particular applications. . . . Furthermore, it was possible to develop antibody-like molecules with many different formats, including scFv, Fab and F(ab')₂ fragments, single-chain antibodies, fusion proteins, and multivalent antibodies.” Pet. at 22-23.

Therefore, as the '968 patent provides disclosure (*e.g.*, a working example of producing a fusion protein that contains an antibody fragment and a TGF β RII immunomodulatory moiety, refuting unpredictability) in combination with general knowledge in the art (as described by Petitioner's Expert) provides guidance and predictability for a POSITA to produce the claimed fusion proteins.

iv. Petitioner fails to establish that the unpredictability and lack of guidance for identify whether the claimed fusion proteins specifically bind to EGFR (*Wands* Factors 2-7) weighs against enablement.

Petitioner argues that the '968 patent does not provide working examples or guidance on how to determine whether the claimed fusion proteins “specifically bind EGFR”. Pet. at 69. Petitioner argues that “the '968 Patent provides no information on how to test this functionality—not even an assay or a working example of how to screen for the targeting moiety binding EGFR as part of the claimed fusion protein” (Pet. at 70) and that “the only guidance to practice ‘the full scope of the invention [is] to use trial and error to narrow down the potential candidates to those satisfying the claims’ functional limitations.’” (Pet. at 69).

The claimed targeting moiety, *i.e.*, antigen binding portion of the fusion protein, is derived from a well-known, well studied, FDA approved anti-EGFR antibody, cetuximab (Erbitux®). Cetuximab is a chimeric anti-EGFR antibody based on a murine antibody developed by Drs. John Mendelsohn and Gordon Sato

in the 1980s. EX2025 at 1. A chimeric antibody was created from the murine anti-EGFR antibody by NCI based on positive clinical trial results and was shown to better binding affinity and produced greater tumor effects compared to the murine antibody. EX2025 at 2. Cetuximab has been shown to specifically bind to EGFR and was initially approved by the FDA for the treatment of colorectal cancer and head and neck cancer in 2004. EX2026 at 1. In fact, the initial label for cetuximab indicates that the antibody is “a recombinant human/mouse monoclonal antibody that binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR).” EX2027 at 1. As such, this antibody is well characterized, especially its binding specificity for EGFR, and is well known in the field of antibody therapeutics.

The targeting moiety of the fusion proteins claimed in the '968 patent uses the binding portion of cetuximab. In fact, the regions of the antibody that provide the specific binding characteristics are identified and emphasized in Figure 3 with underlining (*i.e.*, the variable heavy chain and variable light chain). EX. 1001, Fig. 3. The '968 patent utilizes the specific binding profile of cetuximab in combination with an immunomodulatory moiety to produce a synergistic effect and improve treatment of cancer. As long as the antibody fragment of the claimed fusion proteins comprises the variable heavy and variable light chain, specific binding to EGFR is not only predicted but expected. Indeed, claim 1 requires that

the targeting moiety comprises the binding regions of cetuximab, the variable heavy chain (amino acids 1-119 of SEQ ID NO:2) and light chain (SEQ ID NO: 71), which by definition includes the variable light chain.

Petitioner's expert, Dr. Hale, acknowledges that cetuximab "was constructed which consisted of the mouse heavy and light chain variable regions linked to human immunoglobulin constant regions. Goldstein 1995 (EX1055) at p.1311. This is the antibody that became known as cetuximab (trade name Erbitux®)." EX1003 at 22. Dr. Hale further confirms that cetuximab's EGFR-binding properties were extensively documented, noting that "[e]xtensive in vitro and in vivo experiments have shown that cetuximab inhibits the invasive and metastatic ability of different tumour types" EX1003 at 22.

Therefore, the disclosure in the '968 patent (*i.e.*, the cetuximab heavy and light chains with the variable regions underlined and emphasized) in combination with general knowledge in the art (*i.e.*, specific binding of cetuximab to EGFR and methods for determining such binding, as acknowledged by Dr. Hale) provide guidance and predictability for a POSITA to determine whether a fusion protein containing the cetuximab antigen binding regions specifically binds EGFR. Indeed, a POSITA would have had no uncertainty about whether the claimed fusion proteins bind EGFR—as the specific binding of cetuximab to EGFR has been well established in the art—therefore there is no undue experimentation. *See Koito*

Mfg., 381 F.3d at 1156 (noting the Federal Circuit “has repeatedly explained that a patent applicant does not need to include in the specification that which is already known to and available to one of ordinary skill in the art” to comply with the enablement requirement”); *Streck*, 665 F.3d at 1288 (“It is well-established, however, that a specification need not disclose what is well-known in the art.”).

v. Petitioner fails to establish that the quantity of experimentation (*Wands* Factor 1) weighs against enablement.

Petitioner argues that due to the alleged “lack of guidance and working examples for either or testing any of the claimed molecules, the inherent uncertainty in the art for the nature of the invention, and the amount of experimentation required, a POSITA would not be able to make and use the full scope of the claimed invention without undue experimentation.” Pet. at 73.

Petitioner then argues that undue experimentation would be required to practice the full scope of the claims. Pet. at 55. “[U]ndue experimentation is analyzed by applying the factors set forth in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988).” *Aradigm*, PGR2017-00021, Paper 10 at 9-10. Specifically, the *Wands* “[f]actors for assessing whether a disclosure would require undue experimentation include: ‘(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in

the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.’” *Bayer Healthcare*, 989 F.3d at 981 (quoting *Wands*, 858 F.2d at 737).

These arguments fail for the reasons set forth above. As discussed above, claim 1 encompasses approximately 56 fusion proteins when Petitioner’s own expert’s formula is properly applied to the claim limitations. As claim 9 is narrower in scope than claim 1, it encompasses fewer than 56 possible fusion proteins. This is an entirely reasonable number of fusion proteins for a POSITA to design, produce, and test.

Dr. Hale’s hypothetical 9-step research plan begins with “[d]ecide whether the three polypeptide chains should be expressed separately or from the same cell” and includes decisions about “which expression vector and which host cell should be used.” EX1003 at 80-84. Dr. Hale himself acknowledges that “the foregoing research plan is merely hypothetical, but in the absence of any guidance or working examples, it gives an indication of the many aspects which a POSA would need to imagine for themselves.” EX1003 at 85. But the specification is not devoid of guidance. As discussed previously, the specification provides the complete amino acid sequences of all claimed components, with the variable heavy and light regions underlined and emphasized) (EX1001 at Figure 3), a working example demonstrating the viability of the immunomodulatory moiety in a fusion protein

with an antibody fragment (EX1001 at Example 1), and the identification of recombinant DNA methods for production. EX1001 at 43:40-52.

Moreover, Dr. Hale's 9-step plan describes nothing more than the standard workflow for producing any recombinant protein. These are the routine steps that every POSITA in this field undertakes as a matter of course. If this level of experimentation were deemed "undue," virtually no biologic therapeutic patent could satisfy the enablement requirement.

The state of the art further supports enablement. Dr. Hale concedes that "[s]ome of the steps necessary for development of the claimed molecules had counterparts in the prior art. For example, general methods of producing recombinant monoclonal antibodies were known, including methods for producing chimeric or humanized antibodies. Furthermore, numerous fusion proteins had been described and a number of different peptide linkers were known." EX1003 at 86. By 2010, according to Dr. Hale, "there were a number of fusion proteins in clinical development and some had been approved and marketed. . . . Most of them included one or more immunoglobulin domains." EX1003 at 23-24. Fc fusion proteins which had been assigned an INN "by the World Health Organization by March 2010 included abatacept, aflibercept, alefacept, atacicept, baminercept, belatacept, briobacept, eftrenonacog and rilonacept." EX1003 at 23-24. Antibody fusion proteins were also known, including "Zemab (anti-HER2 scFv linked to

pseudomonas exotoxin), MFECP1 (anti-CEA scFv linked to carboxypeptidase) and EMD 273066,” and “[b]y March 2010, only a few such antibody fusion proteins had been assigned an INN name; they included citatuzumab bogatox, moxetumomab pasudotox, naptumomab estafenatox, oportuzumab monatox and tucotuzumab celmoleukin.” EX1003 at 24-25.

The fusion proteins claimed in the '968 patent combine well-characterized components: cetuximab-derived antibody sequences with known EGFR-binding activity, the TGF β RII extracellular domain with demonstrated TGF- β sequestration activity (confirmed in the working example), and a standard (GGGGS)₃ linker. Dr. Hale confirms that “[t]he different protein domains which make up fusion proteins are commonly linked by a short peptide, the sequence of which is optimised to ensure that the fusion protein can be manufactured efficiently and the biological activity of each component is maintained. Often a flexible linker consisting of one or more copies of four glycine residues and one serine residue (GGGGS) is used.” EX1003 at 25.

A POSITA armed with the '968 patent specification's disclosures and knowledge of the prior art would not face undue experimentation in making and using the fusion proteins that fall within the scope of claim 1 or claim 9. As noted above, there is no requirement that the specification disclose what is well known in

the art. Any experimentation required is routine, not undue, and the specification provides sufficient guidance to enable the full scope of the claims.

vi. Dependent claim 2 is enabled.

Petitioner asserts that although claim 2 narrows the scope of independent claim 1 by specifying that the targeting moiety is a Fab or scFv antibody fragment it does not cure the (purported) enablement defects of claim 1. Pet. at 75. Petitioner asserts that although full length antibodies are excluded, claim 2 (purportedly) still covers any Fab or scFv—including “a wide variety of possible molecular architectures, orientations and modes of association.” Pet. at 77. Further, Petitioner contends that the '968 patent specification does not provide working examples of a fusion protein with a Fab or scFv. Pet. at 76. Petitioner then argues that an scFv consists solely of the variable heavy and light chain sequences and excludes constant domains such as is included in SEQ ID NO:71. Finally, the Petitioner argues that the art remains unpredictable, the specification provides no instruction on how to construct, express, assemble or test Fab or scFv based fusion proteins for specific binding to EGFR. Pet. at 76.

Claim 2 excludes species of fusion proteins including full length antibodies further reducing the number of fusion proteins encompassed by claim 1. As discussed previously, claim 1 encompasses a reasonable number of fusion proteins for a POSITA to make and test without undue experimentation, and claim 2 further

reduces the number of fusion proteins that fall within the scope of claim 1. Also as discussed previously, the '968 patent specification provides a working example of making a fusion protein with an antibody fragment and that the claimed fusion proteins contain the antigen binding portion of the well characterized, FDA approved EGFR binding antibody cetuximab. A POSITA could easily practice the full scope of the invention based on the disclosure in the '968 patent and knowledge in the art. Finally, as discussed above, there exist versions of scFvs that contain constant regions (*e.g.*, scFv-C_L, scFv-Fc, and scFv-C_H1-C_L) and therefore scFv molecules are not limited to only variable regions.

Therefore, claim 2 is fully enabled.

vii. Dependent claims 3, 4 and 8 are enabled.

As Petitioner recognizes, *see* Pet. at 78, dependent claims 3, 4 and 8 are even narrower than the claim(s) they depend on. *See, e.g., Littelfuse, Inc. v. Mersen USA EP Corp.*, 29 F.4th 1376, 1380 (Fed. Cir. 2022) (“By definition, an independent claim is broader than a claim that depends from it.”); *ABS Glob., Inc. v. Inguran, LLC*, 914 F.3d 1054, 1076 (7th Cir. 2019) (“A proper dependent claim cannot fail for lack of enablement while its independent claim stands, because the dependent claim’s scope is a subset of the independent claim’s scope.”); *In re Tanaka*, 640 F.3d 1246, 1250-51 (Fed. Cir. 2011) (noting that “dependent claims are also less vulnerable to validity attacks given their more narrow subject matter”). Claims 3,

4, and 8 further limit claim 2, which then further limits claim 1. As discussed previously, claim 1 encompasses a reasonable number of fusion proteins for a POSITA to make and test without undue experimentation, and claim 2 further reduces the number of fusion proteins that fall within the scope of claim 1. Also as discussed previously, the '968 patent specification provides a working example of making a fusion protein with an antibody fragment and that the claimed fusion proteins contain the antigen binding portion of the well characterized, FDA approved EGFR binding antibody cetuximab. A POSITA could easily practice the full scope of the invention based on the disclosure in the '968 patent and knowledge in the art. Finally, as discussed *supra* § IV.B.2, claim 3 should be construed as requiring that the antibody fragment has a light chain or a variable heavy chain, or both a light chain and a variable heavy chain.

Therefore, claims 3, 4 and 8 are fully enabled.

viii. Dependent claims 5-7 are enabled.

Petitioner contends that claims 5-7 “further narrow the scope of the asserted subgenus by introducing a specific polypeptide linker and by requiring that the linker be fused to the light chain domain and the immunomodulatory moiety in particular orientations.” Pet. at 80. Petitioner further argues that “the common specification does not disclose a single working or prophetic example of a light

chain-linked antibody construct, nor a light chain-linked Fab or scFv incorporating the claimed sequences. *Supra* Section VI.A.2.(d); EX1003, ¶¶140-46.” Pet. at 81.

Claims 5-7 further limit claim 4, and claim 4 further limits claims 1 and 2. As discussed previously, claim 1 encompasses a reasonable number of fusion proteins for a POSITA to make and test without undue experimentation, claims 5-7 further reduce the number of fusion proteins that fall within the scope of claim 1. Also as discussed previously, the '968 patent specification provides a working example of making a fusion protein with an antibody fragment and that the claimed fusion proteins contain the antigen binding portion of the well characterized, FDA approved EGFR binding antibody cetuximab. Further, the '968 patent specification provides specific support for the linker to be fused to the N-terminus or the C-terminus of an Fc region:

In another aspect, the immunomodulatory moiety is fused to the C-terminus of the targeting moiety. In another aspect, the immunomodulatory moiety is fused to the N-terminus of the targeting moiety. In one aspect, the fusion molecule is represented by X-Fc-Y, wherein X is the targeting moiety, Fc is an immunoglobulin Fc region, and Y is the immunomodulatory moiety. In another aspect, the fusion molecule is represented by Y-Fc-X, wherein X is the targeting moiety, and Y is the immunomodulatory moiety.

EX1001 at 35:42-43. A POSITA could easily practice the full scope of the invention based on the disclosure in the '968 patent and knowledge in the art.

Therefore, claims 5-7 are fully enabled.

For all of the foregoing reasons, Petitioner has failed to establish that any claim of the '968 patent is unpatentable for lack of enablement, and Ground 2 should be denied.

VI. THE BOARD SHOULD NOT OPINE ON GROUNDS 3-6

Petitioner alleges in Grounds 3-6 that “claims 2-8 [are purportedly] unpatentable for improper dependency under 35 U.S.C. § 112(d) and unpatentable for indefiniteness under 35 U.S.C. § 112(b).” Pet. at 2; *see* Pet. at 88-91. Because Petitioner has failed to meet its burden to establish that the '968 patent is PGR eligible, none of the arguments in Grounds 3-6 should be reached. *See, e.g., Resmed*, PGR2024-00012, Paper 7 at 24 (not addressing proposed grounds of unpatentability because “Petitioner has not satisfied its burden of proving that it is more likely than not that the pre-AIA priority applications fail to provide written description support for and fail to enable the challenged claims”); *Fox Factory, Inc., v. SRAM, LLC*, PGR2016-00043, Paper 9 at 6-18 (P.T.A.B. Apr. 3, 2017) (not addressing obviousness and indefiniteness grounds after rejecting written description and enablement grounds).

VII. CONCLUSION

Petitioner fails to show that there is insufficient written description or enablement support for the '968 patent claims that causes a break in the chain of priority and has failed to meet the burden to establish that the '968 patent is not entitled to claim priority to the '317 PCT application. *Ecto World*, PGR2024-00049, Paper 10 at 18. For each of the foregoing reasons, the PGR should not be instituted as to the requested grounds.

Dated: May 18, 2026

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

I, Jennifer Librach Nall, certify that this paper complies with the type-volume limitation of 37 C.F.R. § 42.24 because it contains 15,613 words, excluding the parts of the paper exempted by 37 C.F.R. § 42.24(a).

Dated: May 18, 2026

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6, I hereby certify that on May 18, 2026 the foregoing Patent Owner Preliminary Response was served via email on the following counsel of record for the Petitioner:

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