

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BICARA THERAPEUTICS, INC.,

Petitioner

v.

THE JOHNS HOPKINS UNIVERSITY,

Patent Owner.

PGR2026-00025

U.S. Patent No. 12,295,968

**PATENT OWNER'S RESPONSE TO PETITION FOR
POST-GRANT REVIEW OF U.S. PATENT 12,295,968**

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I. INTRODUCTION

Pursuant to 37 C.F.R. § 42.220(a), Patent Owner The Johns Hopkins University submits the following Response to the Petition for Post-Grant Review of U.S. Patent No. 12,295,968 (“the ’968 patent”) submitted by Petitioner Bicara Therapeutics, Inc.

Patent Owner has filed a Motion to Amend canceling claims 2-8 of the ’968 patent concurrently with this Response. That motion moots Grounds 3-6 in their entirety, and moots Grounds 1 and 2 as applied to the canceled claims. This Response accordingly addresses Grounds 1 and 2 only as to claims 1 and 9, which remain at issue.

The Board should reject Petitioner’s challenges. The ’968 patent traces an unbroken priority chain to PCT/US2011/027317 (“the ’317 PCT Application”), filed March 4, 2011, and the specification has at all times fully supported the issued claims. That means Petitioner’s written-description arguments fail. Petitioner’s enablement arguments likewise fail because they conflate routine experimentation with the undue experimentation the law requires and fail to prove that claims 1 and 9 are invalid.

II. BACKGROUND

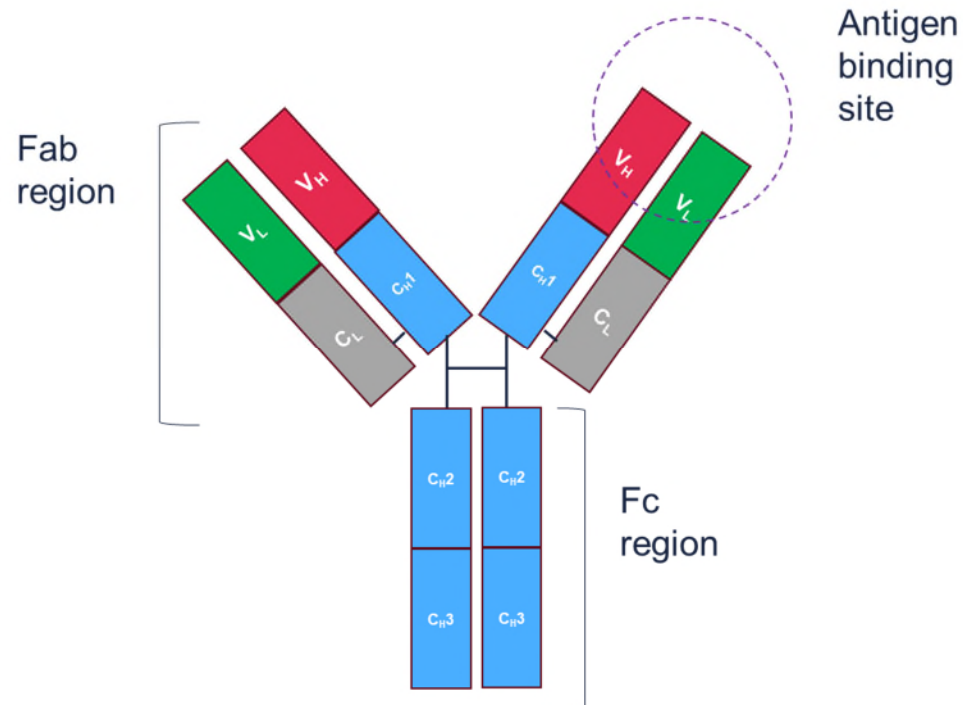
A. Overview of the '968 Patent

The '968 patent covers cancer immunotherapies built from fusion proteins—*i.e.*, proteins built by fusing multiple moieties together. 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. *Id.* at 2:26-31. The claimed fusion proteins harness the proven clinical efficacy of anti-epidermal growth factor receptor (“anti-EGFR”) antibodies (*e.g.*, cetuximab, panitumumab, nimotuzumab, zalutumumab, and necitumumab), *Id.* at 29:39-43, with a transforming growth factor beta receptor II (“TGFβRII”) that boosts the immune system's response to cancer cells. *Id.* at 21:18-26.

B. Technical Background for Antibody Structure and Antibody Fragments

An antibody (ab) is a large protein belonging to the immunoglobulin superfamily that 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

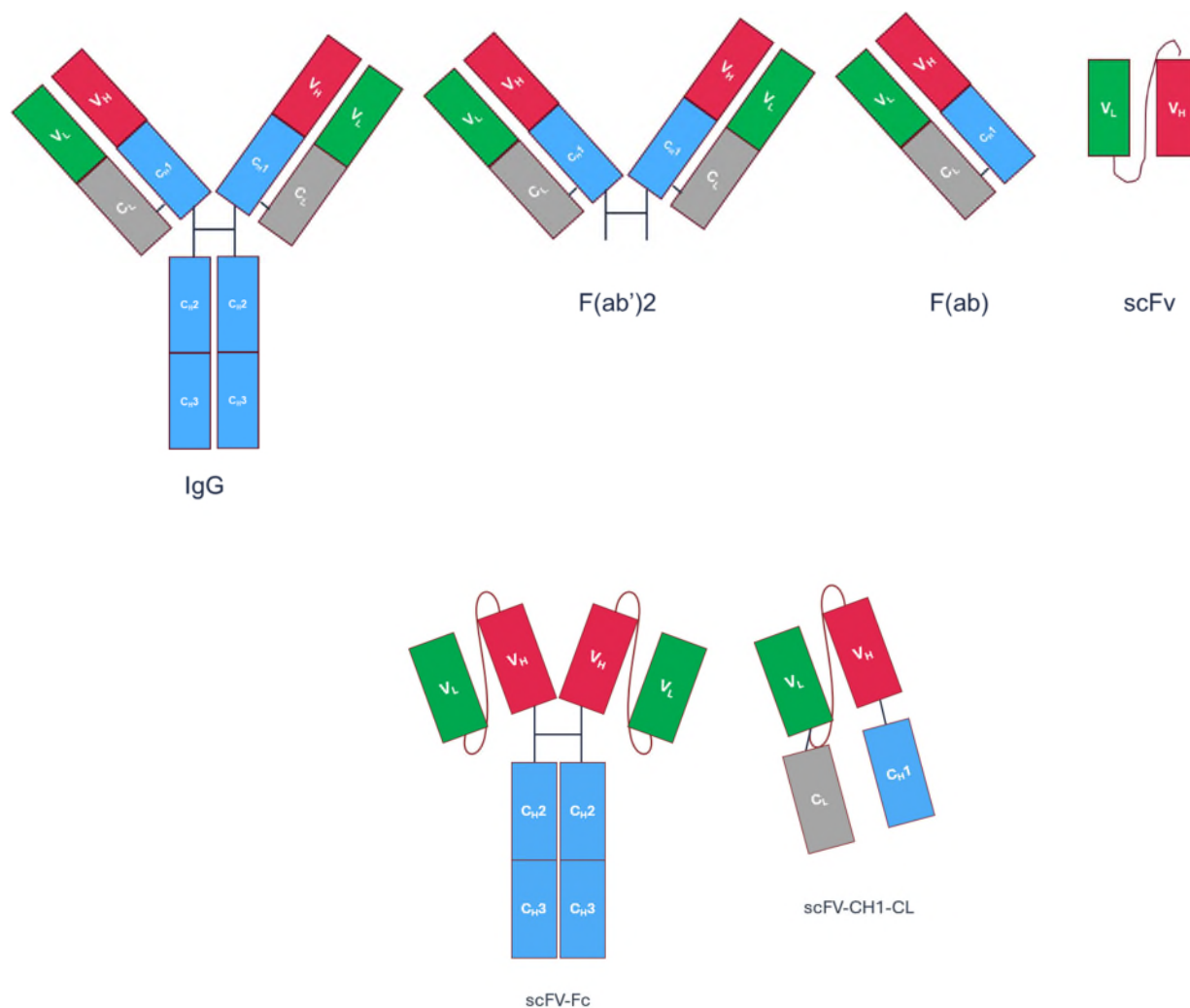
response from the body's immune system. The arms are connected to the stem by a flexible structure known as the hinge region.



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 (CL, CH1, CH2, CH3) are the relatively invariant portion of the heavy and light chain and determine 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 can be produced by proteolytic digestion above the hinge region, which results in two independent Fab fragments, or by recombinant expression methods in any platform (mammalian, yeast, bacterial, etc.). scFv fragments are composed of the variable domains of the heavy and light chains of an antibody genetically connected by a flexible peptide linker. They are often fused to other molecules including the constant regions of antibodies such as scFv-Fc and scFv-CH1-CL_{fc}. 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-CH1-CL 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.

C. Prosecution History of the '968 Patent

U.S. Application No. 18/883,719 (“the ’719 application”), which issued as the ’968 patent, was filed on September 12, 2024, as a continuation of a chain of applications tracing back through five prior U.S. patents (U.S. Patent Nos. 11,274,156, 10,442,860, 9,850,306, 9,441,044, and 8,993,524) to the ’317 PCT Application, filed March 4, 2011. The ’317 PCT Application claims the benefit of U.S. Provisional Application Nos. 61/311,255 (filed March 5, 2010) and 61/435,671 (filed January 24, 2011). EX1002 at 19-20.

In the December 3, 2024 Office Action, the Examiner included a restriction requirement, certain informal objections to the claims, rejections to then-pending claims 2 and 3 for indefiniteness, and rejections to claims 1-3 for double patenting. *Id.* at 398-417. Notably, there were no written description or enablement rejections to issued claims 1 or 9. Following an interview, the Applicant amended initial claim 1, canceled initial claims 3-8, and filed new claims 9-15. *Id.* at 433-440. The Applicant also submitted a provisional election in response to the Examiner’s restriction requirement and a terminal disclaimer. *Id.*; *id.* at 425-427. The Examiner issued a Notice of Allowance on January 19, 2025, noting that the amendments resolved the previous claim rejections, and the application issued as the ’968 patent on May 13, 2025. *Id.* at 459-460, 463-465.

D. Level of 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.

For purposes of this Response, Patent Owner does not dispute Petitioner's proposed level of ordinary skill in the art because, as shown below, the Petition fails to establish unpatentability of claims 1 and 9 even applying Petitioner's own proposed POSITA. Patent Owner reserves the right to dispute Petitioner's POSITA proposal to the extent necessary to respond to new arguments or evidence raised in any Reply.

III. CLAIM CONSTRUCTION

Petitioner proposes two claim constructions: “scFv” and “or.” Pet. at 20-23. Both proposed claim constructions relate only to terms found in dependent claims 2 and 3 of the '968 patent. Because Patent Owner has filed a Motion to Amend seeking to cancel claims 2 and 3 (and claims 4-8) of the '968 patent, this Response does not

further address Petitioner's claim construction arguments and the Board need not resolve them. *See id.*; Patent Owner's Preliminary Response at 6-13.

IV. ARGUMENT

A. Ground 1: The Petition fails to establish that claims 1 and 9 of the '968 patent are unpatentable for lack of adequate written description support.

Petitioner's Ground 1 fails because the specification satisfies the written description requirement for challenged claims 1 and 9, which remain at issue after cancellation of claims 2-8.

1. Relevant Legal Standards – Written Description

“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.’” *Id.* (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].”). Under *Ariad*, a “sufficient” written description for disclosure of a claimed genus “requires the disclosure of either a representative number of species falling within the scope of the genus *or* structural features common to the members of the genus so that one of skill in the art can ‘visualize or recognize’ the members of the genus.” *Ariad*, 598 F.3d at 1350 (emphasis added) (citation omitted).

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

Petitioner cannot carry its burden to show lack of written description 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. EX2040, Davis Decl. ¶¶ 26, 72, 82.

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 pp. 102 (Sequence Listing, Seq ID NO: 2), 117-118 (Sequence listing, SEQ ID NO: 71), 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 pp. 102 (Sequence Listing, SEQ ID NO: 2), 117-118 (Sequence listing, SEQ ID NO: 71), 120 (Sequence listing, SEQ ID NO: 87), 123 (Sequence listing, SEQ ID NO:104), Figs. 1B, 1C, and 3; EX1017 (showing same).

Figures 3, 1B, and 1C below, reproduced with color added, are blaze marks for the "integrated whole" embodiment of claims 1 and 9. EX2040, Davis Decl. ¶¶ 30-31, 47, 74. They expressly disclose and emphasize (*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



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- β RII) 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):
- TIPFHVQK** **SVNNDMIVD** **NRGAVKFPQL** **CKFCDFRST** **CDNQKSCMSN** **CSITSICEKP**
QEVCAVWRK **NDENILETV** **CHDPLPYND** **FILEDAASP** **CIMKEKKRPG** **ETFFMCSCSS**
DECNDNIIPS **EYNTSNPD**

FIG. 1B

FIG. 3 of the '968 Patent



FIG. 3

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):
- TIPFHVQK** **SVNNDMIVD** **NRGAVKFPQL** **CKFCDFRST** **CDNQKSCMSN** **CSITSICEKP**
QEVCAVWRK **NDENILETV** **CHDPLPYND** **FILEDAASP** **CIMKEKKRPG** **ETFFMCSCSS**
DECNDNIIPS **EYNTSNPD**

FIG. 1B

FIG. 1C of the '968 Patent

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

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 “**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 “*Linker.*” As such, each of the claimed elements is clearly disclosed in and supported by the specification of the '968 patent.

In addition, for claims 1 and 9, Figure 3 of the '968 patent provides written description support for the entire claimed invention. EX2040, Davis Decl. ¶¶ 47-48, 74-75. As shown in the annotated figure above, Figure 3 identifies all 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 acid 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).

If there remained any doubt, the original claims themselves provide written description support. Written description—whether the inventor had possession of the claimed subject matter—is assessed against the application as it was filed. *Ariad*, 598 F.3d at 1351. An original claim is part of the disclosure as-filed and can supply written description support for later-issued claims. *See Crown Packaging Tech., Inc. v. Ball Metal Beverage Container Corp.*, 635 F.3d 1373, 1380 (Fed. Cir. 2011) (“Original claims are part of the specification and in many cases will satisfy the written description requirement.”); *see also In re Gardner*, 475 F.2d 1389, 1391-92 (C.C.P.A. 1973) (holding that original claim “itself constituted a description in the original disclosure equivalent in scope and identical in language to the total subject matter now being claimed”); MPEP § 2163(I)(A) (9th ed., Nov. 2024) (“There is a presumption that an adequate written description of the claimed invention is present when the application is filed.”). Here, for example, original claim 1 issued after only

minor amendments; it already recited a targeting moiety comprising amino acids 1-119 of SEQ ID NO: 2 and the amino acid sequence of SEQ ID NO: 71 and a subsequent amendment merely conformed the surrounding language describing the targeting moiety (from “an antibody, scFv, or Fc containing [polypeptide]” to “an antibody or antibody fragment thereof”) and corrected grammar:

Listing of Claims:

1. (Currently Amended) An isolated molecule comprising ~~a targeting moiety fused with an immunomodulatory moiety, wherein:~~

(a) ~~the a~~ targeting moiety comprising [[es]] an antibody~~[[,]]~~ or antibody fragment thereof, ~~scFv, or Fc containing~~ comprising amino acids 1-119 of SEQ ID NO: 2 and the amino acid~~[[s]]~~ sequence 1-107 of SEQ ID NO: 71, ~~and that~~ which specifically binds Epidermal Growth Factor Receptor (EGFR); and

(b) ~~the an~~ immunomodulatory moiety comprising [[es]] 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.

EX1002 at 434. Thus, the as-filed claim language—reciting the specific amino-acid sequences and the EGFR-binding targeting moiety—confirms that the inventors possessed the claimed subject matter no later than the filing date of the application from which it issued.

The structural features recited in those claims are sufficient written description for the claimed genus under *Ariad* because they allow a POSITA to visualize or recognize the members of the genus. This can be seen in Dr. Hale's declaration, which diagrammatically illustrates members of the genus of claim 1.

EX1003, Hale Decl. ¶ 162, Fig. K. The genus of claim 9 is narrower and excludes many of these species, i.e., each species of Figure K in which the TGFβRII immunomodulatory moiety is not linked to the C-terminus of the light chain as recited in claim 9 and any species that does not include the particular linker of SEQ ID NO: 104 as recited in claim 9. EX2040, Davis Decl. ¶¶ 81, 89, 93-95, 109, 116. Therefore, claims 1 and 9 of the '968 patent had adequate written description support.

Petitioner's argument that claims 1 and 9 lack written description rests 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 (*id.* at 27)—overstates the written description requirement and ignores binding precedent. As discussed below, there is no requirement that the specification itself must describe every detail 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. Sep. 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”). This 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)).

Claims 1 and 9 require a targeting moiety that binds to EGFR 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. The Petition alleges that there is insufficient disclosure of the targeting moiety described in claims 1 and 9. Pet. at 28-29. This argument lacks merit.

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, *e.g.*, cetuximab, panitimumab, nimotuzumab, zalutumumab, and necitumumab. *Id.* 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 derived from cetuximab. *Id.* 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. *Id.*; EX2040, Davis Decl. ¶¶ 47-49.

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. at 30. But as already explained, the specification need not describe every claimed detail. The '968 patent provides written description support sufficient 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; EX2040, Davis Decl. ¶¶ 46, 48, 61-66.

Second, Petitioner's argument that a specification always must provide "express disclosure of [each] limitation" or express "blaze marks" for each limitation (Pet. at 26, 30) is wrong. This argument ignores the case law above and 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*, 448 F.3d at 1368 (“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 Figure 3. The emphasis on these two portions of the targeting moiety in Figure 3 **constitutes** blaze marks that clearly indicate the importance of those regions. Petitioner acknowledges the emphasis on these regions of the targeting moiety in Figure 3 but then tries to ignore it, arguing that those portions are part of the entire molecule of Figure 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.

Figure 3 assigns a distinct typographic convention to each structural domain: underlining for the anti-EGFR antibody variable region, plain text for the antibody constant region, italics for the linker, and bold for the TGF β RII extracellular domain. EX2040, Davis Decl. ¶¶ 48, 61. As Dr. Davis explains, a POSITA would recognize the first 119 underlined residues of SEQ ID NO: 2 as a discrete structural unit—the variable heavy-chain domain—because the key identifies the underlined span as the variable region and that span falls within the common length range for a human or murine immunoglobulin variable heavy domain. *Id.* ¶ 62. Dr. Davis further explains that the final eleven residues of a variable heavy domain are highly conserved, even across species, so that a POSITA aligning the first 119 residues of SEQ ID NO: 2 against any representative VH domain would see that WGQGTLVTVSA corresponds to the last eleven residues of that VH—confirming the identification of

the domain and supplying the “blaze mark” for where to fuse the variable domain to another protein. EX2040, Davis Decl. ¶ 62.

The absence of the literal phrase “amino acids 1-119 of SEQ ID NO: 2” elsewhere in the specification does not change that technical disclosure. Indeed, Dr. Hale concedes that written description need not be in the exact words of the claims and may be satisfied by any combination of words, structures, figures, diagrams, and formulas contained in the specification. EX1003, Hale Decl. ¶¶ 114-115. Applying his own standard, Figure 3’s annotated disclosure of the variable heavy-chain domain satisfies the requirement. EX2040, Davis Decl. ¶¶ 63-65. The first 119 residues are identified graphically as the anti-EGFR variable region, and reciting the words “amino acids 1-119 of SEQ ID NO: 2” would simply be a numerical way of expressing the VH domain of the antibody that binds EGFR—which Figure 3 already discloses. A POSITA would not need or expect the specification to restate a residue range in claim-style words when the figure already identifies the same structural unit. The later appearance of that phrase in the issued claims—which by definition use words, rather than images like Figure 3—is therefore not evidence that the underlying structure lacks written description support in the specification. *Id.* ¶¶ 64-65.

Nor does Dr. Hale’s Appendix C tabulation change the result. The 35 exemplary fusion proteins containing antibody targeting moieties he identifies do

not negate the specification's express disclosures that a targeting moiety may include an antibody fragment, an scFv format, an Fc-containing polypeptide, or a fragment containing variable domains. EX1001 at 27:38-43, 29:24-35, 34:40-52, 35:56-62. A sequence listing of a complete expressed chain supplies full sequence context, while a figure separately identifies a functional fragment or domain within that chain, and a POSITA would not infer from the *format* of the sequence listing that the expressly identified fragment formats were excluded. EX2040, Davis Decl. ¶ 66; EX1003, Hale Decl. ¶¶ 80-81, Appendix C. Nor does Dr. Hale's tally of how often particular terms appear in the specification—that EGFR is named three times while CD4 and CD20 appear five times and CD25 ten times, and that “in another aspect” appears more than 115 times—diminish what Figure 3 discloses. EX1003, Hale Decl. ¶¶ 93, 154. The frequency with which an antigen is named across a set of figures is not a reliable measure of what a POSITA would understand from a particular figure. EX2040, Davis Decl. ¶ 67.

Petitioner's argument to the contrary is conclusory and fails for multiple 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*, 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.*, IPR2018-00576, Paper 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, 725 (Fed. Cir. 2021). In addition, the Petition acknowledges that the specification uses blaze marks of underlining (Pet. at 33-34, 88), bolding (*id.* at 45 n.11), and italics (not mentioned in the Petition), but fails to explain why those blaze marks are insufficient. And Petitioner’s reliance on Dr. Bedi’s April 17, 2025 declaration from the file history of U.S. Application No. 18/811,627 fares no better. Pet. at 37-39; EX1044 at 1-2. As Dr. Davis explains, that declaration addressed a different antibody directed to a different target—not the specific anti-EGFR sequences at issue here, the Figure 3 annotations, or the TGFβRII fusion that Figure 3 depicts. EX2040, Davis Decl. ¶ 68.

Third, Petitioner's argument that the '968 patent discloses only full-length antibodies used as the targeting moiety and does not support antibody fragments ignores numerous disclosures in the specification. *Id.* 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 specification includes many other 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.

Id. 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).**

Id. 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.

Id. at 36:62-65.

As discussed above, Figure 3 also 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). The '968 patent thus describes a targeting moiety as an antibody or antibody fragment, describes both terms, gives examples (Fab, Fab', F(ab')₂, Fd,

scFv, single-chain antibodies, sdfv, and fragments with either a VL or VH domain), and discloses the specific claimed sequence—support 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. EX2040, Davis Decl. ¶¶ 40, 46, 66.

Fourth, Petitioner's argument that the claimed targeting moiety is an unusual or unrecognizable fragment rests on a straw man. Specifically, Petitioner and Dr. Hale contend that the minimal construct would contain an unpaired cysteine at position 214 of the light chain, leading to instability, aggregation, or failure of expression. EX1003, Hale Decl. ¶¶ 101, 119, 169. An unpaired cysteine is only a problem, if at all, if it is never paired, and the open-ended term “comprising” permits the additional structure that pairs it. EX2040, Davis Decl. ¶ 69. And a POSITA would understand this. In particular, a POSITA examining the recited elements would recognize that three-quarters of a Fab is already present and that adding a CH1 domain to the C-terminus of the variable heavy-chain domain defined by amino acids 1-119 of SEQ ID NO: 2 is the most logical next step. The CH1 domain carries a cysteine positioned to form a covalent disulfide bond with Cys214 of the light chain—in other words, regardless of the heavy-chain class or subclass selected, Cys214 would not be unpaired. A POSITA would further understand that CH1 terminates before the hinge-region cysteines that form the interchain disulfides

between heavy chains. These are basic Fab design features well known to any POSITA, and Dr. Hale's analysis simply disregards them. *Id.* ¶¶ 69, 115(a)-(b).

Petitioner's argument also fails because claim 1 does not preclude additional heavy-chain structure. A Fab format, which includes a CH1 domain to pair with the light-chain C-kappa domain and resolve the free cysteine, is a standard and well-understood antibody-fragment architecture, as Dr. Davis explains and as Dr. Hale acknowledges. *Id.* ¶ 115(a)-(b); EX1003, Hale Decl. ¶ 48. A full-length antibody is equally available, in which event the POSITA continues the heavy chain from the Fab through the hinge, CH2, and CH3 domains. Dr. Hale concedes that Figure 3 discloses a full-length antibody targeting moiety and that all 35 exemplary fusion proteins containing an antibody targeting moiety use full-length antibodies. EX2040, Davis Decl. ¶ 115(a)-(b); EX1003, Hale Decl. ¶¶ 81, 121-122, Appendix C. Under either architecture, the light-chain cysteine is paired and Petitioner's and Dr. Hale's argument lacks merit.

Finally, Dr. Hale's observation that he is unaware of an isolated molecule having just a heavy-chain variable region combined with a complete immunoglobulin light chain being described in the scientific literature does not answer the written-description question. EX1003, Hale Decl. ¶ 119. Written description asks whether the specification conveys possession to a POSITA; it does not require that the claimed construct already be known, previously made, or separately named in the

literature, and here a POSITA would readily understand that the inventors possessed the claimed invention. EX2040, Davis Decl. ¶ 71; *see also id.* ¶ 29.

Fifth, Petitioner's argument that "there is no disclosure of the specific combination of all the limitations as an integrated whole for each claim" (Pet. at 26) is likewise based on misstatements of fact and 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. EX2040, Davis Decl. ¶¶ 31, 74. As Patent Owner has demonstrated "how each limitation...is disclosed in combination with all of the other claim limitations," Patent Owner has sufficiently considered each claim "as an 'integrated whole' when assessing written description." *Respironics, Inc. v. Zoll Med. Corp.*, IPR2013-00322, Paper 46 at 24 (P.T.A.B. Sep. 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).¹

¹ 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

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).

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.'" *Id.* (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

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 adequate written description support.

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) explains 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) (alterations in original) (first quoting *In re Smythe*, 480 F.2d 1376, 1382 (C.C.P.A. 1973); then quoting *In re Rasmussen*, 650 F.2d 1212, 1215 (C.C.P.A. 1981)). That precedent, adopted by the *en banc* Federal Circuit in *South 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 Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 765 (Fed. Cir. 1988) (“Where there is direct conflict, the precedential decision is the first.”).

Sixth, the specification expressly states that, “in another aspect,” an immunomodulatory moiety is a polypeptide fused to the C-terminus of the light chain of a targeting antibody. EX1001 at 35:48-50. Read with Figure 3’s anti-EGFR sequence, linker, and TGFβRII markings, that disclosure conveys to a POSITA that light-chain-side fusion was an intended configuration. EX2040, Davis Decl. ¶ 73.

At his deposition, Dr. Hale argued that the specification did not disclose connecting the light chain of targeting moiety (*e.g.*, cetuximab) to an immunomodulatory moiety (*e.g.*, TGFβRII) via a linker. EX2042, Hale Dep. Tr. at

98:15-99:6, 103:13-21. This argument is contrary to the plain language of the specification and the plain meaning of “fuse” in this art. The '968 patent discloses, for example, that “[i]n one embodiment, 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.” EX1001 at 35:33-36. Dr. Hale stated in his deposition that this passage would be understood to mean that linking of these two moieties is accomplished using *only* a linker, and that fusing can only be accomplished *without* a linker. He used this interpretation to argue that the later passage in that same paragraph disclosing that “the immunomodulatory moiety is a polypeptide that is fused to the C-terminus of the light chain of a targeting antibody” (*id.* at 35:48-50) means that there is no linker between the light chain and the immunomodulatory moiety.

This reading must be rejected. First, it is contrary to the plain and ordinary meaning of the term “fuse” in the protein engineering art, which is often used to refer to joining with a linker. EX2040, Davis Decl. ¶¶ 76, 78-79; *see also, e.g.*, EX2048 (U.S. Pat. Pub. No. 20090252729) at [0005] (“In certain embodiments, the component Fc moieties of an scFc are genetically fused in tandem via a polypeptide linker (e.g., an Fc connecting peptide) interposed between the Fc moieties.”); EX2049 (U.S. Pat. Pub. No. 20060140889) at [0450] (discussing an example spacer SGGGSGGGSGGGG and stating “[b]esides the example spacer, many other

spacers are described in scientific literature to fuse proteins together”); EX2050 (U.S. Pat. No. 9,382,323) at claim 1 (“wherein each of the one or two single chain Fab fragments is fused to the full length antibody via a peptide connector at the C- or N-terminus of the heavy chain of the full length antibody.”). Second, Dr. Hale’s argument is contrary to the doctrine of last antecedent, under which “with or without a linker” modifies “fused.” *See, e.g., Netflix, Inc. v. DivX, LLC*, 166 F.4th 1341, 1346 (Fed. Cir. 2026); *Finisar Corp. v. DirecTV Grp., Inc.*, 523 F.3d 1323, 1336 (Fed. Cir. 2008). Third, it is contrary to the ’968 specification, which is replete with examples of linkers used to connect moieties and which refers to the proteins so formed, including the proteins of Fig. 3 which include a linker between the antibody and TGF β RII, as “fusion” proteins, as Dr. Davis explains. EX2040, Davis Decl. ¶ 76. Dr. Hale confirmed as much in his deposition, acknowledging that a POSITA reading Figure 3 would understand it to be describing what its title says—“[f]usion proteins comprising anti-EGFR antibody and TGF β RII extracellular domain.” EX2042, Hale Dep. Tr. at 74:6-15. Fourth, even if Dr. Hale were correct that the second passage at 35:48-50 could be understood as an example of fusing without a linker, the first passage at 35:33-36 clearly indicates that a linker may be used in other embodiments. EX2040, Davis Decl. ¶¶ 75-76.

In addition, claim 9 does not recite merely an arbitrary collection of unrelated options. It specifies four structural components—the light-chain sequence of SEQ

ID NO: 71, the variable heavy-chain sequence comprising amino acids 1-119 of SEQ ID NO: 2, the TGF β RII sequence of SEQ ID NO: 87, and the linker of SEQ ID NO:104—and then fixes the spatial arrangement by requiring the light chain at the linker's N-terminus and the immunomodulatory moiety at its C-terminus. A POSITA would understand this, and that Figure 3 supplies the sequence context and typographic signposts; column 35, lines 48-50 supplies the light-chain-side orientation. EX2040, Davis Decl. ¶¶ 74, 78; EX2042, Hale Dep. Tr. at 125:18-126:19. Every structural element of claim 9's architecture is, by Dr. Hale's admission, already in Figure 3.

In addition, light-chain-side engineering was technically feasible and known before the relevant date as Dr. Davis explains. Müller (EX2031), for example, describes an scFv-CL construct in which the kappa light-chain constant domain is fused to an anti-CD2 scFv, as well as an scFv-CH1 construct involving an anti-EGFR scFv; additional references describe an scFv-CH1-CL format retaining the constant domains of a natural Fab and analyze the domain interactions of engineered scFv and Fab formats. EX2040, Davis Decl. ¶¶ 77-80; EX2031 at 259-260; EX2034; EX2035. Orcutt et al. (EX2038), published in *Protein Engineering, Design & Selection* with an electronic publication date of December 17, 2009, describes fusions of several different modules to the C-terminus of an antibody light chain and reports no difficulty in making those constructs and no sensitivity to linker length,

as Dr. Davis explains. EX2040, Davis Decl. ¶ 79; EX2038 at 226. That publication predates the earliest priority date and a POSITA would be aware of advances like these reported in journals. EX2042, Hale Dep. Tr. at 51:25-53:7. Together with the specification's blaze marks, a POSITA would have been able to generate the design of claim 9. EX2040, Davis Decl. ¶¶ 77-80. And a POSITA would certainly be able to do so without undue experimentation, as constructing this type of molecule would not present a particular difficulty for a POSITA. EX2040, Davis Decl. ¶ 103.

Seventh, Dr. Hale's premise that the claims require only the variable light-chain and leave the heavy-chain constant region unconstrained is incorrect. The claims recite a specific combination of (a) EGFR binding supplied by the targeting moiety's specified variable-region sequences and (b) the immunomodulatory action of TGFβRII. Neither claim 1 or 9 demands a particular heavy-chain constant region. EX1001 at claims 1, 9; EX2040, Davis Decl. ¶ 111.

A POSITA would understand that therapeutic antibodies are often built on an IgG backbone containing heavy- and light-chain constant regions, not on an unlimited universe of arbitrary sequences. Indeed, Dr. Hale acknowledges that, by 2010, conventional recombinant IgG manufacture was comparatively predictable and routine, that most fusion proteins in clinical development included one or more immunoglobulin domains, and that cetuximab was constructed with mouse variable regions linked to human immunoglobulin constant regions. EX1003, Hale Decl.

¶¶ 56-58, 60-61; EX2040, Davis Decl. ¶¶ 98-100, 105, 123-127. Dr. Hale agreed in his deposition that a POSITA would have been familiar with “well-known antibody fragments, such as a[] F[AB], a single-chain F[V,] and F[C].” EX2042, Hale Dep. Tr. at 33:17-34:6.

The relevant constant-region field is correspondingly bounded. The '968 patent recognizes the relevant immunoglobulin classes and subclasses, including IgG1, IgG2, IgG3, and IgG4, each of which has well-known sequences and is not ordinarily modified absent a specific engineering objective, such as altering half-life or effector function.² EX1001 at 34:23-60; EX2040, Davis Decl. ¶¶ 110-113. The specification supports an IgG1 embodiment: its definition of “antibody” states that an immunoglobulin may be of any type or class, including IgG1, and Figure 3 supplies the relevant constant-region sequence context. EX1001 at 34:35-41, Fig. 3. Thus, only a limited number of heavy-chain constant-region sequences could realistically form the basis of a molecule within the claims, and the constant-region

² In addition, a POSITA would understand that the immunoglobulin subclasses have different use-cases. For example, a POSITA would understand that IgG3 is rarely used and, and IgG2 and IgG4 have niche uses, such as defending against bacterial infections, inflammation, or allergies; only IgG1 would be selected for oncology-related uses. EX2040, Davis Decl. ¶ 114.

question does not convert the claims into an unbounded genus. EX2040, Davis Decl.

¶¶ 112-113; EX1003, Hale Decl. ¶¶ 82-88, 166.

For all these reasons, Petitioner has failed to establish that claims 1 and 9 of the '968 patent are unpatentable for lack of written description support, and Ground 1 should be denied.

B. Ground 2: The Petition fails to establish that claims 1 and 9 of the '968 patent are unpatentable for lack of enablement.

As for Ground 2, this challenge fails because the specification enables claims 1 and 9 without undue experimentation. As with Ground 1, this Response addresses Ground 2 only as to claims 1 and 9, which remain at issue after cancelation of claims 2-8.

1. Relevant Legal Standards – Enablement

“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., 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 *United States 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 Corp. v. Ingevity South Carolina, LLC*, PGR2020-00035, Paper 11 at 13 (P.T.A.B. Sep. 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 Corp. v. Insmed Inc.*, PGR2017-00021, Paper 10 at 9-10 (P.T.A.B. Nov. 15, 2017).³

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). “No one factor is determinative, rather the determination should be made after

³ *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).

weighing all the factors.” *Genome & Co. v. Univ. of Chicago*, PGR2019-00002, Paper 40 at 10 (P.T.A.B. Apr. 14, 2020).

A petition fails to establish lack of enablement when it “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) (finding petition “fail[ed] to adequately address the *Wands* factors”); *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.”).

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

The Petition does not show that the specification fails to enable claims 1 and 9. As discussed earlier, the '968 patent shares a common specification with each of the patents and patent applications in its chain of priority. 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 *Teletronics*, 857 F.2d at 785).

First, written description and enablement ordinarily rise or fall together; having already shown adequate written description above, that showing defeats enablement too. *See Cont'l Auto. Sys., Inc. v. Intell. Ventures II LLC*, No. IPR2022-00972, Paper 16 at 16 (P.T.A.B. Dec. 7, 2022) (“[A] recitation of how to make and use the invention across the full breadth of the claim is ordinarily sufficient to demonstrate that the inventor possesses the full scope of the invention, and vice versa.”) (quoting *LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005)). At a minimum, Petitioner cannot simply reframe its written-description arguments as an enablement challenge. *See, e.g., Instrumentation Lab'y Co. v. HemoSonics LLC*, PGR2019-00047, Paper 8 at 25 (P.T.A.B. Oct. 24, 2019) (“[T]o the extent Petitioner's enablement arguments are based on a lack of written

description support for certain claim elements [], those arguments are not persuasive in view of our determination that there is written description support for the challenged claims in the '144 patent specification.”); *Fox Factory Inc. v. SRAM, LLC*, PGR2016-00043, Paper 9 at 16 (P.T.A.B. Apr. 3, 2017) (“To the extent Petitioner’s argument is that because there is no written description support, there is no enablement, Petitioner has failed in showing there is no written description support. Thus, we are unpersuaded that argument demonstrates sufficiently that there is no enablement of original application claim 17.”).

Second, 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). Indeed, Petitioner presents no testing or any literature suggesting that any molecule falling within the claims could not be made or would not be operable, as is its burden. EX2040, Davis Decl. ¶ 59. As discussed below, Petitioner’s arguments to the contrary are unconvincing and fail to support Petitioner’s conclusion that a “person of ordinary skill in the art [would not be able] to make and use the full scope of the challenged claims without undue experimentation.” Pet. at 2.

a. Petitioner conflates experimentation and undue experimentation.

Petitioner's enablement argument ignores that "[t]he key word is 'undue,' not experimentation." *BASF*, PGR2020-00035, Paper 11 at 13 (quoting *In re 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 makes the same mistake by fixating on whether experimentation would be "extensive" rather than undue. 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*, 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*, PGR2019-00047, Paper 8 at 26 ("[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)).

b. Petitioner fails to establish that the breadth of the claims (*Wands* Factor 8) weighs against enablement.

Petitioner's argument that the claims' "breadth and diversity" alone "supports the lack of enablement" misstates the law and the scope of the claims. Pet. at 62.

Petitioner argues that the breadth of these claims (*Wands* Factor 8) *per se* weighs against these claims being enabled. *Id.* 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 claims 1 and 9 are broad, to carry its burden, the Petition must explain *why* the breadth of the 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 claims 1 and 9 (*Wands* Factor 8) is flawed, because it overstates the scope of the claims. A patentee "must only enable the *claimed* invention." *In re Entresto*, 125 F.4th 1090, 1099 (Fed. Cir. 2025) (emphasis in original) (quoting *Amgen*, 598 U.S. at 610); *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.” *Id.* 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 claim 1. These are not abstract functional descriptors—rather, they are structural requirements that constrain the scope of the claims to molecules that 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. EX2040, Davis Decl. ¶¶ 86-89, 109.

Nor does the absence of an express heavy-chain-constant-region limitation create a written description problem. A claim does not lack written description support merely because it recites a novel structural element but leaves ancillary structural elements unspecified. For example, consider a claim to a car reciting a particular novel engine, a frame to which the engine is attached, a transmission, an axle attached to the frame and the transmission, and a body attached to the frame and enclosing the engine and transmission. That claim does not lack written description simply because many different frames, transmissions, axles, and bodies—known and unknown—would satisfy the claim. The same is true here. Claim 1 recites, in detail, the specific sequences that define the novel targeting moiety (amino acids 1-119 of SEQ ID NO: 2 and SEQ ID NO: 71) and immunomodulatory moiety (SEQ ID NO: 87); it does not separately specify the heavy-chain constant region and need not do so. A POSITA reading claim 1 would understand that the heavy-chain constant region may be supplied from any of the small number of well-characterized antibody architectures discussed below, just as a POSITA reading the car claim would select a suitable frame. Petitioner's argument, if accepted, would invalidate every antibody-fragment claim that does not separately enumerate every possible constant-region sequence—a result inconsistent with the

settled rule that a specification need not describe or enable “every⁴ conceivable and possible future embodiment.” *Rexnord*, 274 F.3d at 1344.

Claim 9 is narrower still than claim 1, 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

⁴ Dr. Hale's deposition testimony confirms. When confronted with an unrelated patent (U.S. Patent No. 11,939,387, marked as Ex. 2036) whose claims likewise leave the heavy- and light-chain constant regions unspecified, Dr. Hale would not say that those claims lack written description or enablement on that basis. EX2042, Hale Dep. Tr. at 132:4-139:21. Dr. Hale has no principled basis to treat the claims any differently here.

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 claim 9 (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; EX2040, Davis Decl. ¶¶ 74, 81, 94.

The same structural element left open by claim 1—the heavy-chain constant region—remains open in claim 9, which likewise recites no heavy-chain constant-region sequence. That does not create the unbounded, random-orientation claim Petitioner describes. A POSITA selecting a heavy-chain constant region for the targeting moiety of claims 1 and 9 would draw from a small, well-known set of antibody architectures that pair the light-chain constant-region cysteine recited in SEQ ID NO: 71—for example, a full-length antibody heavy chain (CH1-hinge-CH2-CH3), a Fab-format heavy chain (CH1 only). EX2040, Davis Decl. ¶¶ 112, 115(a)-(b). Each of these architectures is operative, well understood, and routinely used by POSITAs; none requires undue experimentation to design, express, or test. *Id.*

By contrast, the single construction Dr. Hale identifies as problematic—a targeting moiety consisting of the bare variable heavy-chain domain (amino acids 1-119 of SEQ ID NO: 2) with no heavy-chain constant region at all, fused to the complete light chain of SEQ ID NO: 71—is a case in which the light-chain constant-region cysteine has no heavy-chain partner. EX1003, Hale Decl. ¶¶ 101, 119, 169.

As Dr. Hale concedes (EX1003, Hale Decl. ¶ 119), a POSITA would recognize that particular construction as unlikely to express or fold properly, meaning a POSITA would not pursue it. *See Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984) (claim not non-enabled by inoperative embodiments that a POSITA could identify without undue experimentation); *In re Angstadt*, 537 F.2d 498, 502-03 (C.C.P.A. 1976) (disclosure of operable embodiments alongside inoperative embodiments does not require undue experimentation to practice the invention). Indeed, every one of Dr. Hale's examples of a "full-length antibody" targeting moiety—all 35 of the exemplary fusion proteins he identifies in Appendix C—already supplies a complete heavy chain that pairs the light-chain cysteine. EX1003, Hale Decl. ¶¶ 81, 121-122, Appendix C. Dr. Hale's disclosure thus confirms that a POSITA would select one of the many operative architectures, and not the single inoperative one he points to.

Therefore, despite Petitioner's assertion that 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. EX2040, Davis Decl. ¶¶ 37, 91, 109.

Dr. Hale argues that claim 1 recites several categories of molecules—separate chains, covalently associated chains, two components genetically fused in six pairings, and all three genetically fused in six orders—and that this confirms the

specification is no more than a research assignment. *Id.* ¶¶ 162-163. But Dr. Hale again ignores the language of claim 1. Claim 1 requires the specified sequences, a targeting moiety that specifically binds EGFR, an immunomodulatory moiety comprising SEQ ID NO: 87, and an isolated molecule. Applying ordinary protein-engineering judgment to exclude configurations that are incomplete, chemically conjugated rather than recombinantly expressed, or inconsistent with the “isolated molecule” requirement, only approximately eight structurally sensible constructs satisfy claim 1. EX2040, Davis Decl. ¶¶ 94-95, 115(c). Adding a linker or no-linker variant doubles that number to approximately sixteen constructs, and testing a longer and a shorter linker would bring the total to approximately twenty-four—numbers that were entirely routine to design, express, and test in a drug-discovery or protein-engineering program in the 2010-2011 timeframe. *Id.* ¶¶ 95, 115(d) & n.3.

Fusion proteins encompassed by claims 1 and 9: Petitioner reiterates that the '968 patent broadly defines the terms “targeting moiety” and “immunomodulatory” and discloses broad genera 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 formula:

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

Targets		
1-2 microglobulin	ErbB-4/HER4	mdm-2 melanoma ubiquitous mutated 1
4-1BB (CD137)	estrogen receptors (ER) Ets variant gene 6/acute myeloid leukemia 1 gene ETS (ETC6-AML1) fusion protein	MGAT5
4-1BB ligand(4-1BBL) 707 alanine proline (707-AP)	FATE	MLA-All
ADAM2	FGFR ligand family	MMAI
adenocarcinoma antigen recognized by T cells 4 (ART-4)	fibroblast growth factor receptor (FGFR) family	MORC
adipophilin	fibroblast growth factor-5 (FGF-5)	MUC1n
AF15q14	fibronectin (FN)	MUM-1
alpha-actinin-4	FRAMF	MuSK receptor family

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Targets			Targets			Targets		
		KB (RANK) ligand(RANKL) receptor tyrosine kinase-like orphanreceptor (ROR) receptor family		lineage-specific anti-25 gens	SYT-SSX1 or -SSX2 fusion protein			tumor necrosis factor (TNF) family
caspase-5 (CASP-5)	interferon inducible protein absent in melanoma 2 (AIM-2)	RET receptor family	CPSF	LIPI	telomerase			tumor necrosis factor (TNF) receptor superfamily (TNFRSF)
caspase-8 (CASP-8)	Interleukin-10 (IL-10)	RNF43	CTAGE-1	IL-6 receptor	TEX 15			tumor necrosis factor (TNF) receptor superfamily (TNFRSF)
CD137L	Interleukin-12 (IL-12)	RNF43	CTL-recognized antigen on melanoma (CAMEL)	LMP2	TGF-α receptor			tumor necrosis factor (TNF) receptor superfamily (TNFRSF)
CD152	Interleukin-13 receptor alpha2 chain (IL13Ralpha2)	RYK receptor family		low density lipid receptor/GDP-L facose: beta-Dgalactose 2-alpha-L-fucosyltransferase (LDLR/FUT) fusion protein	TIE receptor family			tumor necrosis factor (TNF) receptor superfamily (TNFRSF)
CD19	Interleukin-4	SAGE	cyclin D 1	MAGE-3	TNFRSF18			tumor necrosis factor (TNF) receptor superfamily (TNFRSF)
CD20	Interleukin-4 receptor (IL-4R)	SGY-1	cyclindependentkinase 4 (CDK4)	MAGE-A12	TPTE			tumor necrosis factor (TNF) receptor superfamily (TNFRSF)
CD25 (IL-2a receptor)	Interleukin-6 (IL-6)	SIRT2	cyclophilin B (Cyp-B)	MAGE-A2	TPX1			tumor necrosis factor (TNF) receptor superfamily (TNFRSF)
CD27	Kalikrein 4	SNRPDI	Cytokine receptors	MAGE-A3	TRAIL-receptor			tumor necrosis factor (TNF) receptor superfamily (TNFRSF)
CD3	KIAA0205	SOX10	cytotoxic T-lymphocyte antigen-4 (CTLA-4)	MAGE-A4	Transforming growth factor-beta (TGF-β)			tumor necrosis factor (TNF) receptor superfamily (TNFRSF)
CD30	K-K-LC	Sp17	death receptor family	MAGE-A6	Transforming growth factor-beta receptor (TGF-βR)			tumor necrosis factor (TNF) receptor superfamily (TNFRSF)
CD33	KLK receptor family	SPANX	dek-can fusion protein	MAGE-A9	Triosephosphate isomerase			tumor necrosis factor (TNF) receptor superfamily (TNFRSF)
CD4	KM-HNI	SPOII	differentiation antigens	MAGE-A1 (MAGE-1)	TRP-1/gp75			tumor necrosis factor (TNF) receptor superfamily (TNFRSF)
CD40	K-ras (KRAS2)	SSX-1	discoidin domain receptor (DDR) family	MAGE-A11	TRP-2			tumor necrosis factor (TNF) receptor superfamily (TNFRSF)
CD40 ligand (CD40L)	LAG-3	STEAPI	EFTUD-2	MAGE-A10	TRP-2-INT2			tumor necrosis factor (TNF) receptor superfamily (TNFRSF)
CD70	LAGE		EGFR ligand family	MAGE-AS				tumor necrosis factor (TNF) receptor superfamily (TNFRSF)
CDKN2A	LAGE-1		Elongation factor 2 (ELF2)	MAGE-B2				tumor necrosis factor (TNF) receptor superfamily (TNFRSF)
cell division cycle 27 (CDC27)	LDHC							tumor necrosis factor (TNF) receptor superfamily (TNFRSF)
Class I (hematopoietin family) and Class II (interferon/IL-10 family) receptors	leukocyte tyrosinekinase (LTK) receptor family	survivin (BIRC5)						tumor necrosis factor (TNF) receptor superfamily (TNFRSF)
COA-1	LIGHT	SYCP1						tumor necrosis factor (TNF) receptor superfamily (TNFRSF)

However, only the highlighted one of those 269 targets is recited in claims 1 and 9: 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, B-9 as shown below:

Targeting Antibodies and Fusion Proteins			
3622W94 mAb	Certolizumab	Ipilimumab	Panorex
893 (human anti-CD40 mAb)	cetuximab	Keliximab	Pertuzumab
Abatacept	CP870	Irdelimumab	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 GTR	Epratuzumab	metelimumab	SMART IDIO Ab
anti-CTLA-4 mAb	Etanercept	Muromonab-CD3	SMART M195 Ab
anti-idiotypic mouse mAb	Farletuzumab	Naptumomab	Teplizumab
Atacicept	GC1008	Natalizumab	Tih (anti-CD6 mAb)
Basiliximab	Gemtuzumab		TNT (chimeric mAb to histone antigens)
BEC2	ozogamicin	Necitumumab	Tocilizumab
Belatacept	Girentuximab	nimotuzumab	Tositumumab-1131
Belimumab	Gliomab-H	NovoMAB-G2	trastuzumab
Bevacizumab	GNI-250 Mab	Obinutuzumab	Tremilimumab
BMS-663513	Golimumab	Ofatumumab	Ustekinumab
Brentuximab vedotin	humanized 13' I LYM-1	Oncolym	
Briakinumab	Ibritumomab tiuxetan	Otelixizumab	Vedolizumab
Catumaxomab	ID11	Ovarex	Zalutumumab
	Infliximab	panitumumab	Zenapax

Yet only one of these antibodies is within the scope of claims 1 and 9: 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, B-1–B-2 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	Fc 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 RIII		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-betaRIII)	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 claims 1 and 9: 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:

$$(269 \text{ 1 target} + 84 \text{ 1 antibody}) \times 23 \text{ 1 immunomodulator} \times 14 \text{ linkers} \times 2 \text{ orientations} = 227,332 \text{ 56}$$

The enablement inquiry asks whether the specification enables “the full scope of the invention *as defined by its claims.*” *Amgen*, 598 U.S. at 610 (emphasis added).

When Dr. Hale's own formula—(targets + antibodies) × immunomodulators × linkers × orientations—is properly applied to claim 1, the number of molecules that fall within its scope is only 56.⁶ And that figure is a *ceiling* rather than a realistic experimental burden, because it retains Dr. Hale's full fourteen-linker and two-orientation multipliers even though the specification identifies the (GGGGS)_n family and Figure 3 fixes the heavy-chain-side orientation. EX2040, Davis Decl. ¶¶ 84-87, 90-91.⁷ The Petition therefore fails to establish that claim 1 encompasses

⁶ Additionally, in Dr. Hale's formula there is no justification for adding the number of targets to the number of antibodies, as Dr. Davis explains. Even retaining Dr. Hale's unmodified fourteen-linker and two-orientation multipliers, the claim-limited calculation is (0 targets + 1 antibody) × 1 immunomodulator × 14 linkers × 2 orientations = approximately 28 combinations. EX2040, Davis Decl. ¶¶ 88-92, 140-142. This 28-combination figure is a ceiling under Dr. Hale's formula; Dr. Davis's 20-combination figure uses a practical subset of five representative linkers and the two available chains. That figure describes the fusion-protein set of molecules a POSITA would actually design, produce, and test using the specification's disclosures. EX2040, Davis Decl. ¶¶ 88-92.

⁷ Dr. Hale confirmed at his deposition that the (GGGGS) linker "was well known" to a POSITA "by March of 2010." EX2042, Hale Dep. Tr. at 57:19-23.

an unreasonably large number of species or that experimentation required to make and test the claimed molecules would be undue. EX2040, Davis Decl. ¶¶ 86-88, 91, 94, 115(c)-(d), 140.

Amgen and Baxalta are distinguishable. Petitioner relies heavily on *Amgen*, 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” (*id.* at 54). Petitioner also cites *Baxalta* for the proposition that there is a “lack of enablement for broad functional claims where specification disclosed 11 working examples of antibodies.” *Id.* at 66.

Claims 1 and 9 of the '968 patent “present[] a very different factual scenario from *Amgen*, in which there were potentially millions of embodiments that had not been enabled.” *ESCO Grp. LLC v. Deere & Co.*, No. 20-cv-01679-WCB, 2023 WL 4199413, at *17 (D. Del. June 22, 2023) (Bryson, J.). In *Amgen*, “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.’” *Id.* at 613-15 (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*. In *Amgen*, the claims at issue were defined entirely by function—binding to specific epitopes on PCSK9 and blocking its interaction with LDL receptors—with no structural limitations. *Id.* at 602-03. Further, the specification in *Amgen* disclosed only a handful of working antibody examples, yet the claims covered potentially millions of undisclosed antibodies identifiable only through trial-and-error screening. *Id.* at 612-15.

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 claim 1. Claim 9 further specifies the linker (SEQ ID NO: 104) and the precise fusion orientation. *Id.* at claim 9. These are all structural limitations absent from the claims in *Amgen*.

These are sequence-defined engineering tasks using known protein domains, materially different from claims defined solely by function that would require a POSITA to screen an undisclosed universe of candidate molecules by trial and error. That claim 1 permits more than one molecular arrangement does not convert the

claimed subject matter into an undefined class of newly discovered proteins. EX2040, Davis Decl. ¶¶ 38, 112.

Claim 9 likewise carries no scope concern. It requires further structural limitations, including the polypeptide linker of SEQ ID NO:104 and fixes both fusion orientations, reducing the scope to two candidate architectures—a Fab-format construct and a full-length-antibody-format construct, each with the TGFβRII domain fused to the C-terminus of the light chain via the (GGGGS)₃ linker. Both are straightforward for a POSITA to design and produce using the specification's disclosures and established recombinant methods, and Dr. Hale acknowledges that claim 9 is narrower than claim 1. *Id.* ¶¶ 89, 93, 116; *see also id.* ¶ 22; EX1003, Hale Decl. ¶ 166.

As demonstrated above, claim 1 encompasses approximately 56 possible fusion proteins using Petitioner's expert's formula, and claim 9 encompasses only 2 possible fusion proteins. EX2040, Davis Decl. ¶¶ 86-89, 93, 94, 115(c)-(d), 116, 140-141; *see also id.* ¶ 22; EX1003, Hale Decl. ¶¶ 56-61, 82-88, 166. Petitioner argues that “the common specification leaves the [POSITA] 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).’).” 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 claim scope from the structural limitations and general knowledge in the art alone.

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.” *Id.* 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 claim 9. 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, Hale Decl. ¶ 56. 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.” *Id.* ¶ 57. A POSITA would

thus have had no uncertainty about whether the claimed sequences bind EGFR—that was already established in the art. Indeed, when asked at his deposition whether he could point to any literature establishing that a POSITA would have difficulty making the fusion proteins of claims 1 and 9, Dr. Hale answered: “As I sit here, no.” EX2042, Hale Dep. Tr. at 153:21-25. A POSITA would apply their ordinary judgment, and would not pursue constructions that were structurally unreasonable or without a prospect of working. EX2040, Davis Decl. ¶¶ 37, 43, 103, 109.

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

As 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. Sep. 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 [POSITA] practice the invention by showing what has worked before.” *Astellas Pharma Inc. v. Zydus, Inc.*, No. 20-CV-1589, 2025 WL 1111447, at *13 (D. Del. Apr. 15, 2025) (quoting *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1310 (Fed. Cir. 2015)).

Dr. Hale himself concedes 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, Hale Decl. ¶ 62.

The specification expressly directs the POSITA to these established methods. The '968 patent states that “[a] targeting moiety, including an antibody, can be coupled to an immunomodulatory moiety including a polypeptide derived from the extracellular domain of TGFBR2. 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.

The specification further provides detailed guidance on the structural components and production of fusion proteins. The '968 patent 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.” *Id.* at 35:31-50. Accordingly, the specification

provides detailed guidance and a roadmap to guide a POSITA to the structural components of the '968 patent's claimed fusion proteins and the production of such fusion proteins. EX2040, Davis Decl. ¶¶ 100, 117-118.

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, 67, 70 (citing *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. As noted above, Dr. Hale concedes this fact. EX1003, Hale Decl. ¶ 62; EX2042, Hale Dep. Tr. at 50:2-20. Thus, 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's three “misleading disclosure” contentions likewise fail. First, Petitioner and Dr. Hale contend that the specification's statement that a hybridoma can produce the polypeptides corresponding to SEQ ID NOS: 1-69 would mislead a POSITA. EX1001 at 35:54-55; EX1003, Hale Decl. ¶¶ 157-158; Pet. at 67. A

POSITA would understand the hybridoma reference as identifying an antibody-producing cell context and would not read that sentence in isolation. The specification separately provides an express recombinant-DNA production instruction directing that a targeting moiety, including an antibody, can be coupled to an immunomodulatory moiety and that fusion-protein coding sequences can be linked at the nucleic-acid level and expressed in a host cell. EX1001 at 43:40-52. Read together, the hybridoma reference identifies a cell type capable of producing the individual antibody chains while the recombinant-DNA instruction provides the technically applicable route for constructing and expressing the fusion proteins. The specification does not present hybridoma production as the exclusive method, and a POSITA with the qualifications Petitioner proposes would not be misled. EX2040, Davis Decl. ¶¶ 146-148; EX1003, Hale Decl. ¶ 111.

Second, Petitioner contends that the reference to solid-phase Merrifield-type synthesis is misleading. EX1003, Hale Decl. ¶ 159. The claimed constructs are multi-domain proteins requiring post-translational modification, disulfide-bond formation, and correct folding—processes solid-phase chemical synthesis does not provide. A POSITA would have recognized the recombinant-DNA instruction at column 43, lines 40-52 as the technically applicable route and would not attempt solid-phase synthesis as the primary production method for a multi-domain antibody-fusion protein. Even if the word “preferred” was overbroad in that passage,

it would not erase the separate, technically appropriate recombinant-DNA instruction. EX2040, Davis Decl. ¶¶ 149-151.

Third, Petitioner notes that U.S. Patent No. 5,736,167, cited in the specification among examples of antibodies at EX1001 at 30:10-12, is titled “Mold Device for Making Safety Shoe.” Pet. at 68. That is an evident clerical error in a prosecution-era citation list. A POSITA would recognize it as such and plainly would not look to the reference about safety shoes for guidance on making antibody fusion proteins; the error is immaterial to how a POSITA would practice the claimed invention. EX2040, Davis Decl. ¶¶ 152-154. The common thread in Petitioner's misleading-disclosure theory is an assumption that a POSITA could not distinguish applicable guidance from inapplicable alternatives—an assumption inconsistent with Petitioner's definition of a POSITA holding a Ph.D. or equivalent experience in the relevant disciplines. *Id.* ¶ 118; EX1003, Hale Decl. ¶ 111.

Petitioner's characterization of Example 1 is also incomplete. Pet. at 18-19, 63. Example 1 is a working example of linker-mediated fusion of the claimed TGF β RII immunomodulatory moiety to an immunoglobulin domain with retained TGF- β -antagonist function, demonstrating that the immunomodulatory domain can be incorporated into a stable fusion format and retain its biological activity. EX1001 at 40:41-41:7; EX2040, Davis Decl. ¶¶ 120-121, 155-156.

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 40:41-41:7.

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 64) and “does not include an antibody targeting moiety as required by claim 1.” *Id.* But although TGF β RII:Fc is not itself an EGFR-targeted molecule, it is probative under *Wands*: it demonstrates that the TGF β RII extracellular domain can be expressed as part of an immunoglobulin-fusion construct and retain TGF- β binding function. EX1001 at 40:41-41:7. The remaining EGFR-targeting component is supplied by the anti-EGFR variable-region sequences disclosed in Figure 3, which are derived from the well-characterized cetuximab variable regions. EX2040, Davis Decl. ¶¶ 43, 104-105.

Second, the specification expressly identifies the methods for producing the claimed fusion proteins. As discussed above, the specification expressly identifies

routine recombinant-DNA methods for producing the claimed fusion proteins. 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. As discussed above, Dr. Hale concedes that the manufacture of conventional recombinant IgG antibodies was, by 2010, a comparatively predictable and routine process. EX1003, Hale Decl. ¶ 62. 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.” *Id.* ¶ 58.

The disclosure in the '968 patent—specifically, Example 1's working example of linker-mediated fusion of the TGFβRII immunomodulatory moiety to an immunoglobulin domain with retained TGF-β-antagonist function—combined with general knowledge in the art provides guidance for a POSITA to produce the claimed fusion proteins. Because TGFβRII is the immunomodulatory moiety recited in both claims 1 and 9, a POSITA who has seen that domain fold and function in one

immunoglobulin-fusion context would understand the remaining work—*i.e.*, substituting the anti-EGFR antibody or antibody-fragment targeting moiety using the specification's sequence disclosures and recombinant methods—to involve components and methods established in the field by 2010, and would not require a separate working example for every sequence-defined embodiment. EX1001 at 40:41-41:7; EX2040, Davis Decl. ¶¶ 119-120, 154-155. The example therefore demonstrates that producing a fusion protein is not inherently unpredictable.

d. Petitioner fails to establish that the unpredictability and lack of guidance for identifying whether the claimed fusion proteins specifically bind to EGFR (*Wands* Factors 2-7) weigh 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” (*id.* 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’” (*id.* at 69).

The claimed targeting moiety, *i.e.*, antigen-binding portion of the fusion protein, is derived from a well-known, FDA-approved anti-EGFR antibody, cetuximab (Erbix®)—one of several clinically validated anti-EGFR antibodies

identified in the specification (including panitumumab, nimotuzumab, zalutumumab, and necitumumab). EX1001 at 29:39-43. 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 have better binding affinity and produced greater tumor effects compared to the murine antibody. *Id.* 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 chimeric 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. EX2040, Davis Decl. ¶¶ 43, 103.

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). EX1001 at 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. Because the antibody fragment of the claimed fusion proteins comprises the variable heavy and variable light chains, 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.

As discussed above, Petitioner's own expert acknowledges that cetuximab's EGFR-binding properties were extensively documented in the art well before 2010. EX1003, Hale Decl. ¶ 56.

Therefore, the disclosure in the '968 patent (*i.e.*, the cetuximab-derived 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) provides guidance and predictability for a POSITA to determine whether a fusion protein containing the cetuximab-derived antigen-binding regions specifically binds EGFR. EX2040, Davis Decl. ¶¶ 101-104. Because antigen-binding specificity is determined by the variable regions of an antibody—not the constant regions—a POSITA would expect that a fusion protein retaining the cetuximab-derived variable heavy and variable light chain sequences would retain EGFR binding, regardless of

the constant region format. *Id.* Cetuximab's 2004 FDA approval and established EGFR binding meant that standard cell-based receptor-binding assays were available by 2010, so confirming retained EGFR binding required established assay formats rather than new assay development. *Id.*; EX1003, Hale Decl. ¶¶ 55-57. 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—and routine confirmation of binding would not constitute undue experimentation.

e. 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 [making] or testing any of the claimed molecules, the inherent uncertainty in the art for the nature of th[e] 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 further argues that undue experimentation would be required to practice the full scope of the claims, applying the *Wands* factors discussed above. *Id.* at 55.

These arguments fail for the reasons set forth above. As discussed above, claim 1 encompasses approximately 56 fusion proteins at most, and claim 9 encompasses only 2 fusion proteins when the claim limitations are properly applied.

As claim 9 is narrower in scope than claim 1, it presents a particularly limited design and testing task. This is an entirely reasonable number of fusion proteins for a POSITA to design, produce, and test. EX2040, Davis Decl. ¶¶ 86-89, 93-94, 106-107, 115(c)-(d), 116.

Dr. Hale's hypothetical nine-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, Hale Decl. ¶ 172. 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." *Id.* ¶ 173.⁸ But the specification is not devoid of guidance. It provides the complete amino acid sequences of the claimed components, with the variable heavy and light regions underlined and emphasized (EX1001 at Figure 3), the TGFβRII:Fc working example accurately described above, and the identification of recombinant-DNA methods for production. *Id.* at

⁸ Dr. Hale confirmed in his deposition that he has never attempted to carry out his nine-step plan for any molecule within the scope of claims 1 or 9, and that he is not aware of any person of ordinary skill who has attempted it and either succeeded or failed. EX2042, Hale Dep. Tr. at 150:3-13.

40:41-41:7, 43:40-52; EX2040, Davis Decl. ¶¶ 95-97, 119-120, 154-155. In addition, each step is a conventional part of making and using a recombinant antibody or fusion protein, and the number of theoretical arrangements is not the number of independent experiments a POSITA would need to perform. EX2040, Davis Decl. ¶¶ 34, 37, 58. Simply put, Dr. Hale identifies no “undue” experimentation, as Dr. Davis explains. *Id.* ¶¶ 95-97.

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, Hale Decl. ¶ 178. He goes on to state that, by 2010, “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.” *Id.* ¶ 59. 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.” *Id.* 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.” *Id.* ¶ 60. The state of the art was therefore sufficiently mature and predictable by 2010 to support sequence-defined antibody-protein and Fc-fusion engineering. EX2040, Davis Decl. ¶¶ 98-100, 123-127.

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 “the 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, Hale Decl. ¶¶ 61, 64; EX2040, Davis Decl. ¶¶ 100, 117-118. The specification’s (GGGGS)_n disclosure therefore supplies a standard tool, and Dr. Hale’s observation that A-linker-B may function differently from B-linker-A describes a limited orientation question resolved by screening defined candidates, not an open-ended search.

Dr. Hale's personal experience also does not establish that these claims were unpredictable. *See* EX1003, Hale Decl. ¶¶ 65-67, 180-181. He points, for example, to his withdrawn patent application concerning particles comprising fusion proteins but fails to disclose the sequences, domain structures, or expression systems used. *Id.* Claims 1 and 9 by contrast specify well-characterized, sequence-defined components. Dr. Hale's struggles with particular molecule orientations likewise have nothing to do with whether a POSITA could construct the molecules claimed here, which are well-defined by the specification and the claims themselves. EX2040, Davis Decl. ¶¶ 131-134.

A POSITA armed with the '968 patent specification's disclosures and the knowledge of the art would not face undue experimentation in making and using the approximately 56 possible arrangements that form a ceiling for claim 1⁹ or the approximately 2 candidate architectures encompassed by claim 9. *Id.* ¶¶ 124-128, 115-116, 140-141. Considering all eight *Wands* factors together, the claims identify specific sequences and, for claim 9, a precise architecture; the specification supplies Figure 3's sequence and structural signposts, linker guidance, the light-chain fusion

⁹ Or, applying the practical subset of five representative linkers and two available chains that provides 20 fusion-protein combinations that a POSITA would actually design and test. EX2040, Davis Decl. ¶¶ 88-91, 94.

orientation passage, recombinant-DNA production guidance, and a working immunoglobulin-fusion example demonstrating retained TGF β RII function. All eight factors therefore support enablement of claims 1 and 9. *Id.* ¶ 145.

For all the foregoing reasons, Petitioner has failed to establish that claims 1 and 9 of the '968 patent are unpatentable for lack of enablement, and Ground 2 should be denied.

C. Grounds 3-6: These Grounds of alleged unpatentability are moot.

Petitioner argues that claims 2-8 are invalid for improper-dependency and indefiniteness. As noted above, Patent Owner's Motion to Amend seeks cancelation of claims 2-8 to simplify and streamline these proceedings. Grounds 3-6 thus are moot and the Board need not address them.

V. CONCLUSION

Petitioner has not proven, by a preponderance of the evidence, that claims 1 and 9 of the '968 patent are unpatentable. The Board should confirm the patentability of those claims and enter a final written decision in Patent Owner's favor.

PGR2026-00025
Patent Owner's Response

Dated: October 6, 2026

Respectfully submitted,

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**CERTIFICATE OF COMPLIANCE
WITH TYPE-VOLUME LIMITATION**

Pursuant to 37 C.F.R. § 42.24 *et seq.*, the undersigned certifies that this Response complies with the 18,700-word type-volume limitation. The Response contains 16,182 words, excluding the parts of the Response exempted from the type-volume limitation.

Dated: October 6, 2026

DLA Piper (US) LLP

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CERTIFICATE OF SERVICE

The undersigned certifies that the foregoing PATENT OWNER'S RESPONSE TO PETITION FOR POST-GRANT REVIEW OF U.S. PATENT 12,295,968 and accompanying Exhibits 2036-2051 were served on Petitioner's lead and backup counsel in their entirety by electronic service at the following email addresses provided below:

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