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Paper 57
Date: January 16, 2024

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

DAIICHI SANKYO, INC. and
ASTRAZENECA PHARMACEUTICALS, LP,
Petitioner,

v.

SEAGEN INC.,
Patent Owner

PGR2021-00030
Patent 10,808,039 B2

Before JEFFREY N. FREDMAN, SHERIDAN K. SNEDDEN, and CHRISTOPHER M. KAISER, *Administrative Patent Judges.*

FREDMAN, *Administrative Patent Judge* FREDMAN.

JUDGMENT
Final Written Decision
Determining all challenged claims unpatentable
35 U.S.C. § 328(a)

I. INTRODUCTION

A. Background and Summary

Daiichi Sankyo, Inc. and AstraZeneca Pharmaceuticals, LP (collectively, "Petitioner") filed a Petition requesting a post-grant review of claims 1–5, 9, and 10 of U.S. Patent No. 10,808,039 B2 (Ex. 1001, "the '039 patent"). Paper 1 ("Pet."). Seagen Inc. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 7 ("Prelim. Resp."). Petitioner filed a Reply to Patent Owner's Preliminary Response. Paper 8 ("First Reply"). Patent Owner filed a Sur-reply to Petitioner's Reply. Paper 9 ("First Sur-reply").

Initially, we exercised our discretion to deny institution under 35 U.S.C. § 324(a) in view of the scheduled trial date of a parallel district court proceeding being nearly four months before our projected statutory deadline for issuing a final written decision, and other Fintiv[1] factors. Paper 11 ("First Denial Decision" or "First Denial Dec."). Petitioner filed a request for rehearing. Paper 12 ("First Reh'g Req." or "First Rehearing Request"). Concurrently therewith, Petitioner requested that the Board's Precedential Opinion Panel ("POP") reconsider the First Denial Decision. Paper 13; Ex. 3001 ("First POP Request"). POP declined to review the issue raised in the First POP Request. Paper 16. Upon reconsideration, we granted the First Request for Rehearing and instituted post-grant review. Paper 17 ("Institution Decision" or "Inst. Dec.").

Thereafter, Patent Owner filed a request for rehearing in light of changed circumstances in the parallel district court proceeding and additionally in the related proceeding PGR2021-00042. Paper 20 ("Second

[1] *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020) (precedential) ("*Fintiv* Order").

Reh'g Req." or "Second Rehearing Request"). Petitioner filed a Response (Paper 24) and Patent Owner filed a Reply (Paper 26). Patent Owner also filed a Patent Owner Response. Paper 29 ("Resp."). In light of the changed circumstances in the parallel district court proceeding, we granted the Second Rehearing Request and exercised our discretion to deny institution. Paper 31 ("Second Denial Decision" or "Second Denial Dec."). Subsequently, Petitioner filed a request for rehearing, arguing that our Second Denial Decision did not accord with the guidance provided by the Director in a Guidance Memorandum[2] regarding discretionary denials in light of parallel district court proceedings. Paper 32 ("Third Reh'g Req." or "Third Rehearing Request"). As with the First Rehearing Request, the Third Rehearing Request was accompanied by a request that POP conduct the requested rehearing. Paper 33; Ex. 3005 ("Second POP Request"). On February 7, 2023, POP denied the request for POP review but provided instructions for us to follow during our consideration of the Third Rehearing Request. Paper 35. In response, we instituted trial. Paper 36.

Following institution (Paper 36), Petitioner filed a Reply (Paper 39, "Second Reply") and Patent Owner filed a Sur-reply (Paper 47, "Second Sur-reply"). Both Petitioner and Patent Owner filed various Objections to evidence (Papers 11, 12, 25, 35). An oral hearing was held on August 24, 2023, and a transcript has been entered into the record (Paper 56, "Tr.").

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[2] *Interim Procedure for Discretionary Denials in AIA Post-Grant Proceedings with Parallel District Court Litigation* (June 21, 2022), available at https://www.uspto.gov/sites/default/files/documents/interim_proc_discretionary_denials_aia_parallel_district_court_litigation_memo_20220621_.pdf ("Guidance Memo").

We have jurisdiction under 35 U.S.C. § 6. This Final Written Decision is issued pursuant to 35 U.S.C. § 328(a). Based on the record before us, we conclude that Petitioner has demonstrated by a preponderance of the evidence that claims 1–5, 9, and 10 of the '039 patent are unpatentable.

B. Real Parties in Interest

Petitioner states that the real parties-in-interest for Petitioner are Daiichi Sankyo, Inc. and AstraZeneca Pharmaceuticals, LP, as well as Daiichi Sankyo Company, Limited and AstraZeneca UK Limited. Pet. 82.

Patent Owner states that the real party-in-interest is Seagen Inc. Paper 5, 1.

C. Related Proceedings

Petitioner indicates that the '039 patent is relevant in the following co-pending matters: *Daiichi Sankyo Co., Ltd. v. Seattle Genetics, Inc.*, No. 1:19-cv-02087- LPS (D. Del.) ("the Delaware-2087 Litigation"); *Seattle Genetics, Inc. v. Daiichi Sankyo Co., Ltd.*, American Arbitration Association Case No. 01-19-0004-0115 (Brown, Arb.) ("the Arbitration"); *Seagen Inc. v. Daiichi Sankyo Co., Ltd.*, No. 2:20-cv-00337 (E.D. Tex.) ("the Texas Litigation"); *Daiichi Sankyo, Inc. et al. v. Seattle Genetics, Inc.*, No. 1:20-cv-01524- LPS (D. Del.) ("the Delaware-1524 Litigation"). Pet. 83.

D. The '039 Patent (Ex. 1001)

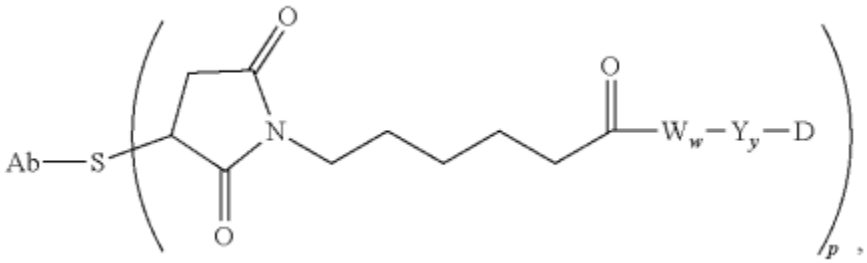
The '039 patent discloses antibody-drug conjugates ("ADCs"). Ex. 1001, 1:58–63. "Most agents currently administered to a patient parenterally are not targeted, resulting in systemic delivery of the agent to cells and tissues of the body where it is unnecessary, and often undesirable. This may result in adverse drug side effects, and often limits the dose of a drug." *Id.* at 2:17–21. "Accordingly, a major goal has been to develop methods for

specifically targeting agents to cells and tissues. The benefits of such treatment include avoiding the general physiological effects of inappropriate delivery of such agents to other cells and tissues." *Id*. at 2:31–35.

> The use of antibody-drug conjugates for the local delivery of cytotoxic or cytostatic agents, e.g., drugs to kill or inhibit tumor cells in the treatment of cancer . . . theoretically allows targeted delivery of the drug moiety to tumors, and intracellular accumulation therein, while systemic administration of these unconjugated drug agents may result in unacceptable levels of toxicity to normal cells as well as the tumor cells sought to be eliminated.

Id. at 2:43–53 (citations omitted).

Disclosed embodiments of the ADCs include the following:



Id. at 331:36–45 (claim 1). "The drug moiety (D) of the [ADCs] are of the dolastatin/auristatin type[,] which have been shown to interfere with microtubule dynamics, GTP hydrolysis, and nuclear and cellular division." *Id*. at 71:21–25 (citations omitted).

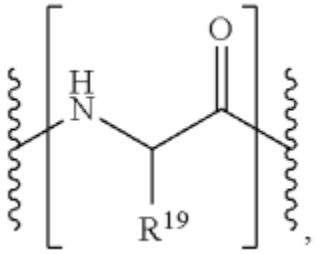
"Ab is an antibody that binds one of the tumor-associated antigens." *Id*. at 111:33–37.

S is sulfur. *Id*. at 331:36–45.

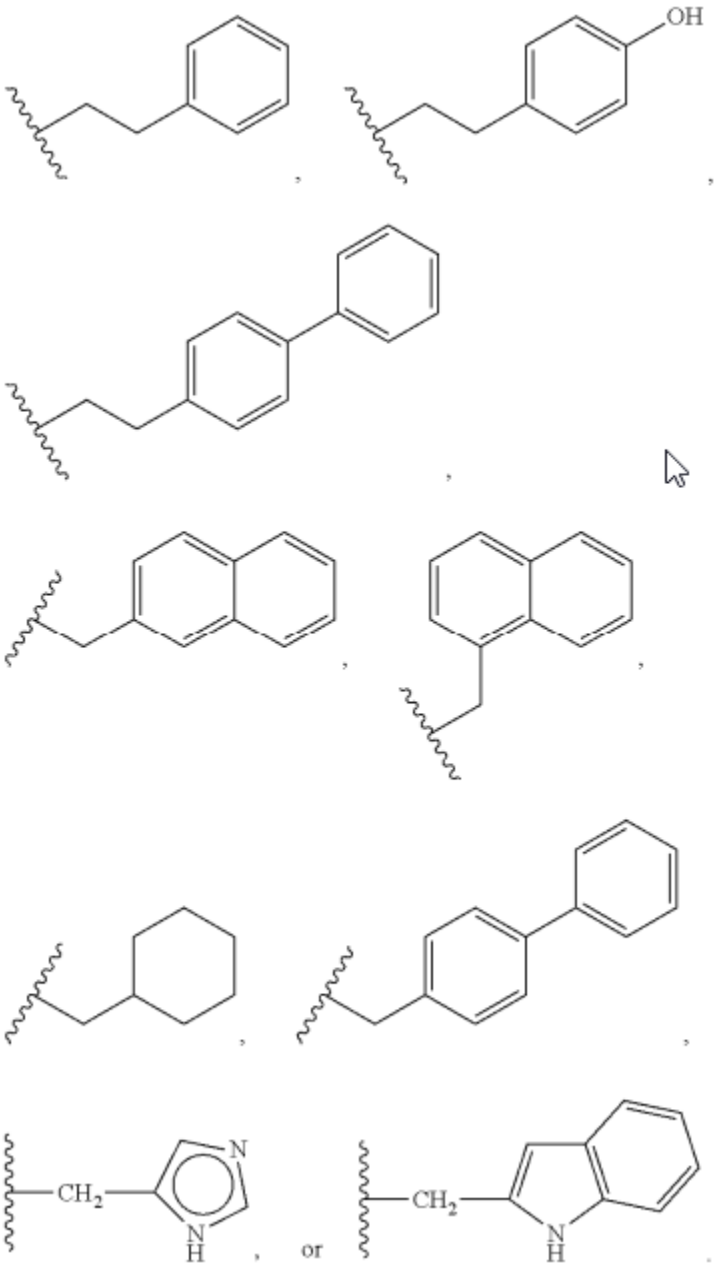
The spacer unit, Y or y, "when present, links an Amino Acid unit [(—W—)] to the Drug moiety when an Amino Acid unit is present." *Id*. at 68:14–16. In some embodiments, "y is 0, 1 or 2." *Id*. at 6:47. The average

number of drugs per antibody in a molecule of a particular formula, p, can range from 1 to 20 drugs per antibody. *Id*. at 61:44–46.

The Amino Acid unit (—W—) can be a "dipeptide, tripeptide, tetrapeptide, pentapeptide, hexapeptide, heptapeptide, octapeptide, nonapeptide, decapeptide, undecapeptide or dodecapeptide unit." *Id*. at 65:49–53. Each —W— unit may have the following formula:



wherein the R^{19} groups on the peptide chain can be selected from, but are not limited to, the groups of "hydrogen, methyl, isopropyl, isobutyl, sec-butyl, benzyl, p-hydroxybenzyl, —CH_2OH, —$CH(OH)CH_3$, —$CH_2CH_2SCH_3$, —CH_2CONH_2, —CH_2COOH, —$CH_2CH_2CONH_2$, —CH_2CH_2COOH, —$(CH_2)_3NHC(=NH)NH_2$, —$(CH_2)_3NH_2$, —$(CH_2)_3NHCOCH_3$, —$(CH_2)_3NHCHO$, —$(CH_2)_4NHC(=NH)NH_2$, —$(CH_2)_4NH_2$, —$(CH_2)_4NHCOCH_3$, —$(CH_2)_4NHCHO$, —$(CH_2)_3NHCONH_2$, —$(CH_2)_4NHCONH_2$, —$CH_2CH_2CH(OH)CH_2NH_2$, 2-pyridylmethyl-, 3-pyridylmethyl-, 4-pyridylmethyl-, phenyl, cyclohexyl,



Id. at 65:65–66:43.

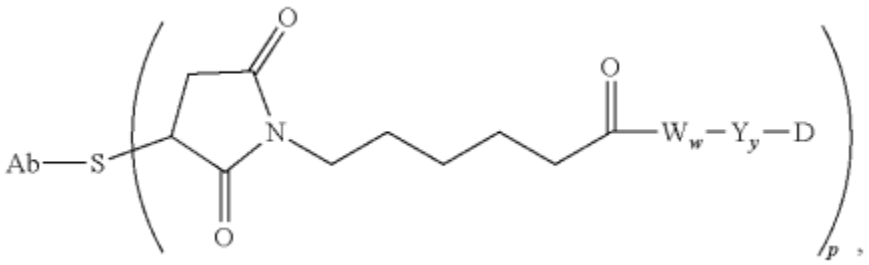
In some embodiments of the invention, "a substantial amount of the drug moiety is not cleaved from the antibody until the antibody-drug conjugate compound enters a cell with a cell-surface receptor specific for the antibody of the antibody-drug conjugate, and the drug moiety is cleaved from the antibody when the antibody-drug conjugate does enter the cell." *Id*.

at 18:56–61. In other aspects of the invention, "the bioavailability of the [ADC] or an intracellular metabolite . . . is improved when compared to a drug compound comprising the drug moiety of the [ADC], or when compared to an analog of the compound not having the drug moiety." *Id.* at 18:62–67.

E. Illustrative Claims

The challenged claims are claims 1–5, 9, and 10 of the '039 patent, and claim 1 is the sole independent claim. Claim 1 is illustrative of the challenged claims and recites:

1. An antibody-drug conjugate having the formula:

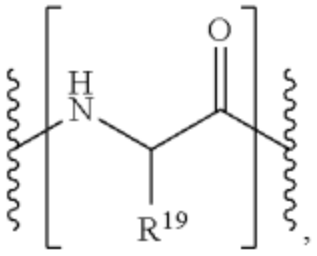


or a pharmaceutically acceptable salt thereof, wherein:

Ab is an antibody,

S is sulfur,

each —W_w— unit is a tetrapeptide; wherein each —W— unit is independently an Amino Acid unit having the formula denoted below in the square bracket:



wherein R^{19} is hydrogen or benzyl,

Y is a Spacer unit,

y is 0, 1 or 2,

D is a drug moiety, and

p ranges from 1 to about 20,

wherein the S is a sulfur atom on a cysteine residue of the antibody, and

wherein the drug moiety is intracellularly cleaved in a patient from the antibody of the antibody-drug conjugate or an intracellular metabolite of the antibody-drug conjugate.

Ex. 1001, 331:35–66; 332:35–40.

F. The Instituted Grounds of Unpatentability

We instituted trial based on the challenge to the patentability of the '039 patent presented in the Petition. Pet. 5.

References	Basis	Claims Challenged	Reference(s)
Written Description	§ 112(a)	1–5, 9, 10	
Enablement	§ 112(a)	1–5, 9, 10	
Subject Matter of the Invention	§ 112(b)	1–5, 9, 10	
Anticipation	§ 102(a)(1)	1–5, 9, 10	Ogitani[3]

Petitioner relies on the Declaration of John M. Lambert, Ph.D. *See* Ex. 1002. Patent Owner relies on the Declaration of Carolyn R. Bertozzi,

[3] Ogitani et al., *Bystander killing effect of DS-8201a, a novel anti-human epidermal growth factor receptor 2 antibody–drug conjugate, in tumors with human epidermal growth factor receptor 2 heterogeneity*, 107 Cancer Science 1039–46 (July 2016) (Exhibit 1009).

Ph.D. Ex. 2058. Based on the statements of qualifications and curricula vitae, we find both Dr. Lambert and Dr. Bertozzi amply qualified to provide technical opinions from the perspective of a person of ordinary skill in the art in this proceeding. *See* Ex. 1002 ¶¶ 9–19; Ex. 2058 ¶¶ 1, 9–12.

II. LEVEL OF ORDINARY SKILL IN THE ART

Petitioner contends that:

> the POSA in the field of the '039 Patent would have had either (1) a Ph.D. in biochemistry or a similar field, or (2) a master's degree in biochemistry or a similar field with at least two to three years of experience with ADC design. (Ex. 1002 ¶ 20.) More education can supplement practical experience, and vice-versa. (*Id.*) This high level of skill in the ADC field is applicable as of the filing of the provisional applications through to July 2019, the '039 Patent's effective filing date.

Pet. 19; *cf.* Ex. 1002 ¶ 20.

Patent Owner contends

> a POSA would possess a Ph.D. in the field of chemistry, biology, molecular/cell biology, biochemistry, or a similar field, and two years of post-doctoral work in immunoconjugates such as ADCs or a related field, given how highly technical the technology at issue in this dispute is. More professional experience could substitute for more formal education.

Resp. 4 (citing Ex. 2058 ¶ 16).

We do not discern a substantive difference between the parties' respective definitions for the level of ordinary skill in the art. While there seems to be a slight difference in whether the ordinary artisan has ADC design experience obtained after a master's degree or postdoctoral, neither party provides clear basis to explain how this will impact the analysis. Accordingly, we find the parties' respective definitions to be equivalent and consistent with the level of ordinary skill in the art as reflected by the prior

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

III. CLAIM CONSTRUCTION

We interpret claim terms using "the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b)." 37 C.F.R. § 42.100(b) (2021). Thus, claim terms "are generally given their ordinary and customary meaning" as understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc).

Here, we construe only those claim terms that require analysis to determine the patentability of the challenged claims. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))); *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'").

Petitioner asserts that the term "drug moiety" requires construction. *See* Pet. 17–18. Petitioner appears to urge based on related Texas Litigation that "[a]n alternative interpretation of 'drug moiety' would limit that term, on the basis of definitional language in the specification, to dolastatin/auristatin derivatives. This Petition is based on the claim

construction urged by PO in the Texas Litigation." *Id.* at 17, footnote 9 (*citing* Ex. 1006). Ex. 1006, which is the complaint filed by Patent Owner in the Texas Litigation, does not include limiting statements regarding the "drug moiety," only stating an exemplary situation where "[i]n DS-8201, the drug that is conjugated to the antibody with the linker is the camptothecin derivative DXd, which acts as a topoisomerase inhibitor." Ex. 1006, 9.

Patent Owner asserts, "[a]s Dr. Bertozzi explains, the term 'drug moiety' is readily understood by the POSA and does not need construction.." PO Resp. 4–5 (citing Ex. 2058 ¶ 19). Patent Owner asserts that "during claim construction in the Texas Litigation, Seagen argued that no construction was needed for the 'drug moiety' term." *Id.* at 5 (citing Ex. 2052 at 9). Patent Owner asserts that "the Texas court rejected Petitioner's narrow reading of the 'drug moiety' term in light of the broad disclosures in the '039 patent and agreed with Seagen's position." *Id.* (citing Ex. 2052 at 14). Patent Owner asserts that "the Board adopt the same approach here and simply apply the plain meaning of the term." *Id.*

We find that the evidence on record better supports Patent Owner's understanding that the term "drug moiety" may be understood using its plain meaning and requires no further construction. We begin with the intrinsic evidence in the '039 patent, which first uses the phrase "drug moiety" to generally refer to "cytotoxic or cytostatic agents" in the context of antibody conjugates that allow "targeted delivery of the drug moiety to tumors." Ex. 1001, 2:44–49. When specifically discussing the term "drug moiety" in the context of the conjugate formula, the '039 patent generally explains

> the bioavailability of the antibody-drug conjugate compound or an intracellular metabolite of the compound in a mammal is improved when compared to a drug compound comprising the

> drug moiety of the antibody-drug conjugate compound, or when compared to an analog of the compound not having the drug moiety.

Ex. 1001, 18:62–67. And while the '039 patent provides an exemplary synthesis of peptide drugs, the '039 patent includes no statement excluding the "drug moiety" from encompassing the compounds recited in the Specification. *See generally* Ex. 1001, 31:39–34:49, 143:18–147:65.

Dr. Bertozzi states, after a review of the '039 patent, that "based on the plain and ordinary meaning, a POSA would understand the 'drug moiety' term to refer to any of these drugs from the various classes as useful for the claimed ADC formula and not be limited to any particular drug." Ex. 2058 ¶ 19. Dr. Lambert does not dispute this interpretation, but rather states:

> [Patent Owner] has asserted that the claim term "drug moiety" is not limited to those of the dolastatin/auristatin type, and encompasses others as well, like the Enhertu® camptothecin derivative. I have been asked to apply this understanding of the term "drug moiety" in my analysis, but I have not been asked to form, and have not formed, an opinion as to whether it is correct in light of governing legal principles.

Ex. 1002 ¶ 23.[4]

Accordingly, we construe "drug moiety" to refer to any drugs useful for the recited ADC formula and not limited to any particular drug.

[4] We note that in the Oral Hearing, Petitioner stated: "We're not limiting, we're not limiting the claim. The claim itself is broad. The claim as written is to encompass all drug moieties. There's no dispute about that." Paper 56, 7:12–14.

IV. PRIORITY

A. Principles of Law

Under 35 U.S.C. § 120, "in a chain of continuing applications, a claim in a later application receives the benefit of the filing date of an earlier application so long as the disclosure in the earlier application meets the requirements of 35 U.S.C. § 112, ¶ 1, including the written description requirement, with respect to that claim." *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1326 (Fed. Cir. 2008).

The test for written description is "whether the disclosure of the application . . . reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). "Based on that inquiry, the specification must describe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed." *Id.* "For example, a propyl or butyl compound may be made by a process analogous to a disclosed methyl compound, but, in the absence of a statement that the inventor invented propyl and butyl compounds, such compounds have not been described and are not entitled to a patent." *Id.* at 1352.

"[W]hile the description requirement does not demand any particular form of disclosure, or that the specification recite the claimed invention *in haec verba*, a description that merely renders the invention obvious does not satisfy the requirement." *Ariad*, 598 F.3d at 1352 (citations omitted). "[T]he test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Id.* at 1351.

B. Priority

1. *Petitioner's Position*

Petitioner asserts claim 1 of the '039 patent "requires that 'W_w' is a 'tetrapeptide' in which each of the four amino acids has (i) a backbone that is not N-methylated and (ii) a side chain that is either 'hydrogen or benzyl,' i.e., the amino acids must be glycine or phenylalanine." Pet. 22. Petitioner asserts "[b]ecause phenylalanine has two possible stereoisomers and glycine has one, the genus of tetrapeptides recited in Claims 1–5, 9, and 10 encompasses 34 (i.e., 81) different species. (*See, e.g.*, Ex. 1002 ¶¶ 81–83, 83 n.13.) PO's priority applications identify none of them." *Id.* at 22–23 (footnote omitted).[5]

Petitioner asserts

> [Patent Owner]'s priority applications identify no linkers having amino acid units—of any length—that are entirely composed of glycine and/or phenylalanine residues. Instead, they prophetically disclose linkers having amino acid units that are a "dipeptide, tripeptide, tetrapeptide, pentapeptide, hexapeptide, heptapeptide, octapeptide, nonapeptide, decapeptide, undecapeptide or dodecapeptide unit." (*See, e.g.,* Ex. 1010 at 23; Ex. 1011 at 23; Ex. 1012 at 73; Ex. 1013 at 67; Ex. 1014 at 85; Ex. 1015 at 87; Ex. 1016 at 87; Ex. 1017 at 86; Ex. 1018 at 86; Ex. 1019 at 86; Ex. 1002 ¶ 84.) They further disclose that each residue within an amino acid unit "independently" has a backbone that is, optionally, N-methylated.

Pet. 23.

Petitioner asserts that based on the priority applications' disclosures, they reference "83^4 (i.e., over 47 million) different species of tetrapeptide

[5] Petitioner refers to the "10 patent applications to which the '039 Patent attempts to claim priority" (Exs. 1010-1019) as "the priority applications." Pet. 48. We do likewise.

amino acid units having the (non-N-methylated) backbone recited in Claims 1–5, 9, and 10. (Ex. 1002 ¶ 83.)" Pet. 24. Petitioner asserts "the priority applications actually identify just two of those—and neither meets the side-chain limitations recited in Claims 1–5, 9, and 10 (i.e., that each R group is independently hydrogen or benzyl)." *Id.*

Petitioner asserts that "the only blaze marks to any subgenus in the application point *away* from the later-claimed genus." Pet. 26. Petitioner asserts the priority applications "*do* disclose a particular subgenus, just not the claimed subgenus. Formula IX encompasses two tetrapeptide sequences, but neither falls within the scope of tetrapeptides recited in Claims 1–5, 9, and 10. Therefore the priority applications do not '"reasonably lead" those skilled in the art' to the claimed genus." *Id*. at 27.

Petitioner asserts that the "first and only disclosure of the claimed subgenus of gly/phe-only tetrapeptides appears in the new claims submitted with the July 10, 2019, application (Ex. 1020 at 397–98[])." Pet. 27–28. Petitioner asserts these "claims introduced new matter that appears nowhere in the specification, in a transparent attempt to cover a competitor's invention—precisely the type of overreach that the written description requirement proscribes." *Id*. at 28 (citing *Ariad*, 598 F.3d at 1353–54).

2. *Patent Owner's Position*

Patent Owner asserts

> The '039 patent discloses detailed information about the Amino Acid unit. In particular, it discloses that the Amino Acid unit "is a dipeptide, tripeptide, tetrapeptide, pentapeptide . . . or dodecapeptide unit," and further specifies that in one embodiment, the Amino Acid unit "is a dipeptide, tripeptide, tetrapeptide or pentapeptide." (Ex. 1001 at 79; Ex. 1010 at 26, 28; Ex. 1014 at 98, 100 (emphasis omitted).)

Resp. 61–62. Patent Owner asserts the "'039 patent defines the side chain R^{19} as selected from a group consisting of 39 side chains, each of which is listed in the patent by precise structure. (Ex. 1001 at 65:45-66:43; Ex. 2058 ¶¶ 222.)" *Id*. at 62.

> Patent Owner asserts the tetrapeptide formula IX
>
> provides a total of four types of amino acids for use in the tetrapetides: glycine (H), phenylalanine (benzyl), leucine (isobutyl), and alanine (methyl). (*Id*.) The formula then depicts two tetrapeptides, made up of two sets of these four amino acids. The first exemplary tetrapeptide consists of three types of amino acids: glycine, phenylalanine, and leucine. The second exemplary tetrapeptide consists of just two types of amino acids: alanine and leucine.

Resp. 63. Patent Owner asserts that

> As Dr. Bertozzi explains, a POSA would not have blindly tested all of the millions of potential tetrapeptides. Rather . . . the exemplary tetrapeptides would have narrowed the skilled artisan's choices to two amino acids and their respective isomers: glycine or phenylalanine (with the understanding that phenylalanine has two stereoisomers). (Ex. 2058 ¶¶ 225-26.)

Id. at 64.

Patent Owner analogizes the instant situation to *Novartis Pharms. Corp. v. Plexxikon Inc.*, No. PGR2018-00069, Paper 16 at 14-17 (P.T.A.B. Jan. 16, 2019) and *In re Driscoll*, 562 F.2d 1245, 1249-50 (C.C.P.A. 1977), asserting that like "*Novartis* and *Driscoll*, the R^{19} recited in claim 1 of the '039 patent is selected from a Markush group of a finite number of substituents (39 substituents in the '039 patent as compared to 23 in *Novartis* and 14 in *Driscoll*) in the formula provided in the specification." Resp. 67.

Patent Owner distinguishes Petitioner's caselaw, asserting "the claim at issue in *Ruschig* was directed to a *single compound*, not a genus

encompassing multiple compounds. *Ruschig*, 379 F.2d at 1552, 1556–57 ("Specific claims to single compounds require reasonably specific supporting disclosure."); Resp. 67. Patent Owner asserts that "the claimed compounds are within the disclosed formulas, which explicitly enumerate a tetrapeptide and glycine and phenylalanine as express options." Resp. 69. Patent Owner asserts that this is different than *Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1164 (Fed. Cir. 2019) where "the scope of the claimed genus included compounds with fluorine in the 2'-down position, a possibility not contemplated in the specification, [so] the Federal Circuit found that specification did not describe the full scope of the claim." *Id*. at 68–69.

Patent Owner asserts that the Specification of the '039 patent specifically describes three tetrapeptides "GFLG (glycine-phenylalanine-leucine-glycine) and ALAL (alanine-leucine-alanine-leucine)" as well as "GSVQ (glycine-serine-valine-glutamine)." Resp. 70–71. Patent Owner asserts that these "would have guided a POSA to gly/phe tetrapeptides. (Ex. 2058 ¶¶ 133-37.)" *Id*. at 71. Patent Owner asserts

> A POSA would have considered substituting a phenylalanine at this position for multiple reasons. First, literature on cathepsin activity suggests that it processes substrates with phenylalanine at the P2 position more efficiently than other residues. (Ex. 2058 ¶ 134.) Second, phenylalanine is used at this position in peptides used in assays for cathepsin B. (*Id.*) Third, the tripeptide examples provided in the '039 patent all use phenylalanine in the P2 position, suggesting it could also be used in that location in a tetrapeptide sequence. (Ex. 2058 ¶ 134; Ex. 1001 at 67:18-33.)

Id. at 72.

Patent Owner asserts "of the over 40 scientific articles relied on by Petitioner and its expert, *only four* are dated before the 2004 non-provisional

application." Resp. 75–76. Patent Owner asserts "[b]ecause Petitioner has failed to provide any justification for its reliance on a different date than the claimed priority date, it has failed to meet its burden to show that the '039 patent claims were not adequately described as of the claimed priority date of the patent." *Id*. at 76.

3. *Experts' views of priority for claim 1 in '039 patent to priority documents*

a. Dr. Lambert

Dr. Lambert states that

> the '039 Patent's specification and priority applications mention conjugates having *optional* amino acid units selected from a massive genus having up to twelve amino acid residues. The residues in this massive genus may have either of two potential backbone structures (one of which is N-methylated (Ex. 1001 at 65:55–64 (structure on right))), and 39 potential side chains. Except for glycine, which has no chiral center, all described amino acids have a chiral alpha-carbon; however, three of the described side chains have an additional chiral center, providing them with four stereoisomers. In total, therefore, the '039 Patent provides 83 potential alternatives for each non-N-methylated amino acid residue of its peptides of 1–12 residues in length.

Ex. 1002 ¶ 82. Dr. Lambert explains that the "particular subgenus of tetrapeptides recited in the '039 Patent's claims covers just 81 (i.e., 3^4) species." *Id*. ¶ 83. Dr Lambert further states "the broader genus of amino acid units mentioned in the specification and priority applications, even if limited to tetrapeptides having the backbone structure recited in the '039 Patent's claims, would cover over 47 million (i.e., 83^4) species." *Id.* ¶ 83. Dr. Lambert states the "priority applications disclose that anywhere from zero to 12 amino acids can form the amino acid unit of the claimed ADCs" and that the "unit could be a "dipeptide, tripeptide, tetrapeptide, pentapeptide,

hexapeptide, heptapeptide, octapeptide, nonapeptide, decapeptide, undecapeptide or dodecapeptide unit," i.e., the amino acid unit has between two and twelve amino acids." *Id.* ¶ 84. Dr Lambert states that "with regard to the type of amino acids that can form the amino acid unit, the provisional priority applications disclose a large number of possibilities." *Id.* ¶ 85. Dr. Lambert finds "no 'blaze marks' to the selection of the gly/phe-only tetrapeptide tree present in Claim 1." *Id.* ¶ 84.

Dr. Lambert states he "reviewed the publicly-available sworn testimony of the named inventors of the '039 patent, Drs. Svetlana Doronina, Brian Toki, Toni Kline, and Peter Senter that became available after I prepared my first Declaration." Ex. 1132 ¶ 84. Dr. Lambert stated:

> Dr. Kline noted that blaze marks for a tetrapeptide containing only Gly and Phe were "not called out" and that "[n]othing points you toward [Gly/Phe-only containing tetrapeptides] or away from [Gly/Phe-only containing tetrapeptides]." More specifically, "of the limited examples described in the patent" Dr. Kline was "not aware of" any examples in the patent in which an ADC containing a tetrapeptide linker containing only glycine and phenylalanine was described. Dr. Toki agreed, noting that he did not recall working with tetrapeptides composed of only Gly/Phe residues, and was not aware of any linker disclosed in the patent that contains a tetrapeptide compounds composed only of Gly and Phe residues.

Id. ¶ 85 (footnote omitted) (citing Ex. 1099 81:31–82:21, 83:13–23; Ex 1100 63:25–64:12).

b. Dr. Bertozzi

Dr. Bertozzi states that

> [t]he specification of the '340 application and the '534 provisional application . . . state that the amino acid unit "is a dipeptide, tripeptide, *tetrapeptide*, pentapeptide . . . or dodecapeptide unit," and further states that in one embodiment,

> the amino acid unit "is a dipeptide, tripeptide, *tetrapeptide* or pentapeptide."

Ex. 2058 ¶ 70. Dr. Bertozzi states regarding the amino acid formula that the "applications state that each R^{19} side chain is selected from a group of 39 side chains, including hydrogen and benzyl, which are the side chains claimed in claim 1 of the '039 patent." *Id.* ¶ 71. Dr. Bertozzi states the applications "identify two tetrapeptide units as exemplary peptide units, including one with a glycine-phenylalanine-leucine-glycine sequence." *Id.* Dr. Bertozzi states that "the W_w unit in claim 1 is directed to a tetrapeptide in which each amino acid is either glycine or phenylalanine." *Id.* ¶ 61.

Dr. Bertozzi states that the inventors "sought to test the theory that an amino acid unit in a protease-cleavable linker must be demonstrated to cleave by cathepsin B in order to cleave intracellularly. They found this was not the case." Ex. 2058 ¶ 76. Dr. Bertozzi states:

> The specification of the '039 patent reflects their findings as it recites various examples of di-, tri-, and tetrapeptides, which would have informed the POSA that the inventors reevaluated the premise that tetrapeptides designed for use in prodrugs would not work in ADCs because they cleaved poorly with cathepsin B. They expressly included Gly-Phe-Leu-Gly despite the criticism of that motif by others. The patent's disclosure would have motivated the POSA to reevaluate art that used tetrapeptide motifs such as Gly-Phe-Leu-Gly, including the use of such motifs in prodrugs (which is where Gly- Phe-Leu-Gly first appeared in the literature).

Id. Dr. Bertozzi then discusses other work performed by the inventors not included in the specification or the priority applications, noting that enzymes other than cathepsin B may be involved in the cleavage process. *See Id.* ¶¶ 77–82. Dr. Bertozzi acknowledges that the "'039 patent further exemplifies the inventors' expanded view of what amino acid sequences could be used in

ADCs by including sequences made of different stereochemistry or methylated amino acids." *Id.* ¶ 83.

Dr. Bertozzi states "whether or not Seagen scientists actually made a specific example of a gly/phe tetrapeptide is not a factor in determining whether the '039 patent describes and teaches a POSA that the asserted claims include ADCs with gly/phe tetrapeptides." Ex. 2058 ¶ 131. Dr Bertozzi states that three other tetrapeptide sequences, GFLG, ALAL, and GSVQ described in the '039 patent "would have guided a POSA to gly/phe tetrapeptides. A POSA looking to make ADCs with tetrapeptide linkers would have started with the tetrapeptide sequence examples in the '039 patent, and in particular, the GFLG sequence due to the extensive publication history on that sequence by Kopecek *et al*." Ex. 2058 ¶¶ 132–133 (citing Ex. 2053 at 6:26–33, 12:10–36, 12:64–13:23, 14:21–63, 15:30–57, 16:28–60, 28:12–45, 30:16–45, 31:5–53; Ex. 2054; Ex. 2055; Ex. 2056.)

Dr. Bertozzi states reasons why POSAs (a) would "consider glycine to be a perfectly suitable amino acid at P1," (b) "would have considered substituting a phenylalanine at [the P2] position for multiple reasons," and (c) that the "'039 patent also discloses that in a tripeptide, this position can be occupied by glycine or valine. (Ex. 1001 at 67:29-31.) A POSA could consider using glycine if they wished to have a less hydrophobic linker (as glycine is less hydrophobic than phenylalanine)" and (d) that "[a]t the P4 position, the '039 patent tetrapeptide examples use glycine or alanine, and a POSA would have known that either could be used in the tetrapeptide linker." Ex. 2058 ¶¶ 133–136.

Dr. Bertozzi states "[i]t would have been routine for a POSA to synthesize multiple different peptides and test them for their properties.

There were general protocols that a POSA could follow to obtain different peptide sequences." Ex. 2058 ¶ 138. Dr. Bertozzi states:

> In sum, a POSA also would have known, relying on the disclosure of the '039 patent, that a broad range of amino acid sequences, including tetrapeptides of any motif, could be used in an ADC with a protease-cleavable linker. As I discussed above, Seagen scientists had discovered that many peptide sequences, not just those that are substrates for cathepsin B, would cleave intracellularly.

Id. ¶ 141. Dr. Bertozzi states that

> far from the millions of potential peptide sequences that Dr. Lambert supposes one of ordinary skill in the art would have considered, the examples shown in the '039 patent and the priority non-provisional applications would have narrowed the choices to the claimed amino acids: glycine or phenylalanine (with the understanding that phenylalanine has two stereoisomers). (*Id.* at ¶ 83.)

Id. ¶ 225. Dr. Bertozzi states "[w]hile the provisional applications do not disclose an example tetrapeptide with only glycine or phenylalanine amino acids, the description provides sufficient disclosure as noted above, and one of ordinary skill in the art would have understood the specification to cover gly/phe tetrapeptides." *Id.* ¶ 229.

4. *Analysis*

We note that "[i]t is not sufficient for purposes of the written description requirement of § 112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997).

To prevail in this post-grant review of the challenged claims, Petitioner must prove unpatentability by a preponderance of the evidence.

35 U.S.C. § 326(e); 37 C.F.R. § 42.1(d). The petitioner has the burden from the onset to show with particularity why the challenged claims are unpatentable. *See Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016). This burden of persuasion never shifts to the patent owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review).

We find that Petitioner and Dr. Lambert have provided a preponderance of the evidence to show that the '039 patent should not receive benefit of priority to the earlier filings because the priority applications lack descriptive support for the W_w element as recited in claim 1, the sole independent claim.

But even if we solely rely on Dr. Bertozzi's declaration statements, which Patent Owner submitted as evidence to demonstrate that the earlier filings do provide written description support for the W_w element as recited in claim 1, we also find the preponderance of the evidence shows the '039 patent should not receive benefit of priority to the earlier filings because the Bertozzi Declaration demonstrates the absence of descriptive support for the W_w element as recited in claim 1.

Dr. Bertozzi states that "the W_w unit in claim 1 is directed to a tetrapeptide in which each amino acid is either glycine or phenylalanine." Ex. 2058 ¶ 61. Dr. Bertozzi acknowledges that "the provisional applications do not disclose an example tetrapeptide with only glycine or phenylalanine amino acids." *Id.* ¶ 229.

In her deposition, Dr. Bertozzi answered the question "would you agree with me that that would represent only 81 out of about 47 million species that are identified in the specification?" by stating

> I mean, I understand from my reading of Lambert's declarations that the math kind of works out to be about that, but I'm not doing it myself off -- off the cuff here. GF-only tetrapeptides in which phenylalanines could be either D or L, that is the right number. It's 81. The 47 million, I'll have to take Dr. Lambert and your word for that one.

Ex. 1102, 169:11–23.

We do not find any statement by Dr. Bertozzi that the disclosure in the provisional and earlier Specifications would allow a person of ordinary skill in the art to inherently, necessarily, or immediately envisage a tetrapeptide with only glycine or phenylalanine amino acids. Rather, Dr. Bertozzi uses language suggesting disclosures "would have guided a POSA to gly/phe tetrapeptides" or that "one of ordinary skill in the art would have understood the specification to cover gly/phe tetrapeptides." Ex. 2058 ¶¶ 133, 229. A "mere wish or plan" for obtaining the claimed invention does not satisfy the written description requirement. *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566 (Fed.Cir. 1997). And "a description that merely renders the invention obvious does not satisfy the [written description] requirement." *Ariad*, 598 F.3d at 1352.

Dr. Bertozzi points to a number of different disclosures to support written description in the priority applications even for just the W_w amino acid element, relying on a selection of peptide length, stereochemistry, methylation, and side chain selection for each amino acid of the peptide where "each R^{19} side chain is selected from a group of 39 side chains." Ex. 2058 ¶¶ 70–71, 83. *Novozmyes* found such selection insufficient for descriptive support where the priority application "provides formal textual support for each individual limitation recited in the claims . . . [but] nowhere describes the actual functioning [invention] . . . that those limitations

together define." *Novozymes A/S v. Dupont Nutrition Biosciences APS*, 723 F.3d 1336, 1349 (Fed. Cir. 2013). "Working backward from a knowledge of [the claims], that is by hindsight, [Patent Owner] seeks to derive written description support from an amalgam of disclosures plucked selectively from the [priority] application[s]." *Id.* at 1349.

We are not persuaded by Patent Owner's argument based on the institution decision in *Novartis Pharms. Corp. v. Plexxikon Inc.*, No. PGR2018-00069, Paper 16 at 14–17 (P.T.A.B. Jan. 16, 2019) and *In re Driscoll*, 562 F.2d 1245 (CCPA 1977). We note *Novartis* is not precedential and finds "formula Ib describes a genus in which –N(H)C(O)– is a preferred substituent for L_1." *Novartis*, Paper 16 at 15. That is different than the instant facts where there is no indication that the gly/phe tetrapeptides are preferred and Dr. Bertozzi, at best, notes the ordinary artisan could "consider using glycine" or "would have considered substituting a phenylalanine" without pointing to specific disclosures in the priority applications identifying either glycine or phenylalanine as preferred. *See* Ex. 2058 ¶¶ 133–136.

Driscoll differs from the instant facts because the *Driscoll* disclosure listed "fourteen distinct classes of compounds, each class having a single member of the R group at the 5-position of the thiadiazole moiety and variable substituent groups on the urea moiety." *Driscoll*, 562 F.2d at 1249. As already discussed, there are many more selections with multiple choices that would be necessary to obtain the claimed gly/phe tetrapeptides. That the claimed gly/phe tetrapeptides might be made because a POSA could modify the specifically disclosed GFLG, ALAL, and GSVQ tetrapeptides in light of disclosures in the '039 patent and there are reasons a POSA might consider

using glycine and phenylalanine, Ex. 2058 ¶¶ 132–136, "For example, a propyl or butyl compound may be made by a process analogous to a disclosed methyl compound, but, in the absence of a statement that the inventor invented propyl and butyl compounds, such compounds have not been described and are not entitled to a patent." *Ariad*, 598 F.3d at 1352. And as in *Ariad*, there is no indication in the priority applications that the gly/phe tetrapeptides were described, much less preferred. "Substantial evidence supports the . . . finding that 'guidance to make the particular selections chosen by the appellant, rather than making any other selection, is not found in the [priority] application.'" *In re Wako Pure Chemical Industries Ltd.*, 4 Fed. Appx. 853 at 5 (Fed. Cir. 2001).

We find Dr. Lambert's statements regarding the size of the genus of compounds described relative to the gly/phe tetrapeptides supportive of Petitioner's reliance on the reasoning in *In re Ruschig*, 379 F.2d 990 (CCPA 1967).

> Specific claims to single compounds require reasonably specific supporting disclosure and while we agree with the appellants, as the board did, that naming is not essential, something more than the disclosure of a class of 1000, or 100, or even 48, compounds is required. Surely, given time, a chemist could name (especially with the aid of a computer) all of the half million compounds within the scope of the broadest claim, which claim is supported by the broad disclosure. This does not constitute support for each compound individually when separately claimed.

Ruschig, 379 F.2d at 1556–57.

Dr. Lambert reasonably calculates that the "genus may have either of two potential backbone structures . . . and 39 potential side chains. . . . three of the described side chains have an additional chiral center, providing them with four stereoisomers." Ex. 1002 ¶ 82. Dr. Lambert concludes "the '039

Patent provides 83 potential alternatives for each non-N-methylated amino acid residue of its peptides of 1–12 residues in length." *Id.* Dr. Lambert calculates the "genus of amino acid units mentioned in the specification and priority applications, even if limited to tetrapeptides having the backbone structure recited in the '039 Patent's claims, would cover over 47 million (i.e., 83^4) species." *Id.* ¶ 83. We note that Dr. Bertozzi accepted Dr. Lambert's calculation and no contrary calculation is provided in evidence by Patent Owner. *See, e.g.*, Ex. 1102, 169:11–23; Resp. 67.

And while we appreciate that *Ruschig* was referring to a single compound rather than the small genus of W_w units as recited in claim 1, we think the same reasoning supports the conclusion that a disclosure of 47 million species does not describe a subgenus limited to only 81 species. Ex. 1002 ¶¶ 82–83. We find the requisite description lacking in the priority applications as it is an "undifferentiated description. . . [that] failed to provide sufficient 'blaze marks' to guide a reader through the forest of disclosed possibilities toward the claimed compound, which resided among the myriad others that also could have been made." *Novozymes*, 723 F.3d at 1346.

We also find Patent Owner's argument that the reasoning in *Ruschig* is limited to compound claims rather than subgenus claims unavailing. In *Boston Scientific*,

> the inventors similarly disclosed a genus (analogs of rapamycin), but claimed a narrower sub-genus (macrocyclic triene analogs of rapamycin). However, nothing in the [] patent indicates that the claimed triene analogs might be of special interest. . . . the lack of such blaze marks in the [] patent prevents any conclusion that the patent contains sufficient written description of the claimed triene analogs of rapamycin.

Boston Scientific Corp. v. Johnson & Johnson, 647 F.3d 1353, 1367 (Fed. Cir. 2011). *See also Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571 (Fed. Cir. 1996)("[S]imply describing a large genus of compounds is not sufficient to satisfy the written description requirement as to particular species or sub-genuses.")

We remain unpersuaded by Patent Owner's reliance for descriptive support on three tetrapeptides "GFLG (glycine-phenylalanine-leucine-glycine) and ALAL (alanine-leucine-alanine-leucine)" as well as "GSVQ (glycine-serine-valine-glutamine)." Resp. 70–71. Patent Owner asserts that these "would have guided a POSA to gly/phe tetrapeptides. (Ex. 2058 ¶¶ 133-37.)" *Id*. at 71.

We find that the disclosure of these three tetrapeptides in the '039 patent does not suggest the use of the gly/phe tetrapetides. Rather, we find the '039 patent discusses that "[u]seful – W_w- units can be designed and optimized in their selectivity for enzymatic cleavage by a particular enzymes [sic], for example, a tumor-associated protease. In one embodiment, a - W_w- unit is that whose cleavage is catalyzed by cathepsin B, C and D, or a plasmin protease." Ex. 1001, 67:57–60. While the gly/phe tetrapeptides might have been obvious after optimization for a particular protease is performed, "a description that merely renders the invention obvious does not satisfy the [written description] requirement." *Ariad*, 598 F.3d at 1352.

In sum, after reviewing the record, including the statements of Dr. Lambert and Dr. Bertozzi, we agree with Petitioner that a preponderance of the evidence shows claim 1 lacks benefit of priority to the priority applications because those applications do not provide written descriptive support for the W_w subgenus recited in claim 1.

V. GROUND 1 – WRITTEN DESCRIPTION

A. Principles of Law

> Although many original claims will satisfy the written description requirement, certain claims may not. For example, a generic claim may define the boundaries of a vast genus of chemical compounds, and yet the question may still remain whether the specification, including original claim language, demonstrates that the applicant has invented species sufficient to support a claim to a genus.

Ariad, 598 F.3d at 1349.

> The 'written description' requirement implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee [inventor] was in possession of the invention that is claimed.

Capon v. Eshhar, 418 F.3d 1349, 1357 (Fed. Cir. 2005). "[T]he determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue." *Id*. at 1359.

B. Claim 1

1. *Petitioner's position*

Petitioner asserts that "the specification must disclose 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." Pet. 31.

Petitioner asserts that the '039 patent does not satisfy the first prong of *Ariad* because it does not describe a representative number of species. *See* Pet. 32. Petitioner asserts "[p]ursuant to PO's claim construction, applied here, the drug moiety (i.e., 'D') is broad enough to encompass all drug moieties, and not just dolastatin/auristatin derivatives." Pet. 31. Petitioner further asserts the "claimed genus of ADCs further requires a 'tetrapeptide' comprised of glycine and phenylalanine amino acids." *Id*. Petitioner asserts the "'039 Patent does not describe the full scope of this claimed genus, because its disclosure is limited to ADCs containing drugs known as dolastatin/auristatins, and none of which comprise the claimed tetrapeptide. (*See, e.g.*, Ex. 1002 ¶¶ 100–14.)" *Id*. at 31–32; *cf*. Pet. Reply 9–10.

Petitioner asserts

> Every single working example in the patent involves an ADC with a dolastatin/auristatin derivative as its drug moiety, a very narrow subset of the claimed drug moieties. (*See, e.g.*, *id.* ¶¶ 105–06.) And because not a single one of those exemplified compounds features the tetrapeptide required by Claims 1–5, 9, and 10, the '039 Patent discloses *zero* examples of an ADC falling within the claimed genus. (*See, e.g.*, *id.* ¶¶ 100–08.)

Pet. 33.

Petitioner asserts that the '039 patent does not satisfy the second prong of *Ariad* because it does not disclose common structural features within the drug moiety genus. *See* Pet. 35. Petitioner asserts the "claim limitation of a 'drug moiety' is not a structural limitation. Instead, it is a functional limitation to anything that can be considered a 'drug.' A 'drug' performs a pharmacological function but does not specify any particular structural feature that accomplishes that function. (*See, e.g.*, Ex. 1002 ¶ 110.)" Pet. 35. Petitioner asserts the "'039 Patent nowhere identifies any

'drug moiety' that is not a dolastatin/auristatin derivative." *Id.* at 37.

Petitioner does acknowledge that

> The '039 Patent does include tables of various therapeutic compounds. (Ex. 1001 at 162:10 (Table 4), 165:42 (Table 6), 168:34 (Table 8).) These compounds are identified as agents to be administered as part of multi-drug therapy *with* the patent's ADCs, not *as* the drug moieties of the patent's ADCs. (*Id.* at 31:39–33:31, 161:60–163:28; *see, e.g.*, Ex. 1002 ¶ 107.)

Pet. 37, footnote 13. Petitioner asserts "a nitrogen atom is not a common structural feature that would permit the POSA to 'visualize or recognize the members of the genus.'" *Id.* at 39. Petitioner asserts "even if it could, [Patent Owner] has not construed its claim even to be limited to ADCs with this feature." *Id.* at 40 (citing Ex. 1009, 1041).

2. *Patent Owner's position*

Patent Owner asserts "the specification broadly discloses that the 'Drug-Linker-Ligand Conjugates can be used to deliver a Drug or Drug unit to a tumor cell or cancer cell' and identifies various drugs (other than dolastatin/auristatin derivatives) known to be useful for ADCs by 2004. (Ex. 1001 at 158:67-159:2.)" Resp. 50. Patent Owner asserts the "specification refers to Dr. Senter's 2003 book chapter that describes the three classes of drugs that could be used in ADCs: those that cause cell death "by mechanisms including tubulin binding, DNA binding, or topoisomerase inhibition. (Ex. 1001 at 3:7-13; Ex. 1014 at 16.)" Resp. 50. Patent Owner asserts that, "[a]s Dr. Bertozzi explains, the POSA would have been guided by the Senter 2003 and Toki 2002 publications referenced in the specification to know that a number of different drugs, other than dolastatin/auristatin derivatives, would be suitable for ADCs of the claimed formula. (Ex. 2058 ¶¶ 93-102, 113-114.)" Resp. 51.

> Patent Owner asserts
>
> > Petitioner adopts an overly restrictive reading of the '039 patent. Petitioner goes so far as to assert that the "figures of the '039 Patent are expressly limited to dolastatin/auristatin derivatives" (Pet. at 13 (*citing* Figs. 1-19)). That assertion is not correct. Several figures not mentioned in the petition include no such limitation. (*See, e.g.*, Ex. 1001 at 68:20-28, Fig. 20. (depicting ADCs with a "Spacer unit [] in which part or all of the Spacer unit remains bound to the Drug moiety after cleavage, particularly enzymatic, of an Amino Acid unit from the Drug-Linker-Ligand Conjugate or the Drug-Linker Compound" without limiting the drug to dolastatin/auristatin derivatives only.)

Resp. 52. Patent Owner asserts "Dr. Lambert's opinion that the '039 patent is limited to dolastatin/auristatin derivatives cannot be squared with the patent itself." *Id*. at 53. Patent Owner asserts

> Dr. Lambert's opinion that figures such as Fig. 22 only depict attachment of a drug only through an "amine, or a secondary amine in the context of the entire specification" is directly contradicted by the patent's description of Fig. 22 as a linker "attached to D by an *ether or amine* linkage." (Ex. 1001 at 68:65-67 (emphasis added).)

Resp. 54. Patent Owner asserts "many of the drugs referenced in the '039 patent as useful for ADCs were already commercially available, thus there was no need to disclose how to synthesize them. (Ex. 2058 ¶ 192.)" Resp. 56. Patent Owner asserts "given that the nature of the claimed invention is an ADC of a particular formula, the '039 patent instead provides details on how to attach a "Drug" (without limiting it to any specific auristatin/dolastatin derivative) to a "Linker." ([Ex. 2058] ¶ 109.)" Resp. 56.

Patent Owner asserts the "'039 patent also provides specific *chemical names* of the linkages applicable to attaching drugs with the shared physical properties to the claimed ADC formula as "ether," "carbonate,"

"carbamate," or "amine" linkages. (Ex. 1001 at 68:48-64 *citing* Figs. 21-22; Ex. 2058 ¶ 219.)" Resp. 58. Patent Owner asserts "these features (*i.e.*, alcohol groups with oxygen atom or amines with nitrogen atom) are shared by a vast majority of chemotherapeutic agents that are disclosed in the patent and could potentially be used in the disclosed ADC formula. (Ex. 2058 ¶¶ 123, 219.)" *Id.*

3. *Experts' views of descriptive support for claim 1 in '039 patent*

a. Dr. Lambert

Dr. Lambert states:

> PO has not provided a representative number of species to cover drugs other than dolastatin/auristatin derivatives, meaning there is no disclosure of ADCs with camptothecin derivatives or derivatives of any of the virtually limitless drugs that fall within the scope of the claimed drug moiety limitation. In fact, the '039 Patent specification is focused on dolastatin/auristatin derivatives and does not describe novel ADCs having non-dolastatin/auristatin derivative drug moieties, let alone such novel ADCs that satisfy other express limitations of Claim 1, such as the Gly/Phe-Only Tetrapeptide Limitation.

Ex. 1002 ¶ 100. Dr. Lambert states "[t]his singular focus with respect to the purportedly novel ADCs is further confirmed by the '039 Patent's Section 9.4, titled "The Drug Unit (Moiety).'" *Id.* ¶ 106. Dr. Lambert states that subsection 9.4 "of the '039 Patent devoted to purportedly novel ADCs having drug units (i.e., "9.4 The Drug Unit (Moiety)") specifies "[t]he drug moiety (D) of the antibody drug conjugates (ADC) are of the dolastatin/auristatin type." (Ex. 1001 at 71:18–21.)" *Id.* Dr. Lambert states that

> [a]lthough the '039 Patent separately lists hundreds of drugs that are not dolastatin/auristatin derivatives, such as "chemotherapeutic agent[s]" (Ex. 1001 at 31:39–33:31) and

> therapeutic agents for therapy of autoimmune diseases (Ex. 1001 at 165:42–60) and infectious diseases (Ex. 1001 at 168:33–170:24), the POSA would understand that those disclosures are directed to drugs that can be used in combination therapy, rather than as drug moieties for the ADCs themselves.

Id. ¶ 107. Dr. Lambert states "[b]ecause the '039 Patent discloses no examples of ADCs containing the tetrapeptide recited in Claim 1, the '039 Patent discloses zero species falling within Claim 1." *Id.* ¶ 108. Dr. Lambert states nowhere "does the '039 Patent Specification disclose common structural features to permit the POSA to understand the full scope of the claimed "drug moiety" genus or even recognize members of that genus, at least because all disclosures are for dolastatin/auristatin derivatives. (Ex. 1001 at 143:17–146:2.)" *Id.* ¶ 113.

b. Dr. Bertozzi

Dr. Bertozzi states:

> The '039 patent and its priority applications shows a person of ordinary skill that the inventors possessed an ADC with the claimed structure shown in Claim 1 that could be used with a broad set of drug moieties. The '039 patent and its priority applications disclose a representative number of species of drug moieties, and describe common structural features of the drug moieties that can be used.

Ex. 2058 ¶ 198. Dr. Bertozzi states the '039 patent "describes embodiments where the drug may be of any class: 'In still another aspect, the invention provides compositions comprising an effective amount of a Drug-Antibody Conjugate having a cleavable Drug unit (moiety) from the Drug-Antibody Conjugate and a pharmaceutically acceptable carrier or vehicle.' (Ex. 1001 at 14:1-5.)" *Id.* ¶ 203. Dr. Bertozzi states "Figure 36 further illustrates a 'methodology useful for making Drug-Linker-Ligand conjugates having

about 2 to about 4 drugs per antibody' without limiting the drug to dolastatin/auristatin derivatives only." *Id*.

Dr. Bertozzi states the "specification clearly describes a variety of other drug moieties aside from those in the auristatin and dolastatin classes that may be used in the context of the invention, and a POSA would have understood that any of the disclosed drug moieties could be used to make the claimed ADC." Ex. 2058 ¶ 204. Dr. Bertozzi states that a "POSA would be guided by the disclosures in columns 2 and 3, including the articles referenced, to understand that a number of different drugs that could be employed in carrying out the claimed invention." *Id*. ¶ 205. Dr. Bertozzi states the '039 patent "specification references the Senter 2003 book chapter that teaches that the drug moiety of an ADC can be any compound that exerts its cytotoxic and cytostatic effects by mechanisms including tubulin binding, DNA binding, or topoisomerase inhibition. (*See* Ex. 1001 at 3:7-12.)" *Id*. ¶ 207. Dr. Bertozzi cites a number of references cited in the Specification that describe antibody-drug conjugates using drugs other than auristatin and dolastatin including Baldwin 1986, Mandler 2000, Mandler 2002, Hinman 1993, Lode 1998, and Liu 1996. *Id*. ¶¶ 209–212.

Dr. Bertozzi disagrees "with Dr. Lambert's characterization of the chemotherapeutic agents in columns 31-33 as referring only to 'drugs that can be used in combination therapy, rather than as drug moieties for the ADCs themselves.' (Ex. 1002 at ¶ 107.)" Ex. 2058 ¶ 214. Dr. Bertozzi states "[s]ome of the disclosures I discussed above would have allowed the POSA to visualize or recognize drugs that can be used in the invention based upon the drug compound's properties such as chemical structures, chemical properties, and other properties such as mechanisms of action." *Id*. ¶ 218.

Dr. Bertozzi states "the '039 patent and its priority non-provisional applications all include within their disclosures a description of a tetrapeptide that consists of amino acids with R^{19} groups of either hydrogen (glycine) or benzyl (phenylalanine)." Ex. 2058 ¶ 222. Dr. Bertozzi states "the description in the '039 patent and the priority non-provisional applications would have guided a POSA to tetrapeptides that only have glycine or phenylalanine. Based on the examples in the specification, a POSA would have understood Seagen's invention to include ADCs with gly/phe tetrapeptides." *Id.* ¶ 226.

4. *Analysis*

a. "drug moiety"

We find that the instant situation is similar to that in *Capon* where the prior art is aware of a number of chemotherapeutic drug compounds and the use of antibody-drug conjugates. Dr. Bertozzi states that the '039 patent recites a large number of drugs and also identifies a number of references cited in the Specification that describe antibody-drug conjugates using drugs other than auristatin and dolastatin including Baldwin 1986, Mandler 2000, Mandler 2002, Hinman 1993, Lode 1998, and Liu 1996. Ex. 2058 ¶¶ 205, 209–212. And we again note that in the Oral Hearing, Petitioner stated, "We're not limiting, we're not limiting the claim. The claim itself is broad. The claim as written is to encompass all drug moieties. There's no dispute about that." Paper 56, 7:12–14.

We are not persuaded by Petitioner that the '039 patent fails to comply with the requirement for description of a reasonable number of drug moiety species capable of use in an antibody-drug conjugate. The '039 patent recites dozens, if not hundreds of different chemotherapeutic agents

useful in the treatment of cancer. Ex. 1001, 31:39–34:49. And, during deposition, while Dr. Lambert repeatedly noted that the chemistry to develop linkers connecting particular drug moieties to antibodies was difficult and time consuming, Dr. Lambert also acknowledged that, prior to the earliest priority filing of the '039 patent, the prior art disclosed that drugs linked to antibodies as ADCs included calicheamicin, several different camptothecins, maytansine, doxorubicin, daunomycin, methotrexate, vendesine, diptheria toxin, ricin, geldanamycin, etoposide, and combretastatin A. Ex. 2151, 30:2–3, 31:24–32:24, 34:14–22, 35:4–8, 42:25–43:2, 44:7–12, 71:12–21. Dr. Lambert also acknowledged that several different chemical linkages to drugs using linkers with an amino nitrogen to a carbonate, carbomate or ether group on a drug, an aromatic alcohol, para-aminobenzoyl, and ether linkage to a phenolic alcohol were known in the prior art. Ex. 2151, 62:7–11, 63:7–15, 68:13–19, 69:10–17.

We are also not persuaded by Petitioner that the '039 patent does not satisfy the second prong of *Ariad* because it does not disclose common structural features within the drug moiety genus. Unlike the unknown structures of NF-κB inhibitors in *Ariad* with no examples of dominantly interfering molecules (*see Ariad*, 589 F.3d at 1356), the '039 patent recites an extensive list of known chemotherapeutic agents whose structures were all known in the prior art. *See* Ex. 1001, 31:39–34:49; Ex. 2058 ¶ 205–213.

We find the instant written description fact pattern different than that of cases like *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330, 1338 (Fed. Cir. 2021) where the claims were drawn to an element termed single-chain antibody variable fragment ("scFv") with insufficient evidence showing which scFVs bind to which targets. Here, the '039 patent recites

dozens of different known chemotherapeutic agents in multiple different classes that would have been expected to kill cancer cells when delivered using the antibody-drug conjugate of the recited claims.

Rather, we think this fact pattern is more analogous to *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357 (Fed. Cir. 2006). *Falko-Gunter* explained that recitation of known

> structures, if one existed, would serve no goal of the written description requirement. It would neither enforce the quid pro quo between the patentee and the public by forcing the disclosure of new information, nor would it be necessary to demonstrate to a person of ordinary skill in the art that the patentee was in possession of the claimed invention.

Id. at 1367. We find that scenario to more accurately describe the instant fact pattern, where the claims of the '039 patent are not focused on the particular cancer drug selected from the large number of known cancer drugs or the antibody used, but rather focus entirely on the linker joining a drug moiety and an antibody or other ligand moiety. *See, e.g.*, Ex. 1001, 44:55–48:23. After an extensive discussion of the linker in that cited section, the '039 patent then states "Ab is any antibody covalently attached to one or more drug units" followed by a listing of a variety of known antibodies. *See id.* at 48:24–50:28. Thus, even if the extensive list of cancer drugs recited in the '039 patent Specification is incomplete as of the date of filing, a fact not in evidence, there is no failure in written description because the '039 patent fails to recite other known cancer drugs not listed.

In sum, after reviewing the record, including the statements of Dr. Lambert and Dr. Bertozzi, we agree with Patent Owner that a preponderance of the evidence shows claim 1 of the '039 patent has written descriptive support for the term "drug moiety."

b. "gly/phe tetrapeptide"

We find that our written description analysis of the gly/phe tetrapeptide as discussed above with regard to priority applies equally in the written description analysis. For the reasons given in our priority section, we agree with Petitioner that, in sum, a preponderance of the evidence shows the claims of the '039 patent fail to comply with the written description requirement because the Specification fails to provide written descriptive support for the gly/phe tetrapeptide W_w subgenus recited in the claims of the '039 patent.

Therefore, overall, we find that a preponderance of the evidence shows the claims 1–5, 9, and 10 of the '039 patent fail to comply with the written description requirement.

VI. GROUND 2 – ENABLEMENT

A. Principles of Law

The enablement requirement asks whether "the specification teach[es] those in the art to make and use the invention without undue experimentation." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). "[T]he specification must enable the full scope of the invention as defined by its claims. The more one claims, the more one must enable." *Amgen Inc., v. Sanofi*, 598 U.S. 594, 610 (2023). To satisfy this requirement, "[t]he specification must contain sufficient disclosure to enable an ordinarily skilled artisan to make and use the entire scope of the claimed invention at the time of filing." *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1381 (Fed. Cir. 2012). "Enablement is a question of law based on underlying factual findings." *Id.* at 1380.

"To prove that a claim is invalid for lack of enablement, a challenger must show . . . that a person of ordinary skill in the art would not be able to practice the claimed invention without 'undue experimentation.'" *Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1188 (Fed. Cir. 2014) (*quoting In re Wands*, 858 F.2d at 736–37). In analyzing undue experimentation, we consider:

> (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.

In re Wands, 858 F.2d at 737.

B. Claim 1

1. *Petitioner's position*

Petitioner asserts

> The '039 Patent fails to enable the POSA to make the full scope of the claimed genus of ADCs and identify which compounds will be "intracellularly cleaved" as the challenged claims require. Accordingly, the specification and priority applications do not satisfy the requirements of 35 U.S.C. § 112(a), rendering the '039 Patent both PGR eligible and unpatentable.

Pet. 44. Petitioner asserts "[c]omplex chemical interactions among ADC components affect its structure and properties. (*See, e.g.*, Ex. 1002 ¶¶ 35–37, 127, 130, 141.)" Pet. 44. Petitioner asserts "[g]iven this complexity, one review article remarked that, as of 2016, it was not surprising that "we have only two commercially available agents despite over one hundred clinical trials evaluating this platform." (Ex. 1025 at 2168.)" Pet. 44.

Petitioner asserts

> Claim 1 embraces a vast genus of ADCs . . . While the claim does limit one aspect of the *linker* that attaches the drug to the antibody—for example, the linker must comprise a tetrapeptide consisting of glycine or phenylalanine . . . the structural limitations of the claim still encompasses an astronomical number of structurally and functionally disparate compounds. (*See, e.g.*, *id.* ¶¶ 127–29.)

Pet. 45–46 (footnote omitted). Petitioner also asserts that whether a composition meets the intracellular cleavage functional limitation of the challenged claims cannot be ascertained without testing and undue experimentation. *See id.* (citing Ex. 1002 ¶¶ 8, 46–51, 122, 154.) Petitioner asserts "the '039 Patent's disclosure offers scarce guidance and extremely limited working examples. (*See, e.g.*, Ex. 1002 ¶¶ 129–38.)" Pet. 46. (footnotes omitted). Petitioner asserts "the hard experimental work of finding methods to make ADCs using other drug moieties has been left to the field. With respect to determining whether an ADC is intracellularly cleaved as the claims require, the '039 Patent offers nothing—not even an assay for testing this limitation." *Id.* at 47.

Petitioner asserts "[a]ttaching a drug moiety to the linker unit in the claimed ADCs would require the drug moiety to have a functional group capable of forming such a bond with a spacer or a gly/phe-only tetrapeptide. (*See, e.g.*, Ex. 1002 ¶¶ 39, 142.)" Pet. 48. Petitioner cites an effort to conjugate the drug maytansine to an antibody, asserting

> [b]ecause maytansine itself "lacked a suitable functional group" for attachment to an ADC linker, Dr. Lambert and his team of scientists conducted years of painstaking research creating "maytansinoids." (Ex. 1026 at 6951; *see, e.g.*, Ex. 1002 ¶¶ 44, 63.) These maytansine derivatives have functional groups that

> allow for attachment to linkers without sacrificing drug activity. (Ex. 1026 at 6952.)

Pet. 49.

Petitioner asserts the "'039 Patent provides no examples or specific disclosure for attaching any drug moiety other than dolastatin/auristatin derivatives." Pet. 49 (citing Ex. 1002 ¶¶ 61, 97, 129–30, 134–35, 139–40, 145). Petitioner asserts "[n]or does the patent disclose a general rubric for attaching any drug moiety to linkers of the claimed ADCs, because no such rubric exists." Pet. 49. Petitioner points to disclosures that the linker technologies were unsuitable for drugs with functional groups such as alcohols or tertiary amines as the linking moiety. *See* Pet. 51–52. Petitioner asserts that Dr. Lambert has examined the '039 patent disclosures "and concluded that they do not enable the synthesis of ADCs other than by coupling to a drug's primary or secondary amine. (*See, e.g.*, Ex. 1002 ¶¶ 112, 135, 145.)." Pet. 53–54.

Petitioner asserts "enabling Claim 1 requires not just a teaching of how to make the ADCs . . . but also of how to identify the ADCs that possess the required functional characteristic of being cleaved intracellularly in a patient." Pet. 56. Petitioner asserts the "'039 Patent does not teach how to identify which ADCs will be intracellularly cleaved as claimed and which ADCs will not. Such cleavage is a biologically complex phenomenon. (*See e.g.*, Ex. 1002 ¶¶ 147–51.)" Pet. 57. Petitioner asserts "as Dr. Lambert explains, the '039 Patent does not disclose *any* assay for identifying ADCs that would meet this cleavage requirement. (*See, e.g.*, Ex. 1002 ¶¶ 133, 150–51, 153.)" Pet. 57–58. Petitioner asserts

> the claimed functional limitation is directed not to *in vitro* cleavage, but to intracellular cleavage *in a patient*. Dr. Lambert,

> an expert with four decades of experience in this field, is aware of no assay that could be used to screen ADCs for *in vivo*, intracellular cleavage in a patient. (*See, e.g.*, *id.* ¶¶ 12–14, 153–54.)

Id. at 60. Petitioner asserts

> the '039 Patent does not even provide a starting point for identifying the ADCs that meet the Intracellular Cleavage Limitation, let alone the requisite disclosure to reach the finish line without undue experimentation. *Wyeth* [*& Cordis Corp. v. Abbott Lab'ys*, 720 F.3d 1380, 1386 (Fed. Cir. 2013)] continued: "Even putting the challenges of synthesis aside, one of ordinary skill would need to assay each of at least tens of thousands of candidates" and it would take "weeks to complete each of these assays." *Id.* Here, the claimed genus is orders of magnitude larger, and the necessary assay does not even exist. (*See, e.g.*, Ex. 1002 ¶¶ 150, 153–54.)

Id. at 61–62.

2. *Patent Owner's position*

Patent Owner asserts "[b]y 2004, scientists were well aware of methods for synthesizing ADCs containing derivatives of chemotherapeutic drugs such as doxorubicin, calicheamicin, camptothecin, paclitaxel, maytansine, daunomycin, methotrexate, geldanamycin, aminopterin, chlorambucil, duocarmycin, idarubicin, melphalan, vinca alkaloids, vindesine, and many more. (Ex. 2058 ¶¶ 91-106.)" Resp. 25–26. Patent Owner asserts

> By 2004, there were numerous well-known methods for attaching drugs to linkers to form ADCs. (*Id.* ¶¶ 91-106.) Using the techniques described in both the '039 patent and in the existing art, a POSA would have understood that:
>
> 1) Drugs with an alcohol group could be connected to a linker in an ADC through a carbonate or ether (connection via an oxygen atom). (Ex. 2058 ¶ 128 . . .

> 2) Drugs with an amine group could be connected to a linker through a carbamate, amide, or direct amine bond (connection via a nitrogen atom). (Ex. 2058 ¶ 128 . . .
>
> 3) Drugs with a thiol group could be attached using routine thiol chemistry (connection via a sulfur atom). (Ex. 2058 ¶ 128 . . . If a drug lacked any of these available functional groups, a POSA could have readily introduced a "handle" to allow it to be joined to a linker in an ADC. (Ex. 2058 ¶ 129.)

Resp. 26–27.

Patent Owner asserts the '039 "patent discusses a number of drugs from various classes that had been used to make ADCs, including 'daunomycin, doxorubicin, methotrexate, and vindesine,' as well as 'maytansinoids' and 'calicheamicin.' (Ex. 1001 at 2:43- 3:50; Ex. 2058 ¶ 91.)" Resp. 28. Patent Owner asserts

> the '039 patent expressly teaches that the linker can be "connected directly to –D via a carbonate, carbamate or ether group." (Ex. 1001 at 68:48-53.) A POSA would have known that carbonate and ether groups are used to connect a drug through an oxygen heteroatom, and thus the drug may have an alcohol as its "handle" for attachment to a linker. (Ex. 2058 ¶¶ 108-109, 187.)

Id. at 29.

Patent Owner asserts "Petitioner fails to acknowledge that the modular nature of ADC technology allows the same linker to be attached to different classes of drugs because of the shared reactive sites. A POSA, however, would have been well aware of this. (Ex. 2058 ¶ 122.)" Resp. 32. Patent Owner asserts the prior art exemplifies where the "same protease-cleavable linker with a dipeptide unit and spacer could be conjugated to doxorubicin, as well as other drugs such as paclitaxel and mitomycin C, noting that an advantage of the linker technology is to "selectively deliver different classes of drugs." (Ex. 2028 at 1; Ex. 2058 ¶ 122.)" *Id*.

Patent Owner asserts the "challenged claims impose no 'activity' requirement, however. If an ADC meets the structural limitations of the claims, and the drug moiety is intracellularly cleaved, the claims are met regardless of the level of activity shown by the released drug. (Ex. 2058 ¶¶ 124, 178, 180, 189.)" Resp. 34. Patent Owner asserts

> Petitioner (1) improperly imports requirements of particular levels of stability of the ADC (*see, e.g.*, Pet. at 48 . . . (2) imposes an unclaimed requirement that an unmodified form of the drug be released (*id.* at 58 . . . and (3) discusses the difficulties in developing an FDA approved drug (*id.* at 44 . . . As with pharmacological activity, none of these features are claimed, and thus they need not be enabled. (Ex. 2058 ¶¶ 179-180.)

Id. at 35.

Patent Owner asserts that Dr. Lambert "testified that 'parts of making an ADC were actually well-established in the field and well-known in the art.'" Resp. 36 (citing Ex. 2059 at 97:5-24, 98:21-99:8). Patent Owner also asserts that "even if the scope of the claims encompassed ADCs that were less effective (or even inoperative), the presence of such embodiments within the scope of a claim does not necessarily render a claim non-enabled. (Ex. 2058 ¶ 181.)" *Id*. at 37.

Patent Owner asserts "Petitioner's enablement argument relies primarily on evidence that did not come into existence until after the filing date of the earliest priority application of the '039 patent." Resp. 37. Patent Owner asserts that the "vast majority of the scientific articles on which Petitioner and its expert rely, however, are dated after this priority date. (Pet. at 48-51, 58-61; Ex. 1002 ¶¶ 122-155.)" *Id*. at 38. Patent Owner asserts that "[e]ven if this post-filing evidence could be relevant, Petitioner has failed to

show that the ADCs disclosed in these post-filing publications fall within the scope of the challenged claims." *Id*. at 39.

Patent Owner asserts "[a]s of 2004, the art was replete with well-known *in vitro* and *in vivo* assays that would have informed a POSA whether a particular ADC was intracellularly cleaved in a patient. (Ex. 2058 ¶¶ 155-166.)" Resp. 41. Patent Owner asserts

> A POSA would have known how to incubate purified cathepsin B with the substrate *in vitro* and measure the speed of drug release, with assay conditions "chosen to approximate the lysosomal medium as a model for intracellular drug release." (Ex. 2027 at 3343; Ex. 2028 at 3348-50, bridging sentence; Ex. 2058 ¶ 156.) Similarly, rat liver lysosomal assays were available for the same purpose, but with a broader array of enzymes that could be found inside a cell. (Ex. 2058 ¶ 156; . . . because the assay conditions would have been chosen to approximate the conditions inside lysosomes, the results of these *in vitro* assays would have been indicative of whether the conjugate was cleavable *in vivo*. (Ex. 2027 at 3343[.)]

Id. at 41–42. Patent Owner asserts "Dr. Lambert's testimony on this point is simply not credible, as it contradicts the views of the ADC field as a whole. (Ex. 2058 ¶¶ 145-171.)" *Id*. at 45. Patent Owner points to other analyses of other ADCs that state they operate by internalization and intracellular cleavage (*see id*. at 46) and particularly point out that the label on Petitioner's product Enhertu states "that it 'undergoes internalization and intracellular linker cleavage by lysosomal enzymes' to cause DNA damage and apoptotic cell death. (Ex. 2150 at 14; Ex. 2058 ¶ 162.)" *Id*. at 47.

Patent Owner asserts the "2016 industry white paper Petitioner cites does not prove lack of enablement of the challenged claims. (Pet. at 60 (citing Ex. 1032).)" because "nothing about the '039 claims requires *complete stability* of the ADC. (Ex. 2058 ¶ 180.)" Resp. 48. Patent Owner

asserts that a "POSA could have used the same *in vitro* assays as those identified in the white paper to approximate *in vivo* conditions in an effort to determine suitability of ADCs for treatment. (Ex. 2058 ¶ 161; Ex. 1032 at 619-622.)" *Id*. at 49.

3. *Wands factors based on cited evidence*

a. Breadth of Claims

Dr. Lambert states the "breadth of the claims, as interpreted by PO, compounds enormously the complexity involved in designing, making and using ADCs. (*See supra* ¶¶ 23, 100.) For example, the "drug moiety" is not expressly limited to any particular compound or type of compounds. (Ex. 1001 at Claims 1–5, 9, 10.)" Ex. 1002 ¶ 127 (footnote omitted). Dr. Lambert states "the claims are limited only by the recitation of a maleimidocaproyl group and the Gly/Phe-Only Tetrapeptide Limitation, meaning the claims potentially cover a vast genus of structurally and functionally disparate ADCs." *Id*.

Dr. Bertozzi states that claim 1 of the '039 patent "is directed to an ADC where the linker has certain defined structural features and where the drug moiety is "intracellularly cleaved in a patient from the antibody." (Ex. 1001 at 332:35-40.)" Ex. 2058 ¶ 89 (footnote omitted).

We find a preponderance of the evidence shows the claims are extremely broad, encompassing an antibody-drug conjugate composed of any antibody and any drug moiety, with the only limit being a smaller linker genus size.

b. Skill in the Art

The level of skill in the art has already been addressed above in Section II.

c. Working Examples

Dr. Lambert states "the working examples in the '039 Patent are limited, and none of them are within the scope of the claims. Among other insufficiencies, the purportedly novel ADCs use only dolastatin/auristatin derivatives." Ex. 1002 ¶ 134. Dr. Lambert states the "none of the 33 Examples disclose how to make and use a novel ADC with a drug moiety other than dolastatin/auristatin derivatives, as the full scope of the claims requires. (*See* Ex. 1001 at 170:26–200:19.)" *Id.* ¶ 135. Dr. Lambert states "none of the purportedly novel ADCs used in the *in vitro* or *in vivo* studies include a tetrapeptide unit, let alone a tetrapeptide unit having only glycine and/or phenylalanine. (*See* Ex. 1001 at 131:33–138:55.)" *Id.* ¶ 136. Dr. Lambert states that in the '039 patent, the ADCs "included either a dipeptide amino acid unit or no amino acid unit of any kind. (*See* Ex. 1001 at 131:33–138:55.)" *Id.*

Dr. Bertozzi does not identify a working example within the scope of claim 1. *See* Ex. 2058 generally. Dr. Bertozzi states regarding working examples that "a POSA would have known how to attach linkers to these drug moieties with a linker of the claimed structure using 'modifications of methods well-known in peptide chemistry.' (Ex. 2027 at 3341.)" Ex. 2058 ¶ 91 (footnote omitted). Dr. Bertozzi also states that the '039 patent "depicts an exemplary chemical synthesis route for attaching a drug to a linker in an ADC." *Id.* ¶ 112. Dr. Bertozzi acknowledges that "whether or not Seagen scientists actually made a specific example of a gly/phe tetrapeptide is not a factor in determining whether the '039 patent describes . . . ADCs with gly/phe tetrapeptides." *Id.* ¶ 131.

Dr. Lambert states, regarding working examples of gly/phe tetrapeptides, that "sworn testimony of the named inventors of the '039 patent, Drs. Svetlana Doronina, Brian Toki, Toni Kline, and Peter Senter . . . supports my opinion that the inventors were not in possession of, and had not conceived, the claimed genus of ADCs as of the priority date." Ex. 1132 ¶ 84. Dr. Lambert states "Dr. Kline was 'not aware of' any examples in the ['039] patent in which an ADC containing a tetrapeptide linker containing only glycine and phenylalanine was described. Dr. Toki agreed, noting that he did not recall working with tetrapeptides composed of only Gly/Phe residues." *Id.* ¶ 85 (footnote omitted) (citing Ex. 1099 at 84:5–19; Ex. 1100 at 63:25–64:12). Dr. Lambert states "Dr. Doronina was not aware of anyone at Seagen making or testing an ADC containing a Gly/Phe-only tetrapeptide linker." *Id.* ¶ 86 (citing Ex. 1098 at 72:18–25). Dr. Lambert states "Dr. Senter testified that no one within Seagen made Gly/Phe-only tetrapeptides, there was no disclosure of the 81 tetrapeptides with only Gly and Phe, and the specification does not narrow down the possibilities to a tetrapeptide of Gly and Phe only." *Id.* ¶ 87 (citing Ex. 1095 at 263:3–17, 263:24–265:10).

We find that a preponderance of the evidence shows that the '039 patent lacks any working examples of an antibody-drug conjugate that incorporates the specific linkers required by claim 1.

d. The amount of direction or guidance presented

(1) Drug attachment to linkers

Dr. Lambert states the "'039 Patent does not provide direction or guidance for the POSA to make and use novel ADCs with drug moieties that are not dolastatin/auristatin derivatives." Ex. 1002 ¶ 129. Dr. Lambert states:

> By PO's own admission, even structural distinctions among dolastatin/auristatin derivatives can render the drug inoperable for attachment. (*See* Ex. 1027 at 15.) For example, Auristatin PE has a "dimethylamine terminus" (i.e., a tertiary amine) in contrast to the auristatins in the '039 Patent that have a primary or a secondary amine, which are the functional groups used for attachment to the ADC linker. (Ex. 1027 at 15; Ex. 1001 at 6:49–7:2, 71:30–36.) While the'039 Patent discloses techniques for attaching dolastatin/auristatin derivatives to linkers through primary and secondary amines, it does not provide techniques for attaching through tertiary amines.

Id. ¶ 144. Dr. Lambert states, regarding the '039 patent, that "[t]here is no general rubric for attaching drugs to linkers, meaning the disclosed teachings for dolastatin/auristatin are not generally applicable to the other drug classes, and the POSA would require experimentation to determine whether and how other drug moiety structures could be attached." *Id*. ¶ 145.

Dr. Bertozzi states the '039 patent cites a 2003 book chapter by Seagen scientists Damon Meyer and Peter Senter. Ex. 2058 ¶ 93 (citing Ex. 2015; "Senter"). Dr. Bertozzi states:

> The list of drugs and ADCs described by Senter 2003 shows that a POSA would have understood that a number of drugs could be used for ADCs and that the same drug could be conjugated to antibodies through a number of linker technologies. (*Id.*) While some of the discussed linker technologies differ from that in the challenged claims of the '039 patent, there is common chemistry for connecting drugs to these linkers and connecting drugs to protease-cleavable linkers.

Id. Dr. Bertozzi states that Senter teaches a variety of linkers and mechanisms and that "[b]y identifying the various mechanisms of action reflected in the Senter 2003 book chapter and referenced in the patent specification, the '039 patent broadly teaches the POSA that a number of different drugs and their analogs would be suitable for ADCs." *Id*. ¶ 102;

See also Id. ¶¶ 94–101. Dr. Bertozzi similarly points to a citation in the '039 patent to Toki that "explains how to attach drugs with an amine or alcohol functional group to protease-cleavable linkers and specifically outlines synthetic routes for preparing drug-linkers with the drugs etoposide . . . and combretastatin A-4." *Id.* ¶ 113 (citing Ex. 2018; "Toki"). Dr. Bertozzi points to a citation in the '039 patent that "Dr. Senter's team that describes various assays the POSA could use to screen for internalizing antibodies. (Ex. 1001 at 4:1-6 *citing* Ex. 2143.)" *Id.* ¶ 150 (citing Ex. 2143). Dr. Bertozzi states the "'039 patent describes in detail the different antibodies that could be used in an ADC, (Ex. 1001 at 78:38-86:35) and specifically identifies tumor-associated antigens that could be used as target receptors for the antibodies. (*Id.* at 86:13-110:57.)" *Id.* ¶ 149.

Dr. Bertozzi states the '039 patent "teaches different chemistries for attaching a variety of drugs to linkers. While drugs may have different structures, they often have heteroatoms such as oxygen, nitrogen, or sulfur that can be used as handles to attach to a linker of the claimed structure through routine experimentation." Ex. 2058 ¶ 108 (footnote omitted). Dr. Bertozzi states

> the specification would have guided the POSA to attach a drug to a linker using oxygen or nitrogen because Figure 22 depicts a possible drug release mechanism where a spacer is "attached directly to -D via an ether or amine linkage." (Ex. 1001 at 68:62-64.) A POSA would have known that an ether linkage is a linkage through an oxygen atom, while an amine linkage is a linkage through a nitrogen atom. The specification, including in Figure 21, also explains that the linker can be attached to a drug directly via a carbamate or carbonate group. (*Id.* at 68:54-58[.)]

Id. Dr. Bertozzi states a "POSA would have been guided by the disclosure of the '039 patent and know that the claimed invention could include use of any

drugs with either a nitrogen atom or an oxygen atom for attachment to the linker for an ADC." *Id.* ¶ 109. Dr. Bertozzi states Figures 33 and 34 of the '039 patent illustrate methods of linking using "auristatin/ dolastatin derivatives . . . But it would have been routine to apply the same reagents under the same or similar chemical reaction conditions to attach a linker to another drug that can bind to the reactive sites depicted in these figures." *Id.* ¶ 110.

We find Dr. Lambert more persuasive on the limited guidance for attachment of drug moieties in the '039 patent. While the '039 patent has an extensive list of chemotherapeutic agents in columns 31–34, neither the '039 patent nor Dr. Bertozzi identify any specific heteroatoms or other "handles" within a single member of the list of chemotherapeutic agents that is recited in the '039 patent specification other than the dolastatin/auristatin type. And when the '039 patent focuses on attachment of specific drug moieties, the '039 patent states the "drug moiety (D) of the antibody drug conjugates (ADC) are of the dolastatin/auristatin type . . . . D is a Drug unit (moiety) having a nitrogen atom that can form a bond with the Spacer unit . . . ." Ex. 1001, 71:20–33. And while the '039 patent specification provides reaction schemas showing how to synthesize the peptide linkers (*see, e.g.*, Ex. 1001, Fig. 25, 144:30–145:52) and how to perform general reactions connecting the linkers to drug moieties (*see, e.g.*, Ex. 1001, 146:3–152:24), the '039 patent entirely lacks a discussion or general rubric of how to place "handles" on drug moieties other than the dolastatin/auristatin type. Ex. 1002 ¶ 145.

We therefore find that a preponderance of the evidence shows that the '039 patent does not provide guidance on the attachment of drugs other than dolastatin and auristatin and their derivatives to the recited linker.

(2) Intracellular Cleavage

Dr. Lambert states the '039 patent "provides no guidance for the POSA to determine whether any of the claimed ADCs are capable of intracellular cleavage in a patient in the manner claimed. In fact, the '039 Patent does not disclose even a single assay capable of identifying whether these ADCs meet this requirement." Ex. 1002 ¶ 133. Dr. Lambert states the

> '039 Patent recites ADCs with zero, one, or two spacer units, each of which could be either a self-immolative spacer or non-self-immolative spacer. (*See* Ex. 1001 at Claim 1; *see also* Ex. 1001 at 68:13–35.) There is no teaching or guidance, however, in the '039 Patent of the impact of these spacer units—and certainly not across the broad scope of the types and combinations of such optional spacer units—on intracellular cleavage in a patient.

Id. ¶ 148.

Dr. Bertozzi states the "'039 patent teaches that useful amino acid units can be designed and optimized in their selectivity for enzymatic cleavage by a particular enzyme, for example, a tumor-associated protease such as cathepsin B, C, and D, or a plasmin protease. (Ex. 1001 at 67:57-61.)" Ex. 2058 ¶ 139. Dr. Bertozzi states that "the '039 patent expressly references a publication that demonstrates how to synthesize a protease-cleavable linker with a phe-lys amino acid unit motif, and the POSA could use a similar synthesis route to prepare a linker with glycine and phenylalanine: (Ex. 1001 at 150:37-42 *citing* Ex. 2113 at 5257-58)." *Id.* ¶ 140.

Dr. Bertozzi states the

> specification of the '039 patent includes data from assays measuring intracellular cleavage . . . The '039 patent also cites many publications that include details and procedures for *in vivo* and *in vitro* studies of intracellular cleavage, and a POSA would have been able to find the necessary guidance for evaluating intracellular cleavage from those cited publications.

Ex. 2058 ¶ 146. Dr. Bertozzi states that before a "drug payload is cleaved from the antibody by intracellular enzymes, the ADC would exhibit very limited toxicity . . . a POSA would recognize that cell death could be used as an indirect measurement of intracellular cleavage: unless intracellular cleavage had occurred, there would not be any observed cytotoxicity." *Id.* ¶ 157. Dr. Bertozzi states the "'039 patent includes as Example 18, a protocol for an *in vitro* cell proliferation assay used to measure ADC efficacy, which would inform a POSA on whether intracellular cleavage occurs. (Ex. 1001 at 130:38-132:63, 183:31-55.)" *Id.* ¶ 167. Dr. Bertozzi states the "'039 patent also included data from various *in vitro* cytotoxicity assays as supporting evidence that the claimed ADCs were intracellularly cleaved. For example, the data in Figure 4(b) and 5(b) show how the administration of the ADC leads to cell death." *Id.* ¶ 168. Dr. Bertozzi states the "'039 patent also includes data from and instructions on how to conduct *in vivo* cytotoxicity tests in rodents to indirectly evaluate intracellular cleavage. (*Id.* at Figs. 13, 14, 15, 16, 17, and 18; 135:43–140:65; 184:15–32.)" *Id.* ¶ 169.

Dr. Lambert states in response to Dr. Bertozzi that

> During her deposition, Dr. Bertozzi could not define the outer bounds of the structure of the spacer unit (Y_y) as used in Claim 1. Instead, Dr. Bertozzi stated that the outer bounds are defined by functional characteristics that are not present in the patent,

> meaning there is no guidance for the POSA in choosing a spacer unit to accompany the drug moiety in an ADC, if the spacer unit is present.

Ex. 1132 ¶ 29 (referencing Ex. 1102 at 96:14–102:15). Dr. Lambert states the "'039 patent does not explain why ortho or para-aminobenzylacetals could be used in ADC linkers that would intracellularly cleave. Without any guidance from the patent or prior art, the POSA would not be able to make or use such groups in the claimed genus of ADCs." *Id.* ¶ 31. Dr. Lambert similarly addresses spacers including 4-aminobutyric acid amides, appropriately substituted bicyclo[2.2.1] and bicyclo[2.2.2] ring systems, 2-aminophenylpropionic acid amides, and the a-position of glycine, stating in each case that the '039 patent does not explain how to incorporate these groups into ADCs and that such incorporation would be unpredictable. *Id.* ¶¶ 34, 39, 41, 43. Dr. Lambert states:

> Toki 2002, at most, discloses methods of conjugating phenolic alcohols to a PAB through a carbonate or ether. Indeed, Seagen's own later 2016 paper, co-authored by named '039 patent inventor Dr. Senter, confirms that Toki 2002 is limited in scope, relates to "releasing only phenolic payloads," and does not disclose a "general solution for using alcohol containing drugs" that Seagen developed and published many years after the priority date.

Id. ¶ 47.

Dr. Lambert states regarding Dr. Bertozzi's statement that cell death would indirectly measure intracellular cleavage that "[g]iven disease states can have enzymes in the extracellular microenvironment that are able to cleave the ADC before it is internalized, if the drug is membrane permeable, the drug can diffuse across the cell membrane without ever cleaving intracellularly." Ex. 1132 ¶ 73.

We find Dr. Lambert more persuasive that the '039 patent provides very limited guidance on how to determine whether a drug attached to the linker is cleaved intracellularly or not. Indeed, when Dr. Bertozzi refers to the in vitro cell proliferation assays recited in the '039 patent, we do not find any specific disclosure where cleavage of the drug conjugate occurs, inside or outside the cells. *See, e.g.*, Ex. 1001, 131:23–32. Dr. Bertozzi points to no statement in the '039 patent showing a direct measurement of intracellular cleavage as opposed to indirect results such as cell death. *See* Ex. 2058 ¶¶ 157, 167.

We therefore find that a preponderance of the evidence shows that the '039 patent provides minimal, if any, guidance on determining whether an antibody drug conjugate is cleaved intracellularly or not.

e. State of the prior art and the unpredictability in the art

(1) General state of the art

Dr. Lambert states "the nature of ADCs[] are 'one of the most complex drug platforms in the oncology armamentarium.' (*See* Ex. 1025 at 2168.)" Ex. 1002 ¶ 124 (footnote omitted). Dr. Lambert states "[b]y 2003, certain drugs were known to be capable of attachment to linkers, but many had failed in ADC clinical trials and only one was FDA-approved. (Ex. 1047 at 3; Ex. 1025 at 2169.)" *Id.* ¶ 41. Dr. Lambert states:

> ADCs with drugs other than maytansinoids, auristatins, or calicheamicins have had limited success. (*See* Ex. 1047 at 2 (noting that "auristatins, calicheamicins, and maytansinoids" represent the payloads for the ADCs of the "last 10+ years").) This was in spite of the fact that the ADC field had long recognized the need for new suitable ADC drug moieties with different mechanisms of actions. (Ex. 1039 at 317 ("To overcome resistance to current drugs, there is a need for new warheads that have different mechanisms of action."); Ex. 1056

> at 975 ("However, the low success rate of ADC[s] can be attributed, at least in part, to the use of payloads with the same mechanism of cell killing for every antigen target and every type of cancer."); Ex. 1025 at 2170 ("The continued exploration of mertansine and auristatin payloads in tumor indications that are not intrinsically sensitive to antimicrotubule agents is therefore intellectually suspect . . . .").)

Id. ¶ 43.

Dr. Bertozzi states regarding enablement that the "challenged claims and the specification do not require any particular level of intracellular cleavage. They certainly do not require any form of therapeutic viability to achieve clinical or commercial success." Ex. 2058 ¶ 89. Dr. Bertozzi states "the degree of difficulty of getting regulatory approval or usefulness of an ADC for treating an indication is not relevant to the nature of the claims at issue here, which do not require any particular level of efficacy and are not directed to methods of treatment." *Id.* ¶ 177.

We note that that statute requires:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, ***to make and use*** the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

35 U.S.C. §112(a) (emphasis added). *Amgen* involved a situation where each of the claims at issue were drawn to a "composition claim defined, not by structure, but by meeting functional limitations." *Amgen, Inc. v. Sanofi, Aventisub LLC.*, 987 F.3d 1080, 1087 (Fed. Cir. 2021).

We find that the same requirement is present here and that the claims require more than *de minimis* intracellular cleavage, but rather require

sufficient delivery into cells to achieve the point of the invention as stated in the '039 patent where "[t]he present invention is also directed to antibody-drug conjugates, to compositions including the same, and to methods for using the same to treat cancer, an autoimmune disease or an infectious disease." Ex. 1001, 1:63–66. We find the statute and caselaw impose a "use" requirement commensurate in scope with the claim which, in this case, requires sufficient "intracellular cleavage in a patient" to function in the treatment of some disease or condition.

(2) Intracellular cleavage

Dr. Lambert states "[g]iven the complexity associated with intracellular cleavage, including the relationship between linkers and both intracellular and extracellular proteases that could cleave those linkers . . . the presence or manner of internalization and eventual cleavage within the cell cannot be predicted." Ex. 1002 ¶ 148. Dr. Lambert supports this unpredictability by noting that "extracellular enzymes are capable of cleaving ADCs prior to reaching the targeted cells, and some cells express antigens that are known not to internalize, and therefore cannot promote the internalization of an ADC." *Id.* ¶ 132. Dr. Lambert explains the "POSA would understand that intracellular cleavage of an ADC in a patient is dependent on, among many other factors, the microenvironment created by the patient's ailment" *Id.* (citing Ex. 1064 that "cathepsin B can 'translocate and function to degrade components of the extracellular matrix.'"). Ex. 1064[6] teaches:

[6] Ruan et al., *Targeting Cathepsin B for Cancer Therapies*, 56 Horiz. Cancer Res. 23–40 (2015) (Exhibit 1064).

> There is evidence that non-tumor cells in the tumor microenvironment can produce cathepsin B and contribute to invasion and metastasis. Indeed, in some highly invasive tumors, large numbers of myeloid cells ($Gr\text{-}1^{+}CD11b^{+}$) that secret cathepsin B are found at the leading edge of tumor margins . . . These tumor-associated macrophages (TMAs) expressed cathepsin B and protected against Taxol-induced tumor cell death in co-culture. These macrophages also protect tumor cells against death induced by other chemotherapeutics, specifically etoposide and doxorubicin.

Ex. 1064 at 4. Dr. Lambert states "even if a given ADC were known to exhibit the claimed manner of intracellular cleavage in patients, the POSA would not assume the same to be true for other ADCs having structural differences, or even for the same ADC if it were used in a different disease state and different tissue microenvironment." Ex. 1002 ¶ 151.

Dr. Bertozzi states "Dr. Lambert exaggerates the effect of extracellular compounds on the cleavage of protease-cleavable linkers." Ex. 2058 ¶ 152. Dr. Bertozzi states that "[w]hile some proteolytic enzymes, such as cathepsins, may be secreted into the extracellular space by tumor cells and cause *some* extracellular cleavage, active protease secretion by cells is tightly controlled to prevent damaging other tissues in the body. This concept was well-known in the literature as of 2004." *Id*. (citing Ex. 2130 at 1134). However, Ex. 2130[7] states "the activity of proteases in cancer is far more complex than initially anticipated and includes tumor promoting as well as tumor-suppressive effects." Ex. 2130 at 1134. Ex. 2130 states "[p]roteases are expressed in the extracellular milieu as inactive proforms that become activated . . . . Thus overexpression of these proteases,

[7] DeClerck et al., *Proteases, Extracellular Matrix, and Cancer*, 164 Am. J. Pathology 1131–39 (2004).

documented in tumors by immunohistochemistry, does not necessarily mean an increase in proteolytic activity." *Id*. at 1134. Ex. 2130 states the "importance of a more complete understanding of the roles of proteases in malignant progression has acquired urgency since the clinical trials using synthetic inhibitors of MMPs [matrix metalloproteinases] have not demonstrated that the inhibitors are efficacious." *Id*. at 1135. Ex. 2130 concludes their discussion of proteases by stating "the field is at a crossroads where challenging questions meet exciting research opportunities supported by novel technologies." *Id*. at 1138.

Dr. Bertozzi states:

> Dr. Lambert acknowledges the wide swath of literature that describe extracellular microenvironments for various diseases. (*See, e.g*. Ex. 1002 at ¶ 132 *citing* Ex. 1060; Ex. 1061; Ex. 1062; Ex. 1063; Ex. 1064; Ex. 1065; Ex. 1066; Ex. 1067.) A POSA would be able to use the information in those publications along with the teachings of the '039 patent to select appropriate components of an ADC while maintaining intracellular cleavage, and no undue experimentation would be required to confirm that.

Ex. 2058 ¶ 153. Dr. Bertozzi asserts that a "POSA would nevertheless be able to predict the range of possible cleavage products based upon the chemistry associated with the chosen spacer and to test for those released compounds using a well-known set of *in vitro* assays to determine whether intracellular cleavage has occurred." *Id*. ¶ 154.

However, Ex. 1061[8] states "cathepsins are widely recognized as important diagnostic and therapeutic targets largely for the diseases that involve ECM remodeling, their multifunctional roles pose a problem in the

[8] Vidak et al., *Cysteine Cathepsins and Their Extracellular Roles: Shaping the Microenvironment*, 8 Cells 1–24 (2019).

design of successful tools for their therapeutic targeting as demonstrated by the systematic failure of a number of cathepsin inhibitors in clinical trials." Ex. 1061 at 13. Ex. 1061 also states that "several drugs are synthesized as prodrugs or antibody-drug-conjugates (ADCs) and become active only after cathepsin cleavage. This concept has been successfully used in oncology with a good example being ADCETRIS®, which is already clinically approved." *Id*. at 12.

Dr. Bertozzi states that "[a]s of November 2004, a POSA would have understood that there exists a wide variety of direct and indirect *in vitro* assays available to evaluate ADCs for intracellular cleavage." Ex. 2058 ¶ 156 (citing Ex. 2027 at 3343; Ex. 2118 at 924, 928; Ex. 2119 at 125.) Dr. Bertozzi states that

> known direct *in vitro* assays for evaluating intracellular cleavage include:
>
> - Using LC/MS to measure the amount of drug released within cells after incubating an ADC with the targeted cells. (Ex. 1002 at ¶ 50.)
> - Using LC/MS to measure drug payload release by incubating ADCs with papain, a known substitute for lysosomal enzymes routinely used to evaluate peptide cleavage. (*See also* Ex. 2119 at 125.)
> - Measuring rate of intracellular release of drug payloads spectrophotometrically with Ellman's reagent. (Ex. 2103 at 1450.)

Id. Dr. Bertozzi also states that "a POSA would recognize that cell death could be used as an indirect measurement of intracellular cleavage: unless intracellular cleavage had occurred, there would not be any observed cytotoxicity." *Id*. ¶ 157. Dr. Bertozzi states that "[r]esearchers can add a fluorescent tag to the ADC of interest and after cell incubation, use

fluorescence microscopy to determine whether the ADCs were entering the cells, and more specifically, whether the ADCs were entering cellular lysosomes where the cleaving proteases were located." *Id.* ¶ 158 (citing Ex. 2118 at 924, 928.) Ex. 2118[9] states "[a]nti-TMEFF2 mAb internalization and Pr1-vcMMAE-mediated cell killing were also observed." Ex. 2118 at 928.

Dr. Bertozzi states that "a POSA would recognize that there were *in vitro* plasma assays in which an ADC was incubated in human or animal plasma to evaluate ADC stability and to determine the amount of drug released extracellularly." Ex. 2058 ¶ 160 (citing Ex. 2027 at 3343; Ex. 2028 at 3348–49, 3350; Ex. 1023 at 864, 868; Ex. 2018 at 1867–68; Ex. 2029 at 779; Ex. 2033 at 1461.) Dr. Bertozzi states that a "POSA would have understood these *in vitro* assays altogether to be predictive of ADC behavior *in vivo*." *Id.* ¶ 163 (citing Ex. 2027 at 3343; Ex. 2028 at 3348-49; Ex. 2029 at 779.)

Dr. Bertozzi states:

> Dr. Lambert also misrepresents the effort necessary to determine whether intracellular cleavage had occurred in different cell lines. (Ex. 1002 at ¶¶ 50, 152 *citing* Ex. 1031 (referring to his personal experience with an ADC with a triglycyl linker).) The claims of the '039 patent only require that the drug moiety be intracellularly released from the antibody. There is no requirement as to what the structure of the cleavage product needs to be, nor a limitation on the number of possible cleavage products as long as the drug moiety is separated from the antibody. The differences observed by Dr. Lambert using

[9] Afar et al., *Preclinical validation of anti-TMEFF2-auristatin E-conjugated antibodies in the treatment of prostate cancer*, 3 Mol. Cancer Therapeutics 921–32 (2004).

> different cell lines therefore do not bear on the question of whether intracellular cleavage had occurred.

Ex. 2058 ¶ 176.

While we recognize Dr. Lambert's statements concerning different microenvironments suggest some degree of unpredictability, Dr. Bertozzi provides significant evidence showing that many assays were known in the prior art for determining whether antibody-drug conjugates were intracellularly cleaved or not *in vitro*. In particular, assays including fluorescence imaging of cells after incubation with fluorescently labeled antibody-drug conjugates, LC/MS, and spectrophotometric measurement of release reasonably support the position that the prior art generally teaches method for measuring intracellular cleavage. Ex. 2058 ¶¶ 156, 158.

We therefore find that a preponderance of the evidence shows that the prior art provides substantial details on methods for determining whether an antibody drug conjugate is cleaved intracellularly or not *in vitro*.

(3) Drugs and linkers

Dr. Lambert states that "Designing ADCs is an extremely unpredictable art that requires an understanding of the complex interactions between the linker and drug, which makes the relative skill required quite high." Ex. 1002 ¶ 141. Dr. Lambert states that "linkers with aromatic peptides tend to be more hydrophobic and may require alterations to the drug to decrease hydrophobicity and avoid aggregation. (*See, e.g.*, Ex. 1047 at 13[])." *Id*. Ex. 1047[10] states:

[10] Leung et al., *Antibody Conjugates-Recent Advances and Future Innovations*, 9 Antibodies 1–27 (2020).

> While a simple concept at first glance, a linker is far more complex than a mundane spanning element between the small molecule payload and the antibody which make up the ADC. It ensures the fundamental principles of targeted drug delivery of ADCs-minimizing premature drug release in plasma and promoting selective release of payload to the target cell. Additionally, it can modulate the physiochemical property of the overall conjugate. This requires the linker design to be stable in circulation and upon antibody-mediated internalization, the payload is efficiently released.

Ex, 1047, 11. "It is well-documented that the addition of a small molecule drug to an otherwise soluble and stable antibody can cause aggregation and other physicochemical instability in the ADC." *Id.*, 16.

Dr. Lambert states that "it is essential that the activity of a drug is not lost when attaching the drug to a linker. . . . ADCs are not mix-and-match, and the POSA would have understood that, for example, ADCs with certain drugs would have different properties that may make them incompatible with the tetrapeptide linkers recited in Claim 1." Ex. 1002 ¶ 142. Dr. Lambert states that, "[f]or example, Auristatin PE has a 'dimethylamine terminus' (i.e., a tertiary amine) in contrast to the auristatins in the '039 Patent that have a primary or a secondary amine . . . [the '039 Patent] does not provide techniques for attaching through tertiary amines." *Id.* ¶ 144. Dr. Lambert states "unsurprisingly there are additional complications in attaching to linkers drug moieties that are not of the dolastatin/auristatin type." *Id.* ¶ 145 (citing Ex. 1029). Ex. 1029[11] states "[c]ertain drug classes thought to be lacking appropriate conjugation handles have been considered unsuitable for use as ADCs. Although it may be possible to modify such a

[11] Kolakowski et al., US 2016/0303254 A1, published Oct. 20, 2016.

drug to include a conjugation handle, such a modification can negatively interfere with the drug's activity profile." Ex. 1029 ¶ 3. Ex. 1029 states "a need for more versatile methods for linking aromatic alcohol and aliphatic alcohol containing drugs to other targeting ligands in addition to antibodies." *Id*. ¶ 5.

Dr. Lambert states "researchers still labor to develop techniques for attaching different drug moieties to linkers . . . one of the '039 Patent's named inventors, sought to validate the synthetic installation of amine functional groups into drug analogs, and determined it is not always synthetically feasible. (Ex. 1028 at 7948.)." Ex. 1002 ¶ 146. Ex. 1028[12] states "introducing an amine functional group may not always be synthetically feasible, and it may have a detrimental impact on the pharmacology of the resulting drug analogue." Ex. 1028, 7948; *cf*. Ex. 1030.[13] "[T]ertiary amine functional group is a common structural motif present in many biologically active molecules, but has not been utilized as a linker element in previously described ADCs for cancer therapy." Ex. 1030, 1535. Ex. 1030 also states "it is not always possible to maintain drug potency in cases where the tertiary amine plays an integral role in drug activity." *Id*.

Dr. Lambert states "Dr. Bertozzi's claim that ADCs are mix-and-match and not highly complex conflicts with her acknowledgement that

[12] Kolakowski et al., *The Methylene Alkoxy Carbamate Self-Immolative Unit: Utilization for the Targeted Delivery of Alcohol-Containing Payloads with Antibody-Drug Conjugates*, 55 Angew. Chem. Int. Ed. 7948–51 (2016).

[13] Burke et al., *Development of Novel Quaternary Ammonium Linkers for Antibody-Drug Conjugates*, 15 Mol. Cancer Therapeutics 1–9 (2016).

there is interdependency in the chemistry between ADC components. This interdependency means the POSA must make careful choices about all components of the claimed ADCs (antibody, amino acid unit, spacer, and drug moiety)." Ex. 1132 ¶ 51 (footnote omitted) (referencing Ex. 1102 at 101:21–102:15).

Dr. Bertozzi states that

> a POSA would have understood that a "handle" may be added to many drugs lacking any of these available functional groups to allow them to be joined to a linker in an ADC. This "handle" could be any of the functional groups I mentioned above, including an amine group, an alcohol group, or a thiol group. Dr. Lambert himself described how his research team modified maytansine to include a chemical handle for attachment in an ADC. (*See* Ex. 1002 at ¶ 44; Ex. 1041 at 300.) The addition of this handle would allow the drug compound to be used in an ADC by applying traditional organic chemistry reactions.

Ex. 2058 ¶ 115. Dr. Bertozzi states that "[b]y 2004, scientists, including the inventors of the '039 patent, had successfully made ADCs with many different types of drugs using these known chemistries." *Id.* ¶ 116. Dr. Bertozzi states that a "POSA would have been aware of these existing conjugates and understood how to apply the chemistry from these successes to other drug moieties." *Id.*

Dr. Bertozzi states that "Dr. Senter demonstrated in 1989 that a drug called mitomycin C (MMC) could be covalently linked to monoclonal antibodies via polyglutamic acid (PGA). (Ex. 2083.) That article discloses chemistry for attaching MMC to carboxyl groups on PGA through aziridinyl amide bonds. (Ex. 2083 at 202-203.)" Ex. 2058 ¶ 117. Dr. Bertozzi also identifies

> a seminal study describing antibody-doxorubicin conjugates linked the drug to antibodies in three different ways: "(1)

> carbodiimide coupling of the doxorubicin amine to antibody carboxyl groups, (2) oxidative cleavage of the carbohydrate moiety of doxorubicin with periodate followed by covalent coupling to antibody amino groups, (3) and glutaraldehyde crosslinking, presumably through the doxorubicin amino group."

Id. ¶ 118 (citing Ex. 2084). However, Ex. 2084[14] also notes that "semicarbazone and thiosemicarbazone conjugates were stable under acidic conditions, and consequently were much less cytotoxic. The hydrazine carboxylate conjugate was unstable even at pH 7.4 and was therefore unsuitable for selective drug delivery." Ex. 2084, 6. Ex. 2084 states that "pronounced therapeutic activities can be obtained with Mab-doxorubicin conjugates, and that the mode of drug attachment is a critical factor in achieving these effects." *Id*. at 7. Ex. 2084 states that "BR96-DOX [doxorubicin] failed in the clinical evaluation." *Id*. at 11.

Dr. Bertozzi states:

> Dubowchik 1998 . . . discloses use of paclitaxel in ADCs and further discloses that linkers can be attached to a variety of locations on a drug. For example, the authors attached the R-Phe-Lys-PABC fragment to two different alcohol groups on paclitaxel that have different steric environments and found that drugs such as doxorubicin, paclitaxel, and mitomycin C would be good candidates for extracellularly-stable drug-linker combinations for targeted drug delivery. (Ex. 2028 at 3351.)

Ex. 2058 ¶ 119. Dr. Bertozzi also states another Dubowchik publication "teaches synthetic routes to attach linkers with peptide units to drugs such as doxorubicin. (Ex. 2027 at 3341.) There, the authors even noted that the drug-

[14] Hellström et al., *Development and Activities of the BR96-Doxorubicin Immunoconjugate*, in Methods in Molecular Biology, Vol. 166: Immunotoxin Methods and Protocols (Walter A. Hall, Ed., 2001).

linkers were prepared "for the most part using modifications of methods well-known in peptide chemistry." (*Id*. at 3342.)" *Id*. Ex. 2028[15] recognizes "it is advantageous to be able to selectively deliver different classes of drugs, using various targeting vehicles, with a versatile mode of linkage." Ex. 2028 at 3347. However, Ex. 2028 also states that "[a]cid cleavable hydrazone linkers have been used successfully to target DOX by means of internalizing monoclonal antibodies but are inapplicable to most other classes of drugs. Lysosomally-cleavable tetrapeptides have been employed, but these are generally slow-releasing and hydrophobic." *Id*. (footnote omitted).

Dr. Bertozzi states:

> Walker 2002 . . . discloses the use of camptothecins as a drug class for ADCs. This article includes general chemical synthesis routes to attach a drug such as camptothecin to the tumor-recognizing antibody BR96 via a protease-cleavable linker. (Ex. 2020.) In describing their work, the authors note that "standard peptide synthetic chemistry was used to assemble the linker" and provided chemical synthesis routes for attaching camptothecin to a spacer moiety. (*Id*. at 218.)

Ex. 2058 ¶ 120. Dr. Bertozzi notes the article discusses "how to attach a spacer unit to the aliphatic alcohol group of a camptothecin" and therefore "by 2004, the POSA would have known how to attach protease-cleavable linkers to alcohol containing drugs using routine chemistry as disclosed by Walker 2002." *Id*.

Dr. Bertozzi states that "Chari 1992, a publication cited in the '039 patent from Dr. Lambert's own research group at Immunogen, describes

[15] Dubowchik et al., *Cathepsin B-sensitive dipeptide prodrugs. 2. Models of anticancer drugs paclitaxel (taxol®), mitomycin c and doxorubicin*, 8 Bioorganic & Medicinal Chem. Letters 3347–52 (1998).

how to synthesize the DM1 derivative for use as an ADC drug moiety from the naturally occurring maytansine. (Ex. 1001 at 3:44-48 *citing* Ex. 2031.)" Ex. 2058 ¶ 121. Dr. Bertozzi states:

> This process involved replacing an existing ether functional group in maytansine by reducing maytansine to an alcohol (maytansinol) then attaching a thiol functional group for linkage in an ADC. Thus, by 1992—over 12 years before the priority date of the '039 patent—a POSA would have also known how to attach linkers to drugs with a thiol functional group.

Id. However, Ex. 2031[16] also states that "[n]umerous attempts to target tumors with conventional antineoplastic drugs conjugated to monoclonal antibodies have met with limited success." Ex. 2031 at 127. Ex. 2031 identifies problems in ADCs including "most linkers that have been used for the conjugation of drugs to antibodies . . . do not efficiently release active drug inside the cell." *Id*. Ex. 2031 teaches a "conjugating linkage is a disulfide bond" and "[t]o obtain a highly cytotoxic drug that has a thiol 'handle,' we have synthesized a new maytansinoid." *Id*. at 128.

Dr. Bertozzi states that

> persons of ordinary skill in the art did not view ADC technology as limited to the particular drug being conjugated. To the contrary, ADC technology was seen as modular, making use of any given linker to attach a desired drug to an antibody targeting a desired antigen. This is further exemplified by various publications that existed prior to 2004 showing that the same linker can be attached to different drugs.

Ex. 2058 ¶ 122. Dr. Bertozzi lists drugs with the location of possible linker attachments identified. *See id*. ¶ 123.

[16] Chari et al., *Immunoconjugates Containing Novel Maytansinoids: Promising Anticancer Drugs*, 52 Cancer Res. 127–31 (1992).

We find Dr. Lambert more persuasive in demonstrating significant unpredictability in attaching drugs and linker where the scope of enablement concern broadly encompasses the attachment of any known drug to the linker composition recited in the claims of the '039 patent. Several of Dr. Bertozzi's cited references support the unpredictability of linking drugs, as Ex. 2028 states that "[a]cid cleavable hydrazone linkers have been used successfully to target DOX by means of internalizing monoclonal antibodies but are inapplicable to most other classes of drugs. Lysosomally-cleavable tetrapeptides have been employed, but these are generally slow-releasing and hydrophobic." Ex. 2028 at 3347. Similarly, Ex. 2031 also states that "[n]umerous attempts to target tumors with conventional antineoplastic drugs conjugated to monoclonal antibodies have met with limited success." Ex. 2031 at 127.

The unpredictability of drug attachment to linkers is highlighted by a comparison of Dr. Bertozzi's cited prior art for antibody attachment to linkers versus drug attachment to linkers. When antibodies are being attached (*see, e.g.*, Ex. 2020 at 218, Ex. 2083 at 202, Ex. 2031 at 127) the references provide no structure information of the antibody. In contrast, in Ex. 2028, while the reference discusses selective delivery with antibodies (*see, e.g.*, Ex. 2028 at 3347), the reference does not feel the need to disclose how an antibody would be attached to the linker-drug composition but does show three schemes for attachment of paclitaxel, mitomycin C and doxorubicin to linkers. *See* Ex. 2028 at 3347–48.

We further note that while Dr. Bertozzi provided references showing the attachment of a small number of drug compounds to a small number of linkers, the '039 patent reasonably encompasses any drug compound

whatsoever, and certainly encompasses the very large number of compounds recited in columns 31–34, for most of which no specific method of attachment to a linker was demonstrated as predictably provided in the prior art. We are therefore persuaded by Dr. Lambert that conjugation of drug compounds with linkers is unpredictable because "ADCs are not mix-and-match, and the POSA would have understood that, for example, ADCs with certain drugs would have different properties that may make them incompatible with the tetrapeptide linkers recited in Claim 1." Ex. 1002 ¶ 142.

We also note that Patent Owner's expert Dr. Bertozzi relies on Senter to show guidance on ADCs for the '039 patent, but Senter was not specifically incorporated by reference. "To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents." *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000).

We find that a preponderance of the evidence shows that the scope of the claims of the '039 patent regarding drugs and linkers is very unpredictable and that the art does not resolve this unpredictability.

f. Quantity of Experimentation

Dr. Lambert states:

> As recent reviews of the field explain, "chemistries and linker designs coupled with DAR load greatly affect plasma stability, biophysical properties, and consequently pharmacokinetics of the conjugate." (*See, e.g.*, Ex. 1047 at 2.) In light of these complicated and unpredictable interactions, scientists cannot identify, *a priori*, which combinations of drugs, linkers, and DARs will be useful in a given case. Making empirical

> determinations via trial-and-error experimentation is critical. (*See, e.g.*, Ex. 1040 at 1016.)

Ex. 1002 ¶ 37. Ex. 1040[17] explains that "[m]uch of the selection of the optimal antibody, the ideal linker–payload chemistry, and the optimal number of payload molecules linked per antibody molecule, are determined empirically, with a focus on maximizing the therapeutic index of the ADC." Ex. 1040, 1016.

Dr. Lambert states that "[t]esting is required to evaluate whether the broadly claimed ADCs are stable enough to prevent cleavage in the microenvironment of a diseased tissue in a patient, yet capable of intracellular cleavage after cellular internalization." Ex. 1002 ¶ 150. Dr. Lambert states that in an "*in vitro* ADC cleavage study—which lacked many of the complicating factors found *in vivo*—the results demonstrated that different cell lines produced different results." *Id.* ¶ 152. Dr. Lambert states:

> These *in vitro* experiments were painstakingly difficult, required utilization of radiolabeled drug moieties, and generated different answers as to how our triglycyl linker-ADC was cleaved. Performing these tests to determine whether ADCs that otherwise satisfy the limitations of the claims meet the functional Intracellular Cleavage Limitation would be both impossible to do routinely (given the difficulty of conducting the tests and the scope of the claim) and inadequate (because different cell lines produce different results, and these *in vitro* tests do not reflect what intracellular cleavage occurs in a patient, per the claims' requirement).

Id. Dr. Lambert states:

> The carbamate chemistry disclosed in the '039 patent for linking a PAB group to the N-terminal amine of an auristatin could not

[17] Lambert et al., *Antibody-Drug Conjugates (ADCs) for Personalized Treatment of Solid Tumors: A Review*, 34 Adv. Ther. 1015–35 (2017).

> be adapted as of the alleged priority date to various other linkers or drug moieties without undue experimentation, as the chemistry for doing so was unknown to the POSA and required an enormous amount of effort and ingenuity to develop over the ensuing years (and it remains unknown how to attach many drug moieties to many linkers to create ADCs).

Ex. 1132 ¶ 18.

Dr. Bertozzi states that

> persons of ordinary skill in the art did not view ADC technology as limited to the particular drug being conjugated. To the contrary, ADC technology was seen as modular, making use of any given linker to attach a desired drug to an antibody targeting a desired antigen. This is further exemplified by various publications that existed prior to 2004 showing that the same linker can be attached to different drugs.

Ex. 2058 ¶ 122.

Dr. Bertozzi states that an ordinary artisan in 2004 would have "understood that a 'handle' can be added to many drugs lacking these convenient functional groups to allow them to be joined to a linker in an ADC. This 'handle' could be any of the functional groups I mentioned above, including an amine group or an alcohol group." Ex. 2058 ¶ 129. Dr. Bertozzi states that "as of 2004, a POSA seeking to attach a particular drug to a linker for an ADC had a readily available and well established toolkit to make the claimed ADCs." *Id.* ¶ 130.

We find Dr. Lambert more persuasive in demonstrating that a large quantity of experimentation is required to create any particular antibody-drug conjugate while retaining intracellular cleavage as required by the claims of the '039 patent.

We find that a preponderance of the evidence shows that the quantity of experimentation to enable the full scope of the claims of the '039 patent

would be very large, likely requiring decades of research by multiple research groups. Dr. Lambert persuasively explains that ADC development in one instance "required an enormous amount of effort and ingenuity to develop over the ensuing years (and it remains unknown how to attach many drug moieties to many linkers to create ADCs)." Ex. 1132 ¶ 18. And while Dr. Bertozzi states that there is a "well established toolkit," no specific review article was provided that identifies such a toolkit widely available to the large number of drug moieties recited in the '039 patent specification, much less the larger number of drug moieties that exist in the prior art. Rather, Dr. Bertozzi points to a variety of particular drugs and particular linkers that were developed and characterized in particular papers and extrapolates a toolkit from these papers. *See* Ex. 2058 ¶¶ 93–122.

Dr. Bertozzi pointed to Ex. 1041 to show the predictability by which Dr. Lambert could attach a "handle" to a drug moiety. *See* Ex. 2058 ¶ 115. However, Ex. 1041[18] notes that over a period of "twenty years, a large number of conjugates have been prepared with a variety of cytotoxic organic compounds . . . [w]hen tested on cultured cells, virtually all these conjugates were found to be less potent than the non-conjugated drugs. Also, no cytotoxic selectivity could be demonstrated towards antigen-expressing cells." Ex. 1041 at 292. Ex. 1041 states that "[t]o date, at least four types of highly cytotoxic drugs [] have been conjugated to monoclonal antibodies." Ex. 1041 at 298. Four types out of the many recited in the '039 patent specification. *See* Ex. 1001, 31:39–34:49.

[18] Goldmacher et al., *Immunotoxins and antibody-drug conjugates for cancer treatment*, in Biomedical Aspects of Drug Targeting (Muzykantov et al. (eds.) 2002).

We find that a preponderance of the evidence shows that the quantity of experimentation necessary to create antibody-drug conjugates is high with years and significant inventive research required.

4. *Analysis*

The facts here are consistent with the situation in *Amgen*, which addressed a situation where the claimed "class of antibodies does not include just the 26 that Amgen has described by their amino acid sequences, but a 'vast' number of additional antibodies that it has not." *Amgen*, 598 U.S. at 613. The description in the instant '039 patent describes two drug classes (and no linkers within the scope of the claims) while encompassing a vast number of additional drugs that are not described. *See* Ex. 1001, 31:39–34:49. And, just as the Court in *Amgen* found, a description that leaves readers of the '039 patent to "random trial-and-error discovery," the evidence here also shows trial and error discovery where "[m]uch of the selection of the optimal antibody, the ideal linker–payload chemistry, and the optimal number of payload molecules linked per antibody molecule, are determined empirically." Ex. 1040, 1016; *Amgen*, 598 US at 615.

Considering the *Wands* factors as a whole, we find that the large breadth of the claims, absence of working examples, limited amount of direction and guidance provided by the '039 patent, unpredictability in synthesizing antibody-drug linker conjugates, and extensive quantity of experimentation are balanced against a high level of skill in the art and predictability in testing generated antibody-drug conjugates for intracellular cleavage. Based on our consideration of the entirety of the evidence, we find that a preponderance of the evidence supports the conclusion that undue

experimentation would have been required to make and use the invention commensurate in scope with the claims of the '039 patent.

VII. GROUND 3 – SUBJECT MATTER OF THE INVENTION

A. Principles of Law

"[A] patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898 (2014). "Where it would be apparent to one of skill in the art, based on the specification, that the invention set forth in a claim is not what the patentee regarded as his invention, we must hold that claim invalid under § 112, paragraph 2." *Allen Eng'g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1348–49 (Fed. Cir. 2002).

B. Claim 1

1. *Petitioner's position*

Petitioner asserts that "[t]he claims of a patent must set forth 'the subject matter which the inventor or a joint inventor regards as the invention.' 35 U.S.C. § 112(b)." Pet. 63. Petitioner asserts "[t]his requirement of 35 U.S.C. § 112(b) (previously § 112 ¶ 2) is separate from its definiteness requirement. *See, e.g.*, *Allen Eng'g*." *Id.*, footnote 21. Petitioner asserts "[t]hat the named inventors regarded their inventions as necessarily comprising dolastatin/auristatin derivatives is plain from (i) the '039 Patent's specification, (ii) expert testimony regarding the understandings of the POSA, and (iii) PO's related prosecution efforts." *Id.* at 63–64. Petitioner asserts that "[e]ach of the three categories of 'compounds of the invention'

described in the specification include dolastatin/auristatin drug moieties." *Id.* at 64. Petitioner asserts that the

> dolastatin/auristatin-focused nature of PO's purported inventions is further apparent from the fact that one of the patents that issued from an application to which the '039 Patent claims priority (and with which the '039 Patent shares its specification) contains claims that are directed to dolastatin/auristatin derivatives outside the context of ADCs. (Ex. 1073 at Claims.)

Id.

2. *Patent Owner's position*

Patent Owner asserts "[r]epackaging its written description arguments, Petitioner contends that the '039 patent claims are unpatentable for a supposedly additional reason: that the claims fail to set forth 'the subject matter which the inventor or a joint inventor regards as the invention.'" Resp. 78. Patent Owner asserts that the "Supreme Court's recent interpretation of 35 U.S.C. § 112(b) raises doubts about whether the "regards as the invention" portion of the statute is a requirement separate from that of definiteness. *See Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 902 (2014)." *Id*. Patent Owner asserts "unlike *Allen Eng'g*, in which the claims and the specification were in stark misalignment (with the claims reciting pivoting in a perpendicular plane and the specification stating that the rotation *cannot* be perpendicular), Petitioner provides nothing from the intrinsic evidence to support such a misalignment here." *Id*.

3. *Analysis*

We find that whether or not, after *Nautilus*, there remains a requirement that the claims must set forth the invention, the instant facts as applied under *Allen* do not support a finding that the instant claims fail to do so.

In *Allen*, the issue involved a fast steering motorized riding trowel for finishing a concrete surface. *Allen*, 299 F.3d at 1343. The trowel had a blade to contact the surface that was rotated using a gearbox. *Id*. Allen explained that claims 1–4 and 13 of the patent limited the "pivoting 'its gear box *only* in a plane *perpendicular* to said biaxial plane.'" *Id*. at 1349 (emphasis in original). Allen states that "the specification describes this structure in contrary terms, stating that 'rotation about the axis established by bolt 272 is not permitted; gearbox 85A *cannot* pivot in a plane *perpendicular to* the biaxial plane.'" *Id*. (emphasis in original). Based upon this contradiction, the Allen court held that the claims were indefinite. *Id*.

Unlike *Allen*, Petitioner does not identify any contradictory statement in the instant Specification teaching away from, or suggesting the undesirability of using drugs other than dolastatin/auristatin derivatives in ADC constructs. Rather, Petitioner asserts that a Specification that recites an extensive list of other drugs may not rely upon this list for breadth because there was no example or statement that selection of such other drugs was preferred. We find this argument unpersuasive, as the term "drug moiety" would be understood by the person of ordinary skill reading the Specification to encompass the extensive list of other drugs for the reasons discussed above in the written description analysis section.

In sum, after reviewing the record, we agree with Patent Owner that a preponderance of the evidence shows the claims of the '039 patent set forth the subject matter which the inventor regards as the invention.

VIII. GROUND 4 – ANTICIPATION

A. Principles of Law

A claim is anticipated if a single prior art reference either expressly or inherently discloses every limitation of the claim. *Orion IP, LLC v. Hyundai Motor Am.*, 605 F.3d 967, 975 (Fed. Cir. 2010). "A single prior art reference may anticipate without disclosing a feature of the claimed invention if such feature is necessarily present, or inherent, in that reference." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 958 (Fed. Cir. 2014) (citing *Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003)).

B. Claims

1. *Petitioner's position*

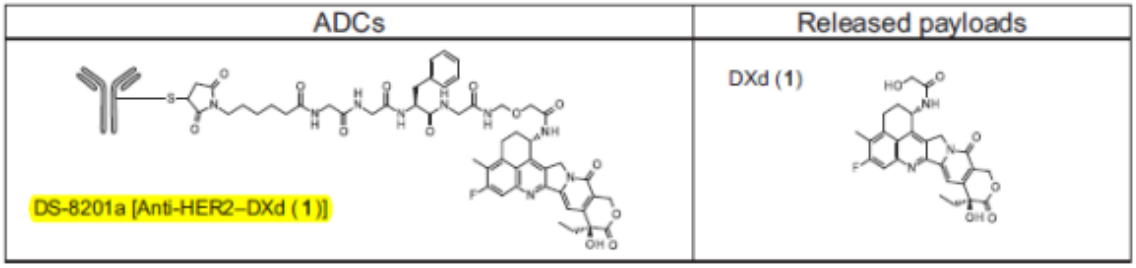
Petitioner states that "PO asserted the '039 Patent against Daiichi Sankyo Japan in the U.S. District Court for the Eastern District of Texas, alleging that Enhertu® (DS-8201) falls within the scope of the claims of the '039 Patent. (*See* Ex. 1006 ¶ 4.)" Pet. 65. Petitioner asserts that assuming DS-8201 "falls within the scope of the '039 Patent's claims as SGI argues in that district court action, those claims would be anticipated." *Id.*

Petitioner asserts that in 2015 "Dr. Yuki Abe publicly disclosed the chemical structure and preclinical use of DS-8201 with skilled artisans at the Antibody Engineering & Therapeutics Conference, an annual meeting of the Antibody Society held in San Diego, California. (Ex. 1034; Ex. 1035 at 10 (Track C at 4:45), 22 (ND2).)" Pet. 66–67. Petitioner also asserts that

> Daiichi Sankyo authors Yusuke Ogitani et al. submitted a scientific journal article regarding DS-8201 titled "Bystander killing effect of DS-8201a, a novel anti-human epidermal growth factor receptor 2 antibody-drug conjugate, in tumors with human epidermal growth factor receptor 2 heterogeneity" in Cancer Science. This article published electronically on June 22, 2016,

> and in print in July 2016. (Ex. 1009.) Therefore it qualifies as prior art to the '039 Patent under 35 U.S.C. § 102(a)(1).

Id. at 67–68. Petitioner states that the "*DS Cancer Sci Article* discloses the structure of DS-8201, an ADC also known as DS-8201a (Ex. 1002 ¶ 159 n.24):



(Ex. 1009 at 1041 (emphasis added).)" *Id*. at 68. Petitioner asserts that "[Patent Owner]'s infringement allegations replicate the structure of DS-8201 and assert that it meets each limitation of at least Claims 1–4 of the '039 Patent." *Id*. Petitioner cites to a claim chart prepared for the Enhertu® District Court litigation that compares each of the claimed elements to DS-8201, showing that each element of each of claims 1–4 of the '039 Patent are satisfied. *See Id*. 69–70. Petitioner further explains how the *DS Cancer Sci Article*, satisfies the respective requirements of claims 5, 9, and 10 that "p is about 8," "wherein the antibody is monoclonal antibody," and "wherein the antibody is a humanized monoclonal antibody." *See id*. 71–72.

2. *Patent Owner's position*

Patent Owner asserts that "Petitioner's contention that the challenged claims are anticipated by Daiichi Sankyo's 2016 *Cancer Science* Publication also fails. (Pet. at 4, 65-72.) First, Petitioner's argument that the challenged claims 'are not entitled to any priority date before the filing of the July 2019 application' is meritless for reasons discussed above." Resp. 79. Patent Owner asserts that "[s]econd, Petitioner has failed to meet its evidentiary

burden to prove anticipation. Petitioner bears the burden of proving unpatentability of the challenged claims, and the burden of persuasion never shifts to the patent owner." *Id*. Patent Owner asserts,

> Petitioner and its expert Dr. Lambert do not describe where each element of the claims is found in the relied-upon prior art. (*See, e.g.*, Ex. 1002 at 5, 98 (describing his limited analysis of the asserted prior art.)) Instead, Petitioner relies solely on Seagen's infringement allegations in the Texas Litigation. . . . Petitioner's citation to Seagen's infringement contentions to support conclusory statements not otherwise supported in the Petition does not satisfy Petitioner's burden of proof.

Id. 78–80.

3. *Expert's views on anticipation*

a. Dr. Lambert

Dr. Lambert states:

> I have reviewed Exhibit 1009, Ogitani et al, *Cancer Sci*, 107 (7) 1039–46 to address two questions posed to me by counsel. First, I have been asked whether DS-8201a, an ADC disclosed in Exhibit 1009, contains a "monoclonal antibody" and a "humanized antibody." The answer is yes, for the following reasons. Exhibit 1009 states DS-8201a is "composed of a humanized anti-HER2 antibody" and that the antibody in DS-8201a is "the anti-HER2 Ab produced with reference to the same amino acid sequence of trastuzumab." (Ex. 1009 at 1039–40.) The POSA would understand this article as stating that the anti-HER2 antibody in DS-8201a is trastuzumab.

Ex. 1002 ¶¶ 158–160. Dr. Lambert states that "[t]o obtain a DAR of 'approximately 7 to 8,' the POSA would have recognized that the sample must contain molecules of DS-8201a in which there are eight linker-drug structures conjugated to an antibody in order for the average for the sample to be 'approximately 7 to 8.'" *Id*. ¶ 163. Dr. Lambert states that "the POSA

would have understood that the DS-8201a composition described in Exhibit 1009 contains ADCs in which the 'p is about 8.'" *Id*.

b. Dr. Bertozzi

Dr. Bertozzi does not appear to address the anticipation issue in her Declaration or in her deposition. *See* Ex. 2058 and Ex. 1102 *generally*.

4. *Analysis*

We again note that in the priority analysis above, we found that the claims are not entitled to benefit to the priority applications. Thus, prior art encompasses any reference published prior to the filing date of July 10, 2019 of the '039 patent.

We find that Petitioner has provided a detailed analysis comparing the limitations of the claims of the '039 patent with the disclosure in Ogitani. *See* Pet. 68–72; Ex. 1009, 1041. The first structure recited in Figure 1 of Ogitani shows an ADC that is composed of an antibody, a linker, and a drug within the express scope of the claims of the '039 patent as explained in the Petition and by Dr. Lambert. *See* Pet. 68–72. Ex. 1002 ¶¶ 158–162.

Patent Owner does not identify any flaw in Petitioner's analysis, but rather appears to suggest that Petitioner is not allowed to copy Patent Owner's infringement contentions to establish anticipation. *See* Resp. 78–80. Patent Owner does not, however, identify any rule of law or reason that would not allow a previously existing comparison of claims and prior art to be used by Petitioner.

In sum, after reviewing the record, we agree with Petitioner that a preponderance of the evidence shows 1–5, 9, and 10 of the '039 patent are unpatentable as anticipated by Ogitani (Ex. 1009).

III. CONCLUSION

After considering the evidence and arguments presently before us in the complete trial record, we conclude that Petitioner has demonstrated, by a preponderance of the evidence, that Challenged Claims 1–5, 9, and 10 of the '039 patent are unpatentable.[19]

[19] Should Patent Owner wish to pursue amendment of the Challenged Claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner's attention to the April 2019 Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding, 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. §§ 42.8(a)(3), (b)(2).

In summary:

Claim(s)	35 U.S.C. §	Reference(s)/Basis	Claim(s) Shown Unpatentable	Claim(s) Not shown Unpatentable
1–5, 9, 10	112(a)	Written Description	1–5, 9, 10	
1–5, 9, 10	112(a)	Enablement	1–5, 9, 10	
1–5, 9, 10	112(b)	Subject Matter of the Invention		1–5, 9, 10
1–5, 9, 10	102	Ogitani	1–5, 9, 10	
Overall Outcome			1–5, 9, 10	

IV. ORDER

In consideration of the foregoing, it is:

ORDERED that claims 1–5, 9, and 10 of U.S. Patent 10,808,039 B2 are determined to be unpatentable; and

FURTHER ORDERED that, because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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