

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SYNAFFIX B.V.,
Petitioner,

v.

HANGZHOU DAC BIOTECH CO., LTD.,
Patent Owner.

IPR2022-01531
Patent 10,131,682 C1

Before ZHENYU YANG, DEVON ZASTROW NEWMAN, and CYNTHIA
M. HARDMAN, *Administrative Patent Judges*.

NEWMAN, *Administrative Patent Judge*.

DECISION

Granting Institution of *Inter Partes* Review on Remand
35 U.S.C. § 314, 37 C.F.R. § 42.4

I. INTRODUCTION

A. Background and Summary

Synaffix B.V. (“Petitioner”) filed a Petition (Paper 2, “Pet.”) requesting institution of *inter partes* review of claims 1–17, 20–21, 24–26, and 29–34 (“the challenged claims”) of U.S. Patent No. 10,131,682 C1 (Exs. 1001, 1002 (reexamination), “the ’682 patent”). Hangzhou DAC Biotech Co., Ltd. (“Patent Owner”) filed a Preliminary Response (Paper 9, “Prelim. Resp.”). With authorization (Paper 10), Petitioner filed Petitioner’s Preliminary Reply to Patent Owner’s Preliminary Response (Paper 11, “Pet. Prelim. Reply”) and Petitioner’s Brief in Response to Patent Owner’s Preliminary Sur-Reply (Paper 15, “Pet. Resp. Brief”), and Patent Owner filed Patent Owner’s Pre-Institution Sur-Reply (Paper 14, “PO Sur-reply”) and Patent Owner’s Pre-Institution Response to Petitioner’s Brief (Paper 16, “PO Resp. Brief”).

Previously, we determined that the information presented in the Petition did not establish a reasonable likelihood that Petitioner would prevail with respect to at least one of the challenged claims, and did not institute *inter partes* review. Paper 17 (“Inst. Dec.”). Petitioner requested Director review of our decision denying institution (Paper 18 (“Request”)). The Director delegated review of the decision to a Delegated Rehearing Panel. Paper 19. Patent Owner was granted the option to file a response to Petitioner’s Request (Paper 22 (“Request Resp.”)). The Director Review Panel (“DRP”) vacated our decision and remanded the case to this panel with a revised construction for claim 1. Paper 23 (“DRP Dec.”).

An *inter partes* review may be instituted only if “the information presented in the petition . . . and any [preliminary] response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect

to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a) (2018). Upon reconsideration of the briefing and the evidence of record in light of the DRP’s claim construction, we conclude that Petitioner has established a reasonable likelihood of prevailing on its assertion that at least one of the challenged claims is unpatentable. Accordingly, we grant institution of *inter partes* review of claims 1–17, 20–21, 24–26, and 29–34 of the ’682 patent.

B. Real Parties in Interest

Petitioner states that the “real-parties-in-interest are Petitioner, Synaffix B.V., and Lonza Group, AG, which recently acquired Synaffix.” Paper 12, 2¹ (Updated Mandatory Notices).

Patent Owner states that it is the real party-in-interest and the assignee of the ’682 patent. Paper 8, 1.²

C. Related Matters

Petitioner states that the ’682 patent was “re-examined as Reexamination Control Number 90/014,390, yielding, *inter alia*, amended claims 1, 3, 20, and new claims 24-26 and 29-34.” Pet. 1.

Patent Owner lists the following related matters: U.S. Patent No. 10,131,682 issued from U.S. Patent Application No. 14/432,073, filed on March 27, 2015, which is a U.S. National Stage of International Application No. PCT/IB2012/056700, filed on November 24, 2012; and U.S. Application No. 90/014,390, filed on October 16, 2019, which is a reexamination of U.S. Patent No. 10,131,682. Paper 8, 1.

¹ Paper 12 is not paginated. We reference the pages therein as if Paper 12 had been paginated beginning at the first page after the cover sheet.

² Paper 8 is not paginated. We reference the pages therein as if Paper 8 had been paginated beginning at the first page after the cover sheet.

D. The '682 Patent (Ex. 1001)

1. Specification Overview

The '682 patent is titled “Hydrophilic Linkers and Their Uses for Conjugation of Drugs to Cell Binding Molecules” and issued from U.S. Application No. 14/432,073 (the '073 Application), a national stage entry of PCT/IB2012/056700 that was filed on November 24, 2012. Ex. 1001, codes (54), (10), (21), (86), and (22).

The '682 patent regards protein/drug conjugates for targeted delivery of drugs to specific cells. Ex. 1001, code (57, Abstract). The Specification discloses that

the use of the cell binding molecule – drug conjugates, such as antibody-drug conjugates (ADCs) with cancers has been limited by the availability of specific targeting agents (carriers) and of conjugation methodologies, which can result in undesirable aggregation of the protein at the higher levels of drug loading required for cancer treatment.

Id. at 2:25–29. The Specification states that “[n]ormally the tendency for cytotoxic drug conjugates to aggregate is especially problematic when the conjugation reactions are performed with hydrophilic linkers.” *Id.* at 2:33–36. Moreover, “higher drug loading increases the inherent potency of the conjugate,” making it desirable to have “as much drug loaded on the carrier” as possible while maintaining binding ability to the protein. *Id.* at 1:37–39.

The '682 patent discloses “hydrophilic linkers containing phosphinate, sulfonyl, and/or sulfoxide groups to link drugs to a cell-binding agent (e.g., an antibody).” Ex. 1001, 2:53–55. The Specification discloses that the hydrophilic linkers containing these specific groups confer the following advantageous hydrophilic properties to the cell binding molecule-drug conjugates: reduced aggregation in water-based media, enabling higher

drug-per-cell binding to molecule ratio, permitting higher potency, and increased drug retention in the target cell after the drug is released from the conjugate. *Id.* at 2:60–65.

Using these hydrophilic linkers, the Specification discloses antibody-drug conjugates with the preferred formula “Cb-(-L-Drug)_n, wherein Cb is a cell-binding agent, L is a hydrophilic linker, Drug is a drug molecule and n is an integer from 1 to 20.” Ex. 1001, 2:55–60. The drug is a cytotoxic agent and is a “small molecule drug” identified in the Specification as “an organic, inorganic, or organometallic compound that may have a molecular weight of for example 100 to 1800, more suitably from 120 to 1400.” *Id.* at 29:46–50. The cell-binding agent “may be of any kind presently known, or that become[s] known, molecule that binds to, complexes with or reacts with a moiety of a cell population sought to be therapeutically or otherwise biologically modified.” *Id.* at 14:39–44. When an antibody is used as a cell-binding agent, this may permit immune-targeted delivery of the drug to a specific cell population, such as “cancer cell antigens, viral antigens, microbial antigens or a protein generated by the immune system that is capable of recognizing, binding to a specific antigen or exhibiting the desired biological activity.” *Id.* at 14:54–57.

Figure 6 discloses, *inter alia*, the synthesis of the linker of embodiment 55 of the Specification, copied below:

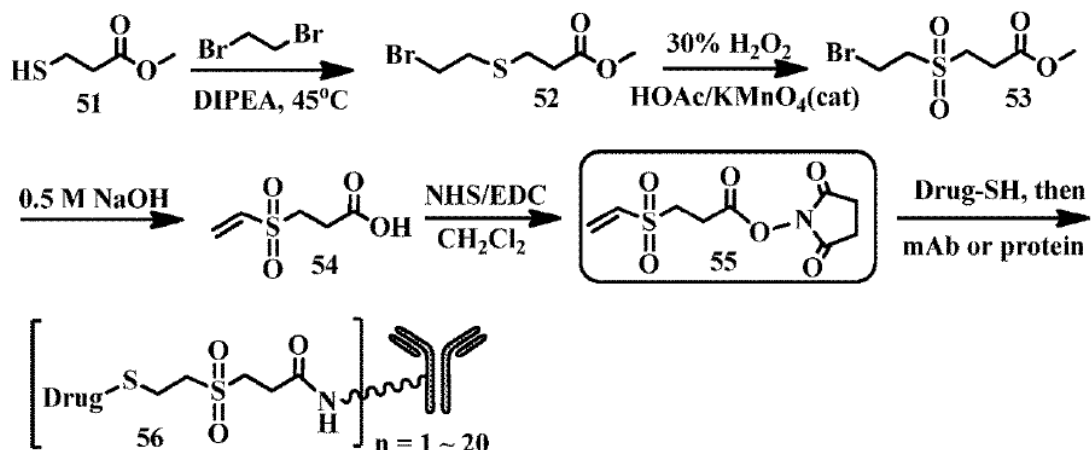


Fig. 6 (Ex. 1001, p. 12). The above figure shows a method of synthesis of embodiment 55 of the invention, which is a vinylsulfonyl linker. *Id.*

Figure 7 discloses, *inter alia*, the synthesis of the linker of embodiment 75 of the Specification, copied below:

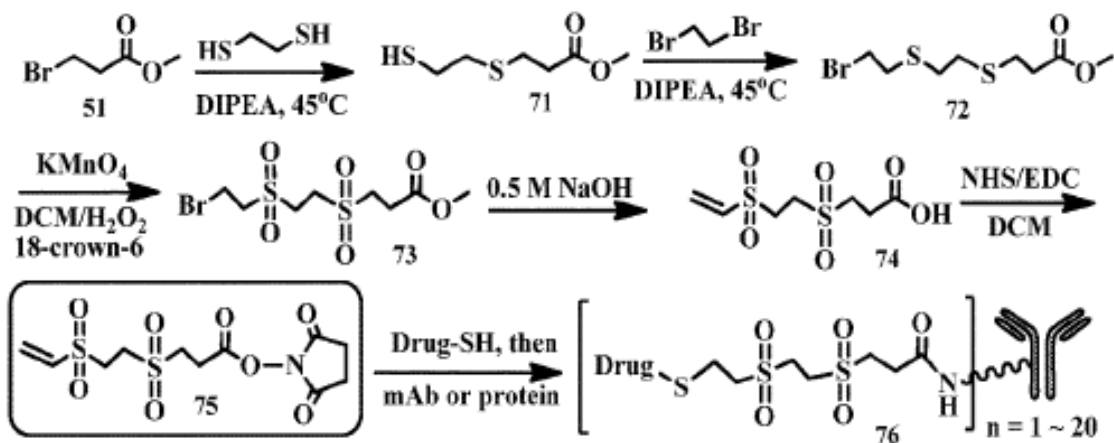


Fig. 7 (Ex. 1001, p. 13). The above figure shows a method of synthesis of embodiment 75 of the invention, which is a disulfonyl linker. *Id.*

Figure 8 discloses, *inter alia*, the synthesis of the linker of embodiment 99 of the Specification, copied below:

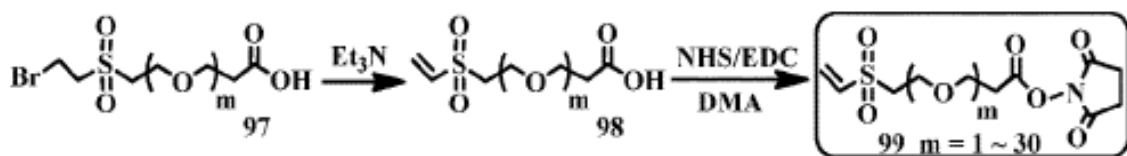


Fig. 8 (Ex. 1001, p. 12). The above figure shows a method of synthesis of embodiment 99 of the invention, which is a mono-sulfonyl linker containing polyethylene glycol. *Id.*

Figure 9 discloses, *inter alia*, the synthesis of the linker of embodiment 119 of the Specification, copied below:

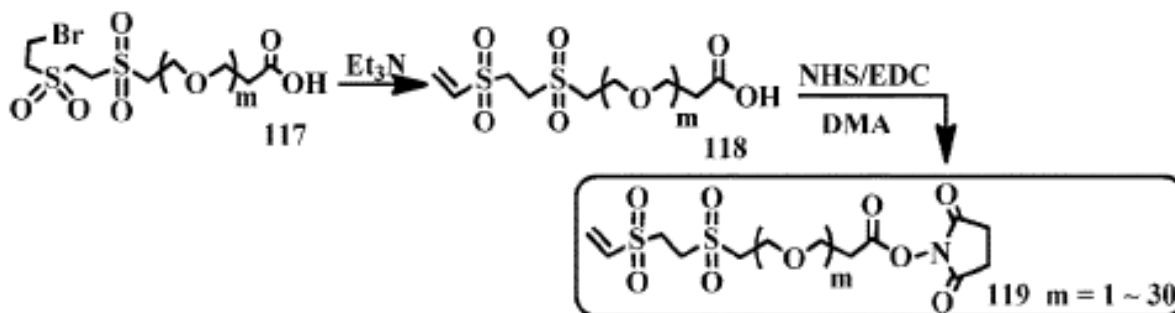


Fig. 9 (Ex. 1001, p. 15). The above figure shows a method of synthesis of embodiment 119 of the invention, which is a di-sulfonyl linker containing polyethylene glycol. *Id.*

Figure 10 discloses, *inter alia*, the synthesis of the linker of embodiment 138 of the Specification, copied below:

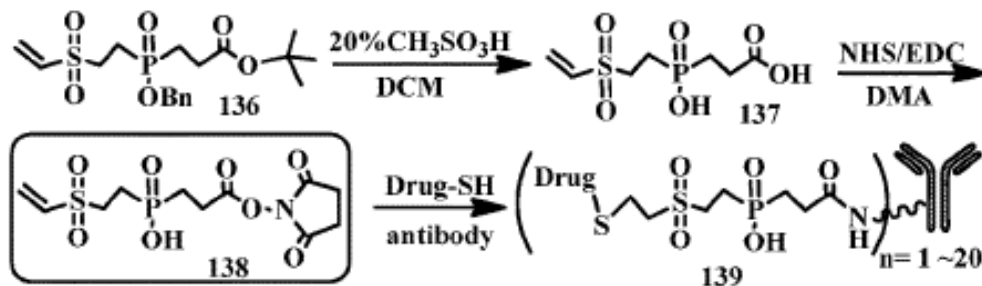
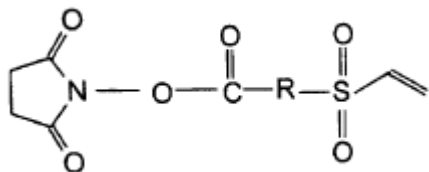


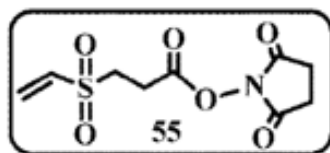
Fig. 10 (Ex. 1001, p. 15). The above figure shows a method of synthesis of embodiment 138 of the invention, which is a hydrophilic linker containing a phosphinic acid and a sulfonyl group. *Id.*

2. Relevant Prosecution History

During examination, the Examiner issued a rejection of claim 1 based on a disclosure in Lees³ of N-hydroxysuccinimide vinylsulfone, copied below.



The graphic above shows the structure of N-hydroxysuccinimide (“NHS”) vinylsulfone, as disclosed in Lees. Ex. 2026, 22. The Examiner found that Lees discloses NHS vinylsulfone as a heterobifunctional linker used to attach a derivatized polysaccharide to one end and a protein to the other. Ex. 1018, 42. The Examiner found that NHS vinylsulfone anticipated formula 55 of the Specification, shown below:



Id. at 42–43. Shown above is formula 55 of the Specification, which was encompassed by then-pending claim 1. Ex. 1001, Figure 6, p. 12.

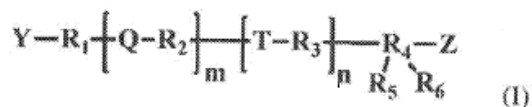
In response, Applicant (now Patent Owner) amended claim 1 as follows to overcome the rejection.⁴

³ Lees, Andrew, WO 97/41897, published November 13, 1997 (Ex. 2026, “Lees”).

⁴ Only the relevant portion of the amended claim (now claim 1) is shown.

LISTING OF CLAIMS:

1. (Currently Amended) A hydrophilic linker of formula (I)



wherein:

Y represents a functional group that enables reaction of the hydrophilic linker with a cell-binding agent;

Q and T are either -P(=O)(OM)-, or -S(O₂)-, or -S(O)-;

m and n are integer from 0 to 5, but not 0 at the same time; provided that when m=1, n=0,

Q is not -P(=O)(OM)-; and when n=1, m=0, T is not -P(=O)(OM)-; and when Q or T is -S(O₂)-, m and n are not 0;

Ex. 1018, 45. This amendment required that where claim elements Q or T were sulfone, m and n could be an integer from 1 to 5, not zero. *Id.* Moreover, Applicant stated that the amendment was made to overcome Lees. *Id.* at 62. (“[C]laim 1 of the present application recites that when Q or T is -S(O)₂-, m and n are not 0, thereby excluding the above noted compound described in Lees.”). *Id.* The Examiner subsequently allowed claim 1. *Id.* at 77.

3. Reexamination of '682 Patent

The '682 patent was reexamined and a reexamination certificate issued January 4, 2021. Ex. 1002, code (45).

E. Challenged Claims

Petitioner challenges the patentability of claims 1–17, 20–21, 24–26, and 29–34 (“challenged claims”) of the '682 patent.⁵ Pet. 1. The claims recite three types of linker structures that can be used to form antibody-drug conjugates, formulas I, II, and IV. These structures are shown in the table

⁵ All claims at issue were amended during reexamination, either directly or by dependency except claims 22–34, which were added during reexamination. Ex. 1002, 1:13–21.

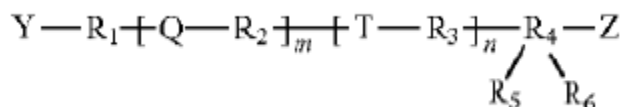
below along with the corresponding formula and the independent challenged claims that recite these structures:

Table 1		
Claim	Structure	Formula
1	$Y-R_1-Q-R_2-T-R_3-R_4-Z$ $\begin{matrix} \diagup & \diagdown \\ R_5 & R_6 \end{matrix}$	I
3, 24, 26	$Cb \left(R_1-Q-R_2-T-R_3-R_4-Drug \right)_q$ $\begin{matrix} \diagup & \diagdown \\ R_5 & R_6 \end{matrix}$	II
20, 29, 30	$Y-R_1-Q-R_2-T-R_3-R_4-Drug$ $\begin{matrix} \diagup & \diagdown \\ R_5 & R_6 \end{matrix}$	IV

Prelim. Resp. 5. The table above shows three types of linker structures, formula I, II, and IV, which can be used to form antibody-drug conjugates of the recited claims. *Id.*

Claim 1 of the '682 patent is representative. The text of claim 1 pertinent to the parties' dispute⁶ recites:

1. A hydrophilic linker of formula (I)



wherein:

Y represents a functional group that enables reaction of the hydrophilic linker with a cell-binding agent;

Q and T are either —P(=O)(OM)—, or —S(O₂)—, or —S(O);

⁶ The R groups are not central to the dispute in this matter. The full text of claim 1 is shown at Exhibit 1002, 1:22–2:14.

m and n are integers from 0 to 5, but not 0 at the same time;
provided that when m=1, n=0, Q is not —P(=O)(OM)-; when
n=1, m=0, T is not —P(=O)(OM)-; and when Q or T is —
S(O₂)—, m and n are not 0;

Z represents a functional group that enables linkage of the
hydrophilic linker to a cytotoxic drug via a disulfide, thioether,
thioester, hydrazone, ether, ester, carbamate, carbonate,
secondary, tertiary, or quaternary amine, imine,
cycloheteroalkane, heteroaromatic, alkoxime or amide bond; ...

Ex. 1002, 1:22–2:13. Claim 1 is directed to structures represented by
formula I, the basic hydrophilic linker. *Id.* Independent claims 3, 24, and 26
are directed to structures represented by formula II, wherein the linker is
conjugated to a cell-binding agent and a drug. *Id.* at 2:14–3:12; 6:30–7:21;
7:28–8:25. Independent claims 20, 29, and 30 are directed to formula IV,
wherein the linker is conjugated to a drug. *Id.* at 4:3–5:3; 9:55–12:19. The
challenged dependent claims recite additional structures or conjugates and
their qualities or recite pharmaceutical compositions containing the
structures. Ex. 1001, 49:10–55:29 (amended by dependency).

F. Prior Art and Asserted Grounds

Petitioner asserts that claims 1–17, 20–21, 24–26, and 29–34 are
unpatentable on the following grounds:

Ground	Claim(s) Challenged	35 U.S.C. § ⁷	Reference(s)/Basis
1	1–3, 6, 24, 25, 33	§ 102(a)	Morales-Sanfrutos ⁸

⁷ The Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112-29, 125 Stat. 284 (2011), amended 35 U.S.C. § 102 and § 103, effective March 16, 2013. Because the application from which the ’682 patent issued was filed before this date, the pre-AIA version of § 102/§ 103 applies. *See* Prelim. Resp. 5.

⁸ Julia Morales-Sanfrutos, et al., *Vinyl Sulfone Bifunctional Tag Reagents for Single-Point Modification of Proteins*, 75: J. ORG. CHEM., 4039–4047 (2010) (Ex. 1005, “Morales-Sanfrutos”).

Ground	Claim(s) Challenged	35 U.S.C. § ⁷	Reference(s)/Basis
			as evidenced by Straus ⁹
2	1, 20, 21, 29–31	§102(a)/ §103(a)	Harris ¹⁰
3	1–8, 10–12, 14–17, 20, 21, 24, 26, 29–31	§103(a)	Singh, ¹¹ Harris
4	9, 13	§103(a)	Singh, Harris, Bhakta ¹²
5	2, 25, 32–34	§103(a)	Singh, Harris, Snow ¹³

Petitioner supports its allegations with the declarations of Ravi Chari, Ph.D. (Ex. 1003), and James Mullins, Ph.D. (Ex. 1012). Patent Owner supports its allegations in opposition with the declaration of Lawrence Nathan Tumey, Ph.D. (Ex. 2001).

II. ANALYSIS

A. Our Original Decision

In our original Decision on institution, we considered the parties’ arguments regarding construction of the claim terms “Y,” “Z,” “Q,” and “T” and “whether Y or Z must act independently or whether they can act in

⁹ W. Straus et al., *Unusual binding sites for horseradish peroxidase on the surface of cultured and isolated mammalian cells: Suppression of binding by certain nucleotides and glycoproteins, and a role for calcium*, 85: HISTOCHEMISTRY 277–286 (1986) (Ex. 1006, “Straus”).

¹⁰ J. Milton Harris, WO 95/13312, published May 18, 1995 (Ex. 1007, “Harris”).

¹¹ Rajeeva Singh, et al., US 2010/0129314 A1, published May 27, 2010 (Ex. 1008, “Singh”).

¹² Sunil Bhakta et al., US 2011/0301334 A1, published December 8, 2011 (Ex. 1011, “Bhakta”).

¹³ Robert A. Snow et al., U.S. Pat. No. 5,414,135, issued May 9, 1995 (Ex. 1010, “Snow”).

concert with an adjoined Q or T compound.” Inst. Dec. 18. We concluded “that Y and Z must independently enable their respective chemical reactions because Patent Owner (as Applicant) disclaimed embodiments in which Y or Z was adjoined to a sulfone compound with no *additional* adjacent sulfone, sulfoxide or phosphinate, in order to distinguish Lees.”¹⁴ *Id.* at 19 (citing Ex. 1018, 42–43, 62). Thus, we interpreted claim 1 as excluding “compounds in which the sole terminal group is vinyl sulfone without one or more adjacent Q and T groups” and stated that claim 1 did not read on embodiments 55, 75, 99, 119, and 138.¹⁵ *Id.* at 24. We further stated that Patent Owner (as Applicant) “disclaimed compounds in which the terminal group is vinyl sulfone without one or more adjacent Q and T groups” when amending claim 1 to overcome the rejection made during prosecution. *Id.* at 23 (citing Ex. 1018, 45, 62). In addition, we interpreted Y and Z as “independently enabling their respective reactions, without assistance from an adjoining Q or T.” *Id.* at 25.

Upon applying the above interpretations, we determined that Petitioner did not establish a reasonable likelihood of prevailing with respect to any of the challenged claims for the Petition’s grounds. *Id.* at 40.

B. The DRP’s Decision

Considering the claim construction set forth in our original Decision, the DRP determined:

the dispositive issue is, when the hydrophilic linker contains a vinylsulfone group, whether one of Y and Z may be understood to be a vinyl group with one of Q and T as a sulfone group (i.e.,

¹⁴ The DRP Decision refers to this interpretation as the “first version of the disclaimer.” DRP Dec. 10.

¹⁵ The DRP Decision refers to this application of the claim construction as the “second version of the disclaimer.” DRP Dec. 11.

the vinyl group and the sulfone group are mapped to separate letters), or instead whether one of Y and Z must be a vinylsulfone group (i.e., the vinyl group and the sulfone group are mapped to the same letter).

DRP Dec. 10.

The DRP considered whether there was disclaimer with regard to claim 1. *Id.* Specifically, the DRP agreed with the first disclaimer version provided in the original Decision: “Patent Owner (as Applicant) disclaimed embodiments in which Y or Z was adjoined to a sulfone compound with no additional adjacent sulfone, sulfoxide or phosphinate, in order to distinguish Lees.” *Id.* (quoting Inst. Dec. 19). The DRP agreed that the Applicant disclaimed compound 55 of the Specification to overcome the rejection over Lees during examination. *Id.* at 10–11 (citing Ex. 1018, 42–43, 62). However, the DRP disagreed with the second disclaimer version set forth in our original Decision, finding it erroneous based upon prosecution history. *Id.* at 11–16. The DRP determined that, “when the hydrophilic linker contains a vinylsulfone group, . . . the vinyl group should be mapped to Y or Z, and the sulfone group should be mapped to Q or T.” *Id.* at 16. The DRP stated “that such mapping satisfies the ‘enables reaction’ and ‘enables linkage’ requirements of claim 1.” *Id.*

The DRP’s Decision did not reach Petitioner’s arguments regarding claim 3. DRP Dec. 16. In its request for rehearing, Petitioner asserted that we engaged in unsupported fact-finding by concluding “that a sulfone ‘becomes complexed to HRP [horseradish peroxidase] through a vinyl-sulfone mediated reaction, making a derivatized protein.’” Request 13 (citing Inst. Dec. 29). Specifically, Petitioner argued that the Decision’s citations did not discuss complexes or derivatized proteins, Patent Owner did not raise such an argument, and these findings were at odds with the ’682

patent's disclosures of reactions schemes. *Id.* (citing Ex. 1001, Figs. 6–7, 10). Because we do not repeat this finding here, we do not address Petitioner's argument further in this Decision.

C. Level of Ordinary Skill in the Art

The level of ordinary skill in the art at the time of the invention is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

Petitioner alleges that an ordinarily skilled artisan of the '682 patent would have had . . . a PhD degree in organic chemistry, biochemistry, medicinal chemistry and/or pharmacology, along with 1-2 years of relevant applied research and/or industry experience in the field of linkers and conjugates for biologically active molecules. Alternatively, a POSA would have had a Master's or Bachelor's degree in one of these same fields with, respectively, at least 3-5 or 5-7 years work experience.

. . . [s]uch a person would have been familiar with protein/drug conjugates, including antibody-drug conjugates, the use of antibodies to selectively target cells and tissues associated with various diseases and conditions, linker design and selective attachment of the linker to proteins/antibodies and drugs, including targeted release of the drugs, as well as the need for water soluble conjugates for use with hydrophobic drugs, and methods for enhancing the potency of the protein/antibody-drug conjugates.

Pet. 18–19 (citing Ex. 1003 ¶¶ 23, 44–79). Patent Owner “adopts Petitioner's proposed level of skill in the art solely for the purposes of this Preliminary Response.” *See* Prelim. Resp. 31.

Based on the information presented, we find that the asserted prior art itself is sufficient to demonstrate the level of skill in the art at the time of the

invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (prior art itself can reflect the appropriate level of ordinary skill in the art). To the extent a more precise definition is required, we apply Petitioner’s unopposed definition for purposes of determining whether to institute review because it is consistent with the disclosures of the asserted prior art references.

D. Claim Interpretation

In an *inter partes* review, the Board construes the terms of a patent claim “in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” 37 C.F.R. § 42.100(b). Under that standard, claim terms generally are given their plain and ordinary meaning as would have been understood by the ordinarily skilled artisan at the time of the invention and within the context of the entire patent disclosure. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). We construe terms in controversy only to the extent necessary to resolve the controversy. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

Petitioner did not propose any terms for interpretation. Pet. 24. Patent Owner proposes constructions for four terms. Prelim. Resp. 32–39. For purposes of this decision, we find it necessary only to interpret claim terms referring to components “Y” and “Z” with regard to whether they must function independently or can work in concert with “Q” and “T” and “cell-binding agent.”

1. “Y,” Z,” “Q,” and “T”

Patent Owner argues that “Y,” as recited in independent claims 1, 20, 29, and 30, “should be interpreted as a component distinct and separate from the other recited components, including ‘Q’ and ‘T’” and that “the ‘Y’ term should be construed as requiring that Y, as functional group distinct from Q/T . . . independently enable[s] the reaction of the linker with a cell-binding agent.” Prelim. Resp. 32 (emphasis omitted). Patent Owner takes a similar position with Z for claim 1, arguing that Z should be a component distinct from Q and T and independently enable reaction with a cytotoxic drug, and with Q and T for all of the independent claims. *Id.* at 34, 36–37; *see also* PO Sur-reply 3–7; PO Resp. Brief. Petitioner disputes Patent Owner’s positions. Pet. Prelim. Reply 4–7; Pet. Resp. Brief 1.

As stated above, when reviewing claim construction for claim 1, the DRP agreed with Petitioner that Patent Owner (as Applicant) “disclaimed embodiments in which Y or Z was adjoined to a sulfone compound with no additional adjacent sulfone, sulfoxide or phosphinate.” DRP Dec. 9–11. The DRP summarized this disclaimer as follows; “when there is a terminal vinylsulfone, Y (or Z) is mapped to vinyl, and Q (or T) is mapped to sulfone, such that there must be at least one additional phosphinate, sulfonyl, or sulfoxide group as Q (or T).” *Id.* at 16. The DRP stated that, “when the hydrophilic linker contains a vinylsulfone group, we determine that the vinyl group should be mapped to Y or Z, and the sulfone group should be mapped to Q or T.” *Id.*

We apply this instruction and interpret claim 1 in this manner. As a result, we do not agree with Patent Owner’s proposed constructions for claim 1 regarding “Y,” “Z,” “Q,” and “T.” *See, e.g.*, Prelim. Resp. 32

We next determine whether this same interpretation and understanding should apply to the remaining independent claims (claims 3, 20, 24, 26, 29, and 30). For this consideration, we note that “the prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention.” *Phillips*, 415 F.3d at 1317.

Patent Owner asserts that it was merely repeating the Examiner’s mapping without adopting that mapping when responding to the Examiner’s rejection of claim 1 over Lees during prosecution. PO Sur-reply 6. However, the DRP disagreed with Patent Owner, finding that Patent Owner did not state in its prosecution papers that it was merely repeating the Examiner’s mapping, did not express disagreement with the Examiner’s mapping, and provided more detail than the Examiner had when characterizing Lees. DRP Dec. 13–14 (citing Ex. 1018, 62). As noted above in the review of the prosecution history, Applicant’s statements included mapping Lees’ vinylsulfone such that its sulfone functioned as Q (or T) and its vinyl functioned as Z. Ex. 1018, 62. In sum, the DRP found “that the Applicant was stating the Applicant’s own mapping of the compound in Lees.” DRP Dec. 14.

In other words, although Patent Owner argues now that vinyl alone cannot function as Z and would not have the ability to react with functional groups in either a cell-binding agent or a cytotoxic drug, Patent Owner had not stated this position to the Examiner during prosecution. Prelim. Resp. 42; PO Sur-reply 4. In view of the DRP’s findings and Patent Owner’s own understanding exhibited in the prosecution history, we apply the DRP’s finding regarding the mapping of a vinylsulfone group to the remaining

independent claims¹⁶ (i.e., that the sulfone should be mapped to Q or T and the vinyl should be mapped to Y or Z).

We apply these interpretations in analyzing the Petitioner's grounds.

2. “*cell-binding agent*” (claims 3, 24, 26)

Patent Owner contends that the term “cell-binding agent” of independent claims 3, 24, and 26 “should be construed as the patentee defined it in the Specification; ‘[a] molecule that binds to, complexes with or reacts with a moiety of a cell population sought to be therapeutically or otherwise biologically modified.’” Prelim. Resp. 37 (citing Ex. 1001, 14:42–44; Ex. 2001 ¶¶ 130–133)) (emphasis omitted). According to Patent Owner, “the ‘cell-binding agent’ is a molecule that is used to target (modify) a specific population of cells, including for therapeutic purposes.” *Id.* (citing Ex. 2001 ¶ 130). Patent Owner argues that the ’682 patent describes “the ‘cell-binding agent’ in terms of its ability to interact with specific cell-associated molecules (e.g., ‘a moiety of a cell population’) that are intended to be targeted with the claimed linker conjugate (e.g., ‘sought to be therapeutically or otherwise biologically modified’).” *Id.* at 37–38 (citing Ex. 1001, 14:43–15:32).

Patent Owner further contends that the claims support its proposed construction, and one of ordinary skill in the art “would recognize from the term ‘agent’ that the cell-binding ‘agent’ is a molecule that is intended to be used to achieve a specific purpose—e.g., binding a specific cell population

¹⁶ See also *Phillips*, 415 F.3d at 1315 (“[b]ecause claim terms are normally used consistently throughout the patent, the usage of a term in one claim can often illuminate the meaning of the same term in other claims,” citing *Rexnord Corp. v. Laitram Corp.*, 274 F.3d 1336, 1342 (Fed. Cir. 2001); *CVI/Beta Ventures, Inc. v. Tura LP*, 112 F.3d 1146, 1159 (Fed. Cir. 1997)).

as taught in the patent.” Prelim Resp. 38 (citing Ex. 2001 ¶¶ 131–132). According to Patent Owner, the ’682 patent “teaches that the linkers of its invention are linkers that target specific cell populations, particularly for therapeutic purposes.” *Id.* (citing Ex. 1001, 1:5–2:67, 1:7–9). Patent Owner further disagrees with Petitioner’s application for the term, arguing that it “effectively eliminates the ‘agent’ term and reduces the cell-binding agent to a moiety that is not used to target cell populations, contrary to the plain language of the claim and intent of the inventor.” *Id.* at 39 (citing Ex. 2001 ¶ 132).

Petitioner disputes Patent Owner’s construction, arguing that Patent Owner attempts to read additional limitations into this term and that the text of the ’682 patent cited by Patent Owner refers to an intended use, not the function of the cell-binding agent. Pet. Prelim. Reply 7–8. Petitioner further contends that the ’682 patent “identifies numerous exemplary CBAs [cell binding agents], such as smaller molecular weight proteins, poly-peptide, peptides, cell nutrient-transport molecules, bioactive polymers, and nanoparticles . . . , which all may bind to a moiety on a cell population under only some conditions, and without necessarily ‘target[ing] a “specific” cell population.’” *Id.* at 8 (second alteration in original). According to Petitioner, “cell-binding agent” should be “any agent that binds to, reacts with, or complexes with cells.” *Id.* at 7.

Patent Owner in turn disputes Petitioner’s construction and generally reiterates its position as set forth in its Preliminary Response. PO Sur-reply 7–9 (citing Prelim. Resp. 37–38).

On this record, we agree with Patent Owner’s construction of “cell-binding agent” as “[a] molecule that binds to, complexes with or reacts with a moiety of a cell population sought to be therapeutically or otherwise

biologically modified” (Prelim. Resp. 37 (citing Ex. 1001, 14:42–44)) because that construction directly reflects the definition recited by the ’682 patent. However, we invite the parties to further address this issue during trial.

If either party intends to further argue claim construction at trial it should do so in a clearly designated section of its brief so as to expressly identify such arguments. *See, e.g.*, 37 C.F.R. § 42.104(b)(3) (content of petition); *see also* Patent Trial and Appeal Board Consolidated Trial Practice Guide (Nov. 2019), 46, 48–49).¹⁷ Claim construction arguments should be clearly labeled and not merely intertwined within patentability arguments.

E. 35 U.S.C. § 325(d)

Patent Owner argues we should exercise our discretion under § 325(d) to deny institution. Prelim. Resp. 22–28; PO Sur-reply 1–3. Petitioner opposes. Pet. 78–80; Pet. Prelim. Reply 1–4. For the reasons discussed below, we do not invoke our discretion to deny institution under § 325(d).

1. Statement of Law

Under § 325(d), in determining whether to institute an *inter partes* review, “the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office.”¹⁸ Our § 325(d) analysis employs a two-prong framework: (1) whether the prior art and arguments presented in the petition are the same or substantially the same as those previously presented to the Office; and (2) if so, whether the petitioner has demonstrated a material error by the Office in its prior consideration of those

¹⁷ Available at <https://www.uspto.gov/TrialPracticeGuideConsolidated>.

¹⁸ The Board institutes trial on behalf of the Director. 37 C.F.R. § 42.4(a).

prior art and arguments. *Advanced Bionics, LLC v. Med-El Electromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 (“*Advanced Bionics*”), 8 (PTAB Feb. 13, 2020) (precedential).

We consider several non-exclusive factors as set forth in *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (Dec. 15, 2017) (precedential as to § III.C.5, first paragraph) (“*Becton, Dickinson*”), which “provide useful insight into how to apply the framework” under § 325(d). *Advanced Bionics*, 9. These non-exclusive factors include:

- (a) the similarities and material differences between the asserted art and the prior art involved during examination;
- (b) the cumulative nature of the asserted art and the prior art evaluated during examination;
- (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
- (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;
- (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and
- (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

Becton, Dickinson, 17–18 (formatting added). “If, after review of factors (a), (b), and (d), it is determined that the same or substantially the same art or arguments previously were presented to the Office, then factors (c), (e), and (f) relate to whether the petitioner has demonstrated a material error by the Office.” *Advanced Bionics*, 10.

2. *Whether the Prior Art and Arguments are the Same or Substantially the Same*

Petitioner argues that we should not exercise our discretion to deny institution under § 325(d) “because the Patent Office has not previously considered the present grounds of invalidity” and this is the first challenge of any kind to the ’682 patent’s claims, as amended during the reexamination. Pet. 78. Petitioner asserts that Harris and Snow were not considered by the Office during prosecution or reexamination and are not cumulative of prior art references disclosed to the Office. *Id.* at 78–79. Petitioner contends that Bhakta was also not before the Office during examination or reexamination. *Id.* at 79. Petitioner acknowledges that Morales-Sanfrutos, Straus, and Singh were listed on an Information Disclosure Statement (“IDS”). *Id.*

Patent Owner asserts that “Petitioner relies on identical or substantially the same prior art and arguments previously considered by the Office.” Prelim. Resp. 22–23. Patent Owner further argues that Petitioner admits Morales-Sanfrutos, Straus, and Singh were listed on an IDS.¹⁹ *Id.* at 15, 18, 21, 23–24 (citing Pet. 8, 10, 79; Ex. 2001 ¶¶ 102–108). According to Patent Owner, with regard to Ground 1, Petitioner relies upon Harris and Snow “for essentially the same teachings as Morales-Sanfrutos—*e.g.*, linkers containing vinyl sulfone groups.” *Id.* at 24 (citing Pet. 5–9, 17). Patent Owner also asserts that “Lees’ PEG linker structure comprising bis vinyl sulfone structure is also the same as compound 1 disclosed by Morales-Sanfrutos.” *Id.* at 27 (citing Ex. 1005, 4041, Fig. 2; Ex. 2001 ¶ 108).

¹⁹ Patent Owner also argues that Singh “substantially overlaps with WO2009/13976 (Singh ’976) (Ex. 2034), which was cited in an IDS form and appeared on the list of considered references by the Examiner.” Prelim. Resp. 26–27 (citing Ex. 2033; Ex. 2001 ¶ 108).

Patent Owner further argues that Lees, which was cited during prosecution, “discloses structures identical to the structures from Harris on which Petitioner relies on for Grounds 2-3.” *Id.* at 25 (citing Pet. 38–42, 49; Ex. 2001 ¶¶ 103–106). To support this argument, Patent Owner provides its own Figure 5, reproduced below, to compare Lees’ linkers and Harris’ linkers.

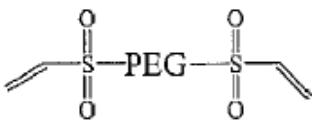
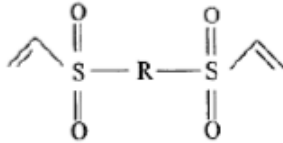
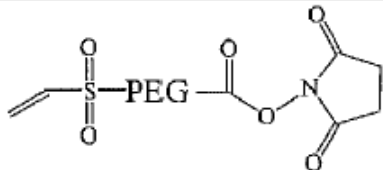
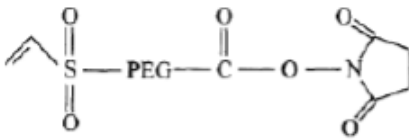
Fig. 5: Identical Linkers Disclosed in Harris and Lees	
Harris	Lees
 Homobifunctional sulfone linker structure	 Homobifunctional sulfone linker structure
 Heterobifunctional linker structure comprising vinyl sulfone and NHS	 Heterobifunctional linker structure comprising vinyl sulfone and NHS

Figure 5, reproduced above from Patent Owner’s brief, compares homobifunctional sulfone linker structures in Harris and Lees. Prelim. Resp. 25. According to Patent Owner, Lees’ homobifunctional structure is the same structure as Harris’ homobifunctional structure, which Petitioner relies upon in Grounds 2–5, and is identical to Snow’s polymeric bis vinyl sulfone linker, which Petitioner relies upon in Ground 5. *Id.* at 25–26 (citing Ex. 2026, 20:10–19; Ex. 2001 ¶¶ 105, 107; Pet. 17, 38–42, 49; Ex. 1007, 16:37–17:5; Ex. 1010, 7:14–27). Patent Owner further contends that Lees’ heterobifunctional vinyl structure in Patent Owner’s Figure 5 is the same structure as Harris’ heterobifunctional structure that Petitioner relies upon in Ground 2. *Id.* at 26 (citing Ex. 2001 ¶ 106; Pet. 42). In view of the above,

Patent Owner further contends that “Petitioner’s arguments concerning Harris’s and Snow’s bis vinyl sulfone linkers are, therefore, cumulative of art expressly considered and overcome by the Examiner during prosecution.” *Id.*

In response, Petitioner argues that Harris and Snow are new references that contain additional disclosures supporting new arguments that the Examiner did not raise during prosecution. Pet. Prelim. Reply 1–3. Petitioner also contends that compounds 2, 4, and 5 of Morales-Sanfrutos differ from Harris. *Id.* at 3–4 (citing Prelim. Resp. 24; Pet. 27–30, 33–36).

Patent Owner reiterates its position that Morales-Sanfrutos, Straus, and Singh were previously before the Office and that Petitioner’s assertion of Harris and Snow and Petitioner’s arguments in support of this combination are substantially similar to the arguments the Examiner made regarding Lees. PO Sur-reply 1–2.

The parties do not dispute that Morales-Sanfrutos, Straus, and Singh appeared on an IDS. Furthermore, we agree with Patent Owner that Lees’s homobifunctional structure (shown in Patent Owner’s Figure 5 above) is substantially similar to the homobifunctional linker taught by Harris and to Snow’s polymeric bis vinyl sulfone linker. Ex. 2026, 20:10–19; Ex. 1007, 16:37–17:5; Ex. 1010, 7:14–27). Therefore, we find that Morales-Sanfrutos, Straus, and Singh are the same art and Harris and Snow are substantially the same art previously presented to the Office.

Because this satisfies the first prong of *Advanced Bionics*, we do not reach the parties’ positions regarding whether Petitioner’s arguments are the same or substantially the same as those previously presented to the Office. Additionally, although Bhakta was not before the Office during prosecution

(*see* Pet. 79), we find that § 325(d) is sufficiently implicated here that we move to prong two of the *Advanced Bionics* analysis.

3. *Whether Petitioner has Demonstrated Material Error*

We next analyze whether Petitioner has demonstrated a material error by the Office under the second prong of *Advanced Bionics*.

Petitioner argues that the Examiner failed to identify Morales-Sanfrutos' anticipatory structures, Singh was not considered during prosecution or reexamination, "the Examiner never acknowledged Singh's teachings that vinyl sulfone is equivalent to maleimide and haloacetamide moieties for thiol-reactive functionality," and that the Office did not consider how one of ordinary skill in the art would have been motivated to replace one or both of Singh's reactive functionalities with vinyl sulfone. Pet. 79 (citing Ex. 1008 ¶ 134; Ex. 1003 ¶¶ 124, 130, 169).

Patent Owner asserts that Petitioner fails to show that the Office materially erred. Prelim. Resp. 22–23. Specifically, Patent Owner argues that "[w]hile Petitioner asserts that the Examiner merely gave ' cursory consideration' to the references . . . Petitioner provides no factual basis to support its position." *Id.* at 27 (citing Pet. 79). Patent Owner further contends that "Petitioner presents no new evidence, or even argument, suggesting that its asserted references include teachings that were unavailable to the Office when the Challenged Claims were found and confirmed to be patentable in prior examination or re-examination." *Id.* at 27–28.

Petitioner argues that "the Examiner cited only the heterobifunctional linker on p. 22 of Lees" during examination and did not address Lees's homobiofunctional sulfone linker, which is disclosed by Harris and upon which Petitioner chiefly relies upon in Grounds 2–5.

Pet. Prelim. Reply 1–2 (citing Ex. 2025; Ex. 1018, 42, 45; Pet. 38–29). Petitioner further contends that, unlike Harris, Lees does not disclose that its PEG linker may be used with pharmaceuticals and proteins or that PEG/sulfone derivatives are highly water soluble. *Id.* at 2 (citing Pet. 6–7, 38–43, 50, 74–76). Petitioner also argues that “Lees discloses a vaccine using a polysaccharide antigen, which [antigen] is not a drug.” *Id.* at 2–3 (citing Ex. 1001, 24:1–3, 24:10–16, 29:42–36:19; Ex. 2026, 7:11–22). In addition, Petitioner asserts that Morales-Sanfrutos, Straus, and Singh were never applied against the claims of the ’682 patent. *Id.* at 3.

Patent Owner reiterates its position that Petitioner fails to describe any material error committed by the Office in its evaluation of the references. PO Sur-reply 1–2. In response to Petitioner’s argument that the Examiner discussed Lees’ heterobifunctional linker but did not discuss Lees’ homobifunctional linker, Patent Owner asserts that “Petitioner failed to proactively identify this in its Petition, which diminishes any showing of material error” by the Office. *Id.* at 2. Patent Owner further argues that Lees discloses its homobifunctional linker multiple times with frequent references, discloses another homobifunctional sulfone structure, and there is nothing in the record to suggest the Examiner was unaware of these disclosures. *Id.* at 2–3 (citing Ex. 2026, 18:10–16, 20:10–21:12, 30:16–31, 32:13–14, Figs. 1(b), 3(c)). Patent Owner further disputes Petitioner’s characterization of how Harris and Snow are relied upon in Grounds 2 and 3. *Id.* at 3.

We find that Petitioner has demonstrated a material error by the Office in the prior consideration of Morales-Sanfrutos, Straus, Singh, and Lees. For instance, under the second prong of *Advanced Bionics*, we consider “(c) the extent to which the asserted art was evaluated during

examination, including whether the prior art was the basis for rejection” and “(e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art.” *Becton, Dickinson*, 17–18.

We agree with Petitioner that the Office overlooked Morales-Sanfrutos’ and Singh’s teachings during examination and reexamination. Pet. 79. Although Morales-Sanfrutos, Straus, and Singh were listed on an IDS, they were not the subject of a rejection during examination or reexamination. Moreover, for the reasons discussed below at this stage with regard to Petitioner’s grounds over Morales-Sanfrutos, as evidenced by Straus, and over Singh, Petitioner sufficiently demonstrates that the Office materially erred in overlooking Morales-Sanfrutos’s and Singh’s teachings regarding their linker structures. *Id.*

Further, to the extent the Lees’ teachings were considered during examination and reexamination, Lees’ disclosure of a homobifunctional sulfone linker was overlooked. Lees’ homobifunctional linker, which Patent Owner argues is substantially similar to Harris’ homobifunctional linker, which Petitioner chiefly relies upon in Grounds 2–5, was not the subject of a rejection during examination. Pet. Resp. Brief 1; Prelim. Resp. 25–26. We agree with Petitioner that only Lees’ heterobifunctional linker was applied in a rejection during examination. Pet. Resp. Brief 1; Ex. 1018, 42–43, 62.

4. Conclusion

For the foregoing reasons, we decline to exercise discretion to deny institution under § 325(d).

F. The Patentability Challenges

1. Ground 1: Anticipation by Morales-Sanfrutos as Evidenced by Straus

A patent claim is unpatentable under 35 U.S.C. § 102 if a prior art reference “discloses every claim limitation.” *In re Montgomery*, 677 F.3d

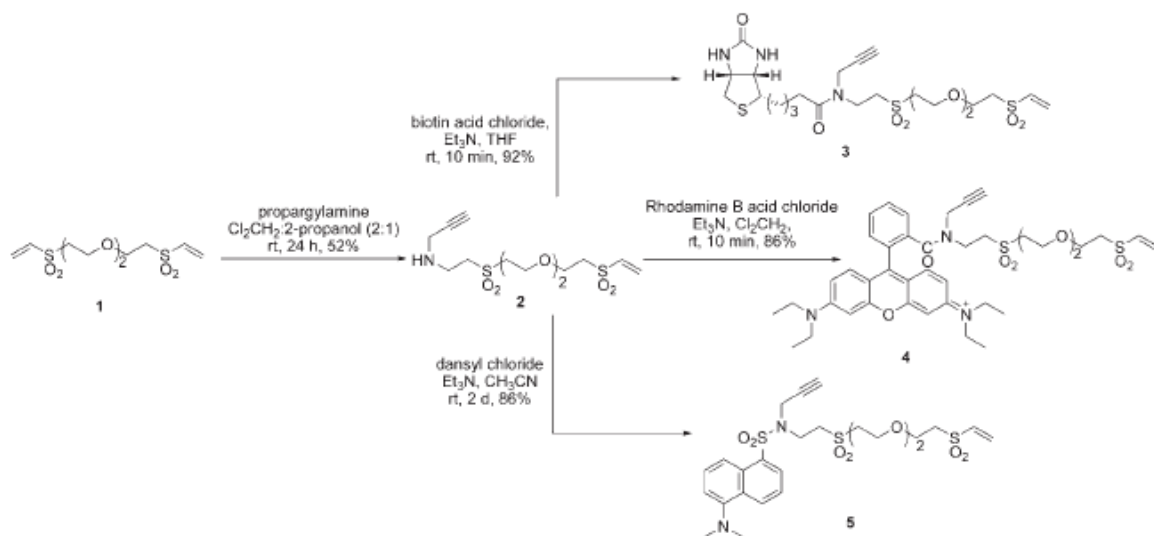
1375, 1379 (Fed. Cir. 2012). In this section, we apply that standard to assess whether Petitioner shows sufficiently, for purposes of institution, that claims 1–3, 6, 24, 25, and 33 are anticipated by Morales-Sanfrutos as evidenced by Straus. Pet. 24–37.

a) Morales-Sanfrutos (Ex. 1005)

Morales-Sanfrutos is titled “Vinyl Sulfone Bifunctional Tag Reagents for Single-Point Modification of Proteins.” Ex. 1005, 4039. Morales-Sanfrutos describes the “synthesis of vinyl sulfone derivatized bifunctional tag single attachment point reagents (BTSAP) bearing biotin and a fluorescent tag,” and their use to introduce detectable labels using chemical reactions occurring at the electrophilic vinyl sulfone group. *Id.* Morales-Sanfrutos teaches that the tags can be coupled to horseradish peroxidase (HRP) by incubating HRP with the vinyl sulfone derivatized bifunctional tags to make labeled proteins, such as HRP-11. *Id.* at 4046.

Morales-Sanfrutos describes the synthesis of BTSAP reagents via a two-step chemical scheme in which (1) an alkyne vinyl sulfone derivatized tag (AVST) was prepared and (2) copper-mediated click reaction of the AVST with a complementary azide derivative was carried out. *Id.* at 4040. Morales-Sanfrutos depicts this as “Scheme 1,” which is reproduced below:

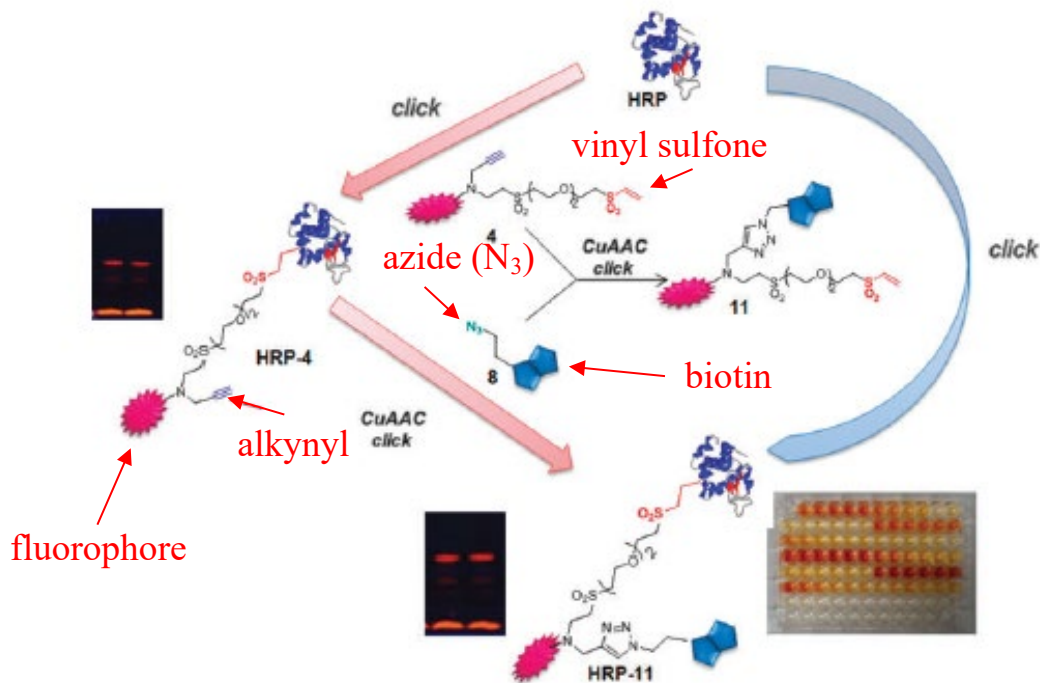
SCHEME 1. Synthesis of Alkyne Vinyl Sulfone Derivatized Tags (AVST) 3-5



Id. at 4041. Scheme 1 depicts a two-step chemical synthesis of BTSAP reagents.

Morales-Sanfrutos further explains that either a one step or a sequential approach may be used. *Id.* at 4043. These alternative approaches are depicted in “Scheme 4.” An annotated copy of Scheme 4 is reproduced below. We have annotated Scheme 4 to identify the components.

SCHEME 4. One-Step versus Sequential Approach for Bifunctional Labeling of HRP



Id. at 4044. Scheme 4 depicts one-step and sequential chemical syntheses of BTSAP reagents. As indicated by the annotations added to this figure, Morales-Sanfrutos explains that the magenta colored sunburst shape represents a fluorophore and the blue colored double pentagon shape represents biotin. *Id.* at 4039.

b) Straus (Ex. 1006)

Straus is titled “Unusual Binding Sites for Horseradish Peroxidase on the Surface of Cultured and Isolated Mammalian Cells.” Ex. 1006, 277. Straus is a study of binding sites for HRP. *Id.* Petitioner alleges that Straus discloses that HRP has been shown to bind at specific sites in cells such as macrophages, fibroblasts, mast cells and endothelial cells. Pet. 36; *see* Ex. 1006, 277.

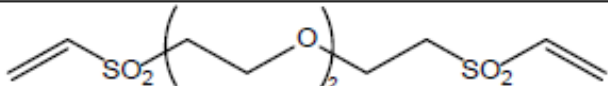
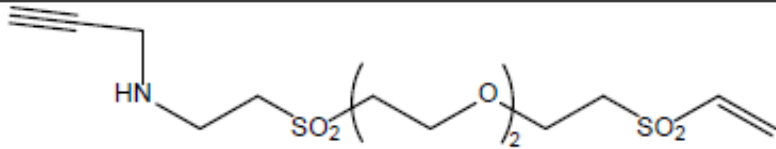
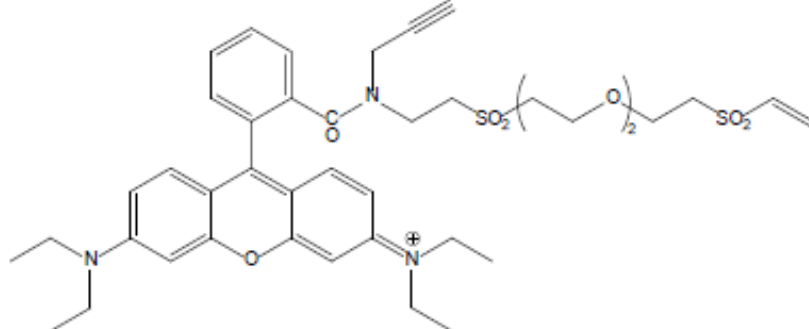
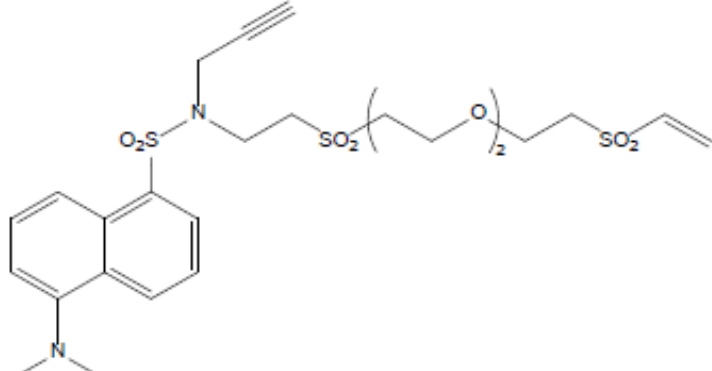
c) Claim 1

Petitioner initially argues that claim 1’s preamble is not limiting because “hydrophilic linker” refers to a property of the compound and its

intended use, this term does not further limit the composition because the body of the claim recites a structurally complete composition, and the term places no further restriction on the inherent hydrophilicity of the compound. Pet. 25–26 (citing Ex. 1003 ¶¶ 80–85). Regardless, Petitioner contends that the preamble is nonetheless taught by Morales-Sanfrutos because the latter discloses each claimed element. *Id.* Patent Owner does not dispute Petitioner’s position. *See generally* Prelim. Resp. On this record, we need not decide whether the preamble is limiting, because even if it is, we agree with Petitioner (and Patent Owner does not dispute) that Morales-Sanfrutos teaches a “hydrophilic linker.”

Petitioner alleges that claim 1 is anticipated by four of the compounds Morales-Sanfrutos discloses in Schemes 1 and 4. Pet. 26–28 (citing Ex. 1005, 4041 (Scheme I), 4043–44 (Scheme 2)). Petitioner lists the four compounds in Table B1 of the Petition, which is reproduced below:

Table B1

Cmpd	Bifunctional PEG Cross-linkers
1	
2	
4 ⁴	
5 ³	

Pet. 27.

Petitioner and its declarant, Dr. Chari, explain that the four disclosed compounds of Morales-Sanfrutos meet the limitations of claim 1 in multiple ways, which are summarized in Table B2, as shown below. Pet. 28–31 (citing Ex. 1003 ¶¶ 82–84).

Table B2

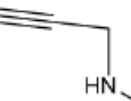
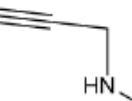
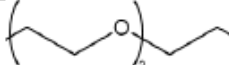
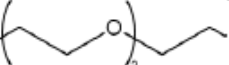
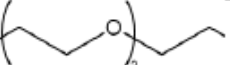
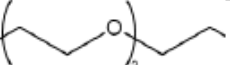
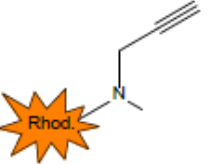
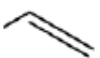
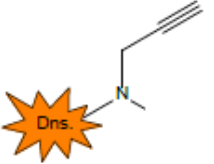
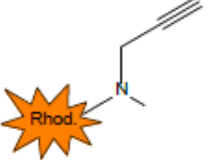
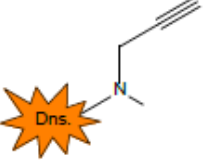
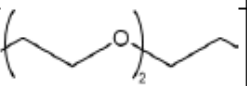
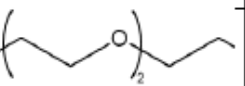
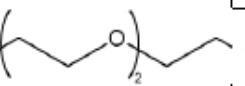
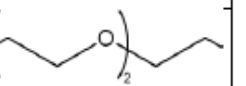
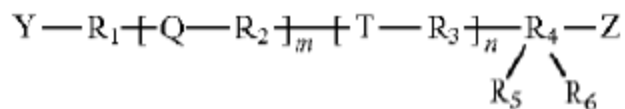
	Morales-Sanfrutos' Compounds 1-2 (Table B1)			
'682 (I)	Compound 1	Compound 2		
		(a)	(b)	(c)
Y				
Z				
R₁	absent ⁵	absent	absent	
m	1	1	1	1
Q	-SO ₂ -	-SO ₂ -	-SO ₂ -	-SO ₂ -
R₂				
p	2	2	2	2
n	1	1	1	1
T	-SO ₂ -	-SO ₂ -	-SO ₂ -	-SO ₂ -
R₃	absent		CH ₂	absent
R₄	absent	absent	CH ₂	absent

Table B2 (continued)

'682 (I)	Compound 4		Compound 5	
	(a)	(b)	(a)	(b)
Y				
Z				
R₁	absent		absent	
m	1	1	1	1
Q	-SO ₂ -	-SO ₂ -	-SO ₂ -	-SO ₂ -
R₂				
p	2	2	2	2
n	1	1	1	1
T	-SO ₂ -	-SO ₂ -	-SO ₂ -	-SO ₂ -
R₃		absent	absent	absent
R₄	absent	absent		absent

Id. at 28–30. We select, as representative of Petitioner’s ground over Morales-Sanfrutos (as evidenced by Straus), Petitioner’s arguments with respect to compound 1, as shown in Table B1 above. We reproduce for reference below claim 1’s Formula (I),



Ex. 1002, 1:22–2:13. Reproduced above is Formula I of claim 1.

Petitioner's proposed Compound I of Morales-Sanfrutos has the following substitutions: Y and Z are vinyl, m and n are 1, and Q and T are sulfonyl.

Pet. 26–29.

Patent Owner argues that Morales-Sanfrutos does not anticipate claim 1 because Petitioner's identification of vinyl as Y and Z and the sulfones as Q and T for compound 1 does not meet these claim elements as properly construed. Prelim. Resp. 40–44. Patent Owner argues that Y and Z are separate groups and it is “improper to map a single prior art structure—Morales-Sanfrutos' singular vinyl sulfone structure—onto both as Petitioner has done.” *Id.* at 42. Patent Owner argues that because the skilled artisan would have known that vinyl sulfone is the reactive functionality (i.e., what Petitioner maps as YQ together), it is improper to map Y and Z to vinyl alone. *Id.* Patent Owner presents similar arguments for compounds 2, 4, and 5 against the splitting of vinyl sulfone between Q and Y and/or T and Z. *Id.* at 44–46.

For the reasons discussed above with regard to our claim interpretation of Y, Z, Q, and T, we do not agree with Patent Owner's argument. As explained in the DRP's Decision, we map the vinyl of vinylsulfone to Q or T and the vinyl to Y or Z. DRP Dec. 16.

With regard to Y, which enables reaction of the claimed linker with a cell-binding agent, Patent Owner asserts that Petitioner admits to vinyl alone not enabling reaction of a linker. Prelim. Resp. 43 (citing Pet. 31). For the reasons discussed above (*see* Section II.B.), we do not agree with Patent

Owner's argument. The DRP determined that, "when the hydrophilic linker contains a vinylsulfone group, . . . the vinyl group should be mapped to Y or Z, and the sulfone group should be mapped to Q or T." DRP Dec. at 16. The DRP stated "that such mapping satisfies the 'enables reaction' and 'enables linkage' requirements of claim 1." *Id.*

With regard to claim 1, Patent Owner next asserts that Morales-Sanfrutos does not disclose a cell-binding agent because Morales-Sanfrutos' linkers are conjugated to HRP, which one of ordinary skill in the art would understand is not a cell-binding agent. Prelim. Resp. 16–17 (citing Ex. 2001 ¶¶ 54, 56, 58; Ex. 1005, 4041). *See also id.* at 46–48 (Patent Owner asserting same argument regarding claims 3 and 14, citing Ex. 2001 ¶ 58). We note that claim 1 does not require a cell binding agent but instead requires Y, a functional group that enables reaction of the linker with a cell-binding agent, which is present in Morales-Sanfrutos.

With regard to claims 3 and 24, as explained above, Petitioner alleges that Straus discloses that HRP has been shown to bind at specific sites in cells such as macrophages, fibroblasts, mast cells and endothelial cells. Pet. 36; *see* Ex. 1006, 277. Patent Owner argues that Straus is not from the same field of endeavor as the '682 patent and does not teach or suggest the use of HRP to target specific cell populations, such as in a therapeutic conjugate. *Id.* at 18–19. Patent Owner also argues that Petitioner fails "to establish that Straus necessarily teaches that HRP is a 'cell-binding agent' as claimed" because Dr. Chari's supporting testimony states a "mere possibility of HRP binding" instead of demonstrating binding would occur. *Id.* at 47–48. Patent Owner argues Dr. Chari's cited testimony does not identify a factual basis and therefore is entitled to no weight." *Id.* at 46.

We disagree. The '682 patent asserts that the invention is directed to “methods of making cell - binding agent - drug (cytotoxic agent) conjugates.” Ex. 1001 Abstract. Straus addresses binding sites on the surface of cultured and isolated mammalian cells. Ex. 1006, 277. For purposes of this decision, we consider Straus to be prior art a POSA would reasonably have consulted in determining what compounds could be used to bind cells.

Further, Petitioner’s argument and Dr. Chari’s testimony that vinyl groups (e.g., the vinyl portion of vinylsulfone) are known to react with a cell-binding agent, such as HRP, are supported by Morales-Sanfrutos’ disclosures regarding the reactivity of vinylsulfone with biomolecules and groups naturally present in proteins. Pet. 31; Ex. 1003 ¶ 86; Ex. 1005, 4041 (disclosing that HRP is a protein) 4043–44 (disclosing that vinyl sulfone reacts with amine, thiol, and imidazole groups naturally present in proteins and Scheme 4 depicting HRP reacting with vinyl sulfone). Petitioner’s arguments and Dr. Chari’s testimony for claim 3, which Patent Owner disputes here for claim 1, cite Straus as support for HRP being “a known cell-binding agent.” Pet. 36 (citing Ex. 1006, 277; Ex. 1003 ¶¶ 59, 90). Although Dr. Chari states that HRP “may” bind to the surface of a variety of cells (Ex. 1003 ¶ 59), Dr. Chari also testifies that “HRP is a known cell-binding agent, as evidenced by Straus” (*id.* ¶ 90). Straus describes the detection of binding sites for HRP on the surface of cultured and isolated cells, that “[t]he occurrence of mannose-specific binding sites for horseradish peroxidase (HRP) in macrophages, fibroblasts, mast cells and endothelial cells of rat tissues has been demonstrated earlier,” and describes studying whether various substances (e.g., sugars and nucleotides containing sugars) inhibited or suppressed binding of HRP to binding sites. Ex. 1006,

277. Straus therefore teaches binding cites for HRP in various types of cells and binding of HRP to such sites, which, for purposes of this decision, would biologically modify the cells due to the attachment of HRP. As a result, Straus' disclosure supports Petitioner's argument and Dr. Chari's testimony and we disagree with Patent Owner's assertions regarding Dr. Chari's testimony. Prelim. Resp. 47 (citing Ex. 1003 ¶ 90). For these reasons, we agree with Petitioner's position that Morales-Sanfrutos, as evidenced by Straus, meets Patent Owner's construction of "cell-binding agent" because HRP-11 binds to specific cell populations and biologically modifies them. Pet. Prelim. Reply 8–9 (citing Ex. 1006, 1).²⁰

With regard to Z, which enables linkage of the linker to a cytotoxic drug, Petitioner contends that claim 1 does not require actual conjugation of the claimed linker to a cytotoxic drug, only that Z enables such a reaction. Pet. 31. Petitioner further asserts that Morales-Sanfrutos demonstrates linkage between an alkynyl and biotin, which Petitioner asserts is a drug. *Id.* at 31–32 (citing Ex. 1005, 4041, 4043–4044; Ex. 1003 ¶ 87). Dr. Chari's testimony mirrors Petitioner's argument. Ex. 1003 ¶ 87.

Patent Owner argues in response that biotin is a tag, not a drug and Morales-Sanfrutos relates to a reporter system, not to therapeutic protein-drug conjugates. Prelim. Resp. 17. Patent Owner contends that "Petitioner fails to show that Morales-Sanfrutos has any disclosure of cytotoxic drugs, much less a functional group, particularly vinyl, that enables linkage to a cytotoxic drug." *Id.* at 44.

²⁰ To the extent the parties wish to explore this issue further, we invite them to do so at trial.

The DRP determined that mapping a vinyl group to Y or Z “satisfies the ‘enables reaction’ and ‘enables linkage’ requirements of claim 1.” DRP Dec. 16.

Patent Owner raises no arguments relating to the remaining claim limitations reciting R, M, H, and K groups. *See generally*, Prelim. Resp. We have reviewed Petitioner’s allegations and supporting evidence and agree that Petitioner has sufficiently demonstrated that Morales-Sanfrutos discloses each of these limitations. *See* Pet. 28–32; Ex. 1003 (Dr. Chari Declaration) ¶¶ 82–85. Accordingly, Petitioner’s mapping of compound 1 demonstrates a reasonable likelihood that Morales-Sanfrutos, as evidenced by Straus, discloses the remaining limitations of claim 1. Pet. 48.

We provide the following additional observations regarding our evaluation of the evidence of record with respect to Morales-Sanfrutos’ other compounds that Petitioner relies upon. As noted above in Petitioner’s Table B2, Petitioner appears to cite the alkynyl of compounds 2(a), 2(b), 4(a) and 5(a) as meeting the limitations of claim 1 element Z. *See* Pet. 30–32; Ex. 1003 ¶¶ 84, 87 (presenting arguments for the alkynyl as Z). Although Petitioner argues that the alkynyl would form a heteroaromatic bond, as claim 1 recites, Petitioner argues that the alkynyl links with Morales-Sanfrutos’ biotin. *Id.* at 31–32. Petitioner does not sufficiently explain on this record why the linkage of alkynyl alone to biotin demonstrates a reasonable likelihood of enabling linkage to either a drug or a cytotoxic drug. Furthermore, Petitioner does not argue that the alkynyl would form the type of bond discussed by the ’682 patent for claim 1 element Z. *See* Ex. 1001, 9:1–7.

With regard to compounds 2(c), 4(b), and 5(b), Petitioner contends that the alkynyl functions as claim 1 element Y, as noted in Table B2 above.

Pet. 30 (citing Ex. 1003 ¶¶ 82–84). However, Petitioner and Dr. Chari do not sufficiently explain on this record why there is a reasonable likelihood that Morales-Sanfrutos' alkynyl group would enable reaction of a linker with a cell-binding agent, regardless of whether the POSA would have had knowledge that HRP was a cell-binding agent. For instance, Morales-Sanfrutos' Scheme 4 shows the alkynyl reacting with the azide group (N₃) of biotin, not with HRP, to form the heteroaromatic bond that Petitioner and Dr. Chari reference when presenting arguments for Z. Ex. 1005, 4044 (indicating “Bifunctional labeling of HRP” and showing HRP at opposing end of molecule from biotin); Pet. 31; Ex. 1003 ¶ 87.

We suggest the parties address these issues at trial.

d) Claim 2

Claim 2 recites “the hydrophilic linker of claim 1, wherein Z comprises a thiol, disulfide, amino, carboxy, aldehydes, maleimido, haloacetyl, hydrazine or hydroxyl group.” Ex. 1001, 49:10–12.

Petitioner asserts that Morales-Sanfrutos anticipates claim 2 because compound 2 includes an amino group, as shown above in Table B1. Pet. 32 (citing Ex. 1003 ¶¶ 87–88). Patent Owner cites in opposition the same arguments it raised against claim 1. Prelim. Resp. 46.

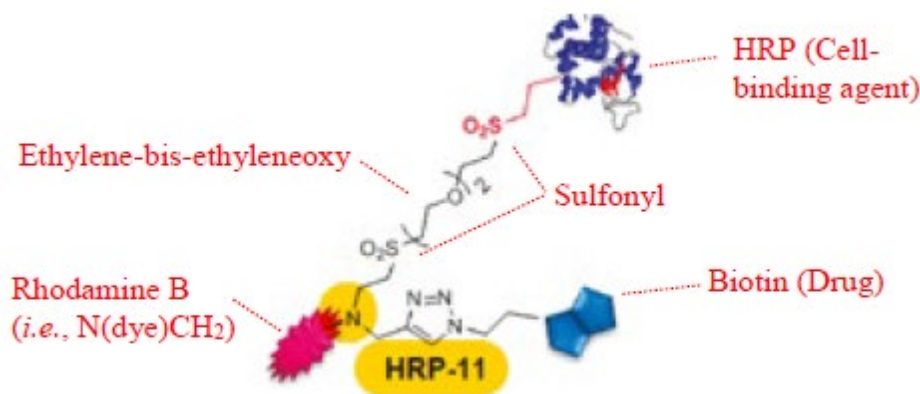
We have concerns regarding Petitioner's arguments for claim 2. As discussed above with regard to claim 1, Petitioner appears to argue that the alkynyl of compound 2 in Morales-Sanfrutos' Table B1 functions as Z, not the amino group recited in the Markush group of claim 2. Pet. 30–32; Ex. 1003 ¶¶ 84, 87. In other words, Petitioner appears to be switching positions between claims 1 and 2 without addressing this inconsistency or how Morales-Sanfrutos, as evidenced by Straus, suggests that the amino

group would function as the Z moiety of claim 1. We suggest the parties further address this issue at trial.

e) Claims 3 and 24

Petitioner contends that the preambles of claims 3 and 24 are not limiting. Pet. 33. Patent Owner does not dispute Petitioner's position. Prelim. Resp. 46–48. For reasons similar to those discussed above for claim 1, we need not decide whether these preambles are limiting, because we agree that, to the extent they are limiting, they are disclosed by Morales-Sanfrutos.

Petitioner cites Morales-Sanfrutos' HRP-11 conjugate to assert that claims 3 and 24 are anticipated. Pet. 33–36 (citing Ex. 1005, 4044 (bottom of Scheme 4); Ex. 1003 ¶¶ 59, 90–96, 99). Petitioner provides an annotated version of HRP-11, which we reproduce below.



Pet. 24. The drawing above shows the HRP-11 conjugate, annotated by Petitioner to define parts of the conjugate. Petitioner argues that HRP functions as Cb, the cell-binding agent, biotin functions as the drug, and other portions of HRP-11 correspond to Q, T, and R groups of claims 3 and 24. *Id.* at 34–36.

As discussed above with regard to claim 1, Patent Owner argues that Morales-Sanfrutos does not disclose a cell-binding agent and Petitioner and

Dr. Chari do not establish that Straus necessarily teaches HRP as a cell-binding agent under the law of inherency. Prelim. Resp. 46–48. Patent Owner further argues that one of ordinary skill in the art “would not understand HRP to be a cell-binding agent” but “would understand HRP to be a reporter as expressly disclosed by Morales-Sanfrutos.” *Id.* at 16 (citing Ex. 2001 ¶¶ 54, 56, 58; Ex. 1005, 4041). For the reasons discussed above with regard to claim 1, we do not agree with Patent Owner’s arguments.

With regard to the recited “Drug” of claims 3 and 24, Petitioner asserts that HRP-11’s biotin is “linked to the rest of the conjugate via a heteroaromatic bond” and the ’682 patent states that drugs may be small molecule drugs including cytotoxic agents and defines a “‘small molecule drug’ as ‘an organic, inorganic, or organometallic compound that may have a molecular weight of for example 100 to 1800, more suitably from 120 to 1400.’” Pet. 34, 36 (citing Ex. 1003 ¶¶ 90–94; Ex. 1001, 29:43–54; Ex. 1045, 4:11–26). Patent Owner argues that “Morales-Sanfrutos expressly discloses that biotin is a ‘tag,’ not a ‘drug’” and that Morales-Sanfrutos discloses a reporter system, which “does not relate to the field of therapeutic protein-drug conjugates and, instead, discloses a reporter system.” Prelim. Resp. 17 (citing Ex. 1005, 4040; Ex. 2001 ¶ 54). On this record, biotin appears to be encompassed by the ’682 patent’s definition of a “small molecule drug,” which is fairly broad in scope. Ex. 1001, 29:43–54. Further, Exhibit 1045 describes the use of biotin as an active ingredient in a medicament that may be used to treat diseases, such as visual impairments. Ex. 1045, 4:11–26.

Patent Owner also reiterates its position that mapping the sulfonyl group of vinylsulfone to Q or T and the vinyl to Y or Z is improper, citing its

arguments for claim 1. Prelim. Resp. 48. As discussed above in our claim construction section, we do not agree with Patent Owner's argument.

In view of Petitioner's arguments and evidence on this record, Petitioner demonstrates a reasonable likelihood that claims 3 and 24 are anticipated by Morales-Sanfrutos, as evidenced by Straus.

f) Claims 6, 25, and 33

Claim 6 depends from claim 3 and specifies that the "cell binding agent is selected from the group consisting of antibodies, proteins, vitamins, peptides, polymeric micelles, liposomes, lipoprotein-based drug carriers, nano-particle drug carriers, dendrimers, and combination thereof." Ex. 1001, 53:5–10. Claim 25 depends from claim 24 and recites that "Q and Tare each independently $-S(O_2)-$ or $-S(O)-$ " with additional recitations for R groups. Ex. 1002, 7:22–25. Claim 33 depends from claim 3 and contains the same recitations as claim 25. *Id.* at 12:29–33.

For claim 6, Petitioner argues that Morales-Sanfrutos' HRP is a protein. Pet. 36–37 (citing Ex. 1003 ¶¶ 59, 90, 98; Ex. 1006, 277).

For claims 25 and 33, Petitioner contends that Morales-Sanfrutos' HRP-11 includes "ethylene in combination with two PEG units $(OCH_2CH_2)_2$ " with the remaining R groups (R_1 , R_3 , and R_4) including alkyl groups. *Id.* at 37 (citing Ex. 1003 ¶¶ 97, 99).

Patent Owner does not present separate arguments for these claims but cites its arguments for claims 3 and 24. Prelim. Resp. 48–49.

On this record, Petitioner demonstrates a reasonable likelihood that HRP is a protein and that Morales-Sanfrutos' HRP-11 meets the limitations of claims 6, 25 and 33.

2. Ground 2: Anticipation or Obviousness Based on Harris

Petitioner asserts that claims 1, 20, 21, and 29–31 are anticipated by Harris, or unpatentable as obvious in view of Harris. Pet. 37–44. We first address Petitioner’s anticipation arguments before addressing Petitioner’s obviousness position.

a) Harris (Ex. 1007)

Harris is titled “Water Soluble Active Sulfones of Poly(ethylene glycol)” (PEG). Ex. 1007, code (54). Harris discloses methods for synthesizing a PEG derivative that is activated with a sulfone moiety. *Id.* at code (57, Abstract). Harris teaches that vinyl and halo-ethyl are conjugation moieties that can couple with sulfone groups to a linker. *Id.* at 6:8–14; 7:8–11. The PEG can have more than one vinyl sulfone attached to become PEG *bis* vinyl sulfone, which is used as a linker or spacer to attach a biologically active molecule to a surface or to attach more than one such biologically active molecule to the PEG molecule. *Id.* at 16:24–17:5. Harris discloses n-hydroxysuccinimide ester and conjugates of biological molecules with reactive thiol moieties that are water soluble. *Id.* at 17:34–18:13. For instance, Harris describes a straight chain PEG derivative having a basic structure of $R-(OCH_2CH_2)_n-Y$ in which n can be from about 5 to 3000. *Id.* at 19:10–15. Harris states that Y may represent $-SO_2-CH=CH_2$ and R may be the same or different from Y. *Id.* at 19:24–27.

b) Claims 1, 20, and 29–31

(1) Petitioner’s Allegations of Anticipation

Petitioner argues that Harris discloses a basic structure of $R-(OCH_2CH_2)_n-Y$ in which R and Y may be vinyl sulfone and/or halo-ethyl sulfone. Pet. 38–39 (citing Ex. 1007, 19:10–15, 19:24–30). According to Petitioner, sulfonyls of this structure would function as Q and T and the PEG

group (OCH₂CH₂) would function as the R₂ moiety of claim 1. *Id.* (citing Ex. 1003 ¶ 103). Petitioner alleges that the “[v]inyl and halo-ethyl groups located adjacent to a sulfone moiety are well-known in the art as functional groups that selectively react with thiol moieties present in cell-binding agents (*e.g.*, antibodies) or cytotoxic drugs to form thioether linkages” and thus would function as Y and Z moieties of claim 1. *Id.* at 38–39 (citing Ex. 1003 ¶¶ 103–104).

For claims 20 and 29–31, Petitioner again cites Harris’ basic structure of R-(OCH₂CH₂)_n-Y in which sulfones would function as Q and T, the PEG group would function as R₂, and a vinyl or halo-ethyl group²¹ would function as Y. Pet. 41 (citing Ex. 1007, 16:34–17:5, 19:10–12, 19:24–30; Ex. 1003 ¶ 108). With regard to the Drug moiety in claims 20, 29, and 30, Petitioner asserts “Harris further teaches that ‘Pharmaceuticals from aspirin to penicillin can be usefully modified by attachment of active sulfone polymer derivatives if these pharmaceuticals are modified to contain thiol moieties.’” *Id.* at 40–41 (citing Ex. 1007, 6:28–31) (emphasis omitted). Petitioner contends that pharmaceuticals containing thiols would therefore attach to Harris’ PEG derivatives via the vinyl sulfone. *Id.* at 41 (citing Ex. 1003 ¶¶ 107–108).

²¹ Petitioner also argues that Harris describes heterobifunctional PEG derivatives including a single sulfone moiety (Q would be absent and the sulfone would function as T) and a N-hydroxysuccinimide (NHS) ester would function as Y. Pet. 42. Patent Owner argues that Petitioner does not cite sufficient support in Harris’ disclosure. Prelim. Resp. 53. For purposes of this decision, we find support for the contention in the cited testimony at Ex. 1003 ¶ 109. We invite the parties to address at trial whether Petitioner has demonstrated a reasonable likelihood that Harris anticipates the challenged claims on this basis.

Patent Owner again argues that Petitioner improperly maps a single prior art element (vinyl sulfone and halo-ethyl sulfone) to two distinct claim elements (Q or T and Y or Z). Prelim. Resp. 49–53. For the reasons discussed above regarding claim interpretation of Y, Z, Q, and T, we do not agree with Patent Owner’s position.

On this record, Petitioner has demonstrated a reasonable likelihood that Harris’ basic structure of $R-(OCH_2CH_2)_n-Y$, in which R and Y may be vinyl sulfone, meets the limitations of claims 1, 20, and 29–31. As argued by Petitioner, the sulfones would function as Q and T and the PEG group would function as R_2 . Pet. 38, 41. We further agree on this record with Petitioner’s position that Harris demonstrates that sulfone polymer derivatives may attach to pharmaceuticals containing thiols, which would satisfy the “Drug” recited by claims 20, 29, and 30. *Id.* at 40–41 (citing Ex. 1007, 6:28–31).

With regard to claim 1, we note the DRP’s determination that mapping a vinyl group to Y or Z “satisfies the ‘enables reaction’ and ‘enables linkage’ requirements of claim 1.” DRP Dec. 16. Therefore, the record at this stage demonstrates a reasonable likelihood that the vinyl of Harris’ vinyl sulfone would function as the Z moiety of claim and enable linkage to a cytotoxic drug, as claim 1 recites. Claims 20, 29, and 30 similarly recite that Y enables reaction of the claimed compound with a cell-binding agent. In view of Harris’ teachings regarding attachment of PEG vinyl sulfone to a protein and the DRP’s finding with regard to claim 1, which includes similar language for Y, Petitioner demonstrates, at this stage, a reasonable likelihood that Harris’ vinyl would function as Y for claims 20, 29, and 30. Pet. 38–29, 41; Ex. 1003 ¶ 104 (citing Ex. 1005, 4043–44; Ex. 1007, 26:7–15); DRP Dec. 16. Therefore, at this stage, Petitioner has

demonstrated a reasonable likelihood that Harris anticipates claims 1, 20, 29, and 30.

With regard to dependent claim 31, we note that, on this record, Petitioner's mapping of Harris' sulfonyls to Q and T and Harris' PEG group to the R₂ group demonstrates a reasonable likelihood that Harris anticipates claim 31. Pet. 41, 43–44. Patent Owner does not present separate arguments for claim 31. Prelim. Resp. 52–54.

On this record, Petitioner demonstrates a reasonable likelihood that that Harris anticipates claims 1, 20, and 29–31.

(2) Petitioner's Allegations of Obviousness

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). In this section, we determine whether Petitioner shows a reasonable likelihood that claims 1, 20, and 29–31 would have been rendered obvious by Harris.

Petitioner argues that claim 1 would have been obvious in view of Harris because one of ordinary skill in the art “would have been motivated to prepare PEG bis vinyl sulfones having, *e.g.*, 5, 34, 45 or 110 ethyleneoxy subunits because Harris teaches that such bifunctional PEGS are water soluble, hydrolytically stable, selective for coupling with thiol moieties, and form stable thioether linkages with proteins and pharmaceuticals.” Pet. 39 (citing Ex. 1007, 6:8–21, 6:28–33, claim 34). Petitioner further asserts that “PEG groups may be linear or branched” and one of ordinary skill in the art “would have had a reasonable expectation of success in making a PEG bis

vinyl sulfone as Example 1 of Harris expressly show[s] how to prepare terminal PEG vinyl sulfone derivatives.” *Id.* at 39–40 (citing Ex. 1007, Examples 2–4; Ex. 1003 ¶ 105). Petitioner’s obviousness arguments for claims 20, and 29–31 rely on the reasoning set forth for claim 1. *Id.* at 42–44.

Patent Owner contends that “Petitioner provides no detailed analysis of how combining any particular structures in Harris achieves the specific combination of elements” recited for the claimed linkers. Prelim. Resp. 51. Patent Owner further argues that “Petitioner does not provide any motivation to combine vinyl or haloethyl—alone and not part of a sulfone group—to achieve a Y/Z group in the claimed linker” and does not “identify any reason to use sulfones (or other claimed spacer structures) as spacer elements.” *Id.* at 52 (emphasis omitted). Patent Owner also relies on these arguments for claims 20 and 29–31. *Id.* at 54.

To the extent Patent Owner relies upon the arguments against splitting vinyl sulfone between moieties Q or T and Y or Z, we do not agree with Patent Owner for the reasons discussed above in the claim construction of those recited moieties. Because we institute on the basis of Petitioner’s other positions, including anticipation by Harris, we reserve the issue of obvious of the challenged claims over Harris for trial.

c) Claim 21

Petitioner alleges that Harris anticipates or renders obvious claim 21. Petitioner cites Harris’ description of pharmaceuticals “‘from aspirin to penicillin’ [that] can be modified to contain thiol (*i.e.*, –SH) moieties.” Pet. 43 (citing Ex. 1007, 6:28–31; Ex. 1003 ¶ 113). Patent Owner does not present separate arguments for claim 21. Prelim. Resp. 52–54.

On this record, Petitioner demonstrates a reasonable likelihood that that Harris anticipates claim 21. We reserve the issue of whether Harris renders claim 21 obvious for trial.

3. Ground 3: Obviousness Based on Singh and Harris

In this section, we determine whether Petitioner shows sufficiently, for purposes of institution, that claims 1–8, 10–12, 14–17, 20, 21, 24, 26, and 29–31 would have been rendered obvious by the combination of Singh and Harris.

a) Singh (Ex. 1008)

Singh is titled “Potent Conjugates and Hydrophilic Linkers.” Ex. 1008, code (54). Singh discloses modifying linkers used to bind drugs to cell binding agents by incorporating a PEG spacer. *Id.* at code (57, Abstract). Singh teaches a compound that includes a PEG spacer, a drug, and an aliphatic, aromatic, or heterocyclic group attached to the drug via a covalent bond (such as a thioether or amide bond), and “a reactive functionality that can form an amide or a thioether bond with a cell-binding agent.” *Id.* ¶¶ 9, 14. Singh describes a reactive functionality as “an amine-, a thiol- or a hydroxyl-reactive functionality,” and states, “[i]n other words, the reactive functionality can react with amine, sulfhydryl(thiol), or hydroxyl group present on cell-binding agent.” *Id.* ¶ 134. Singh further explains that a thiol-reactive functionality “could be a maleimide, a haloacetamide, or a vinyl sulfone to give a thioether bond.” *Id.*

b) Claim 1

Petitioner argues that Singh teaches bifunctional PEG cross-linkers that contain “each element of claim 1, save Q and T.” Pet. 44. Petitioner cites particular examples of Singh’s bifunctional PEG cross-linkers, which Petitioner summarizes in Table A1 (reproduced below). *Id.* at 13.

Table A1

Entry	Bifunctional PEG Cross-linkers	Figs.
1		4, 8
2		6B, 12
3		10
4		13, 15
5		16B, 18

Pet. 13. Table A1, reproduced above, shows examples of Singh's bifunctional PEG cross-linkers.

Petitioner provides Table C1, reproduced below, to illustrate how Singh's PEG cross-linkers meet the elements of claim 1, except for Q and T.

Table C1

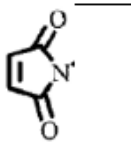
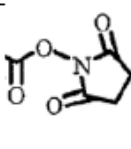
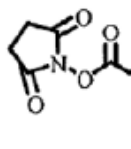
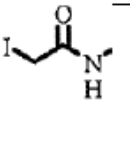
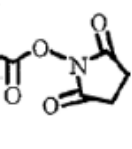
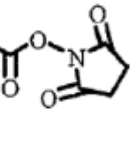
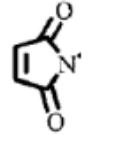
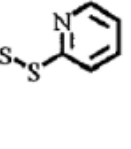
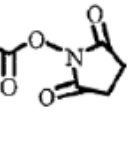
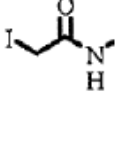
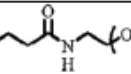
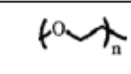
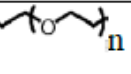
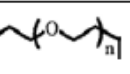
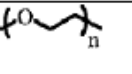
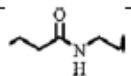
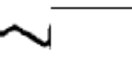
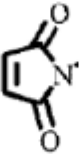
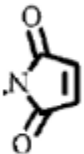
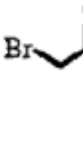
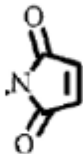
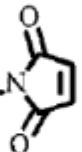
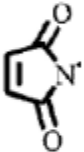
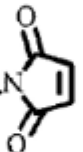
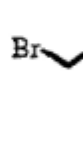
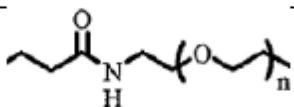
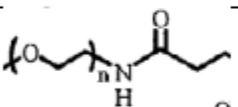
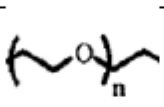
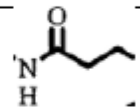
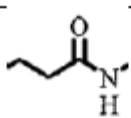
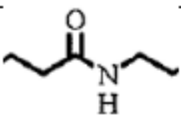
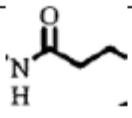
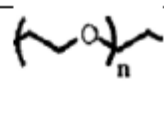
	Singh's Compounds (Table A1)				
'682 (I)	1		2	3	
	(a)	(b)		(a)	(b)
Y					
Z					
R₁	absent	absent	absent	absent	absent
R₂					
p	n=1-2000, 1-100, 1-14, 1-4	n=1-2000, 1-100, 1-14, 1-4	n=1-14	n=1-2000, 1-100, 1-14, 1-4	n=1-2000, 1-100, 1-14, 1-4
R₃	absent	absent	absent	absent	absent
R₄	absent		absent	absent	

Table C1 (continued)

	Singh's Compounds (Table A1)			
'682 (I)	4		5	
	(a)	(b)	(a)	(b)
Y				
Z				
R₁	absent	absent	absent	absent
R₂				
p	n=1-2000, 1-100, 1-14, 1-4	n=1-2000, 1-100, 1-14, 1-4	n=1-2000, 1-100, 1-14, 1-4	n=1-2000, 1-100, 1-14, 1-4
R₃	absent	absent	absent	absent
R₄				

Pet. 46–47. Table C1, reproduced above, illustrates Petitioner's view of how Singh's PEG cross-linkers meet the elements of claim 1, except for Q and T.

We select, as representative of Petitioner's ground over Singh in view of Harris, Patent Owner's arguments with respect to compound 4 (*see* Tables A1 and C1 above). We begin by summarizing Petitioner's arguments

regarding how the teachings of Singh and Harris teach the limitations of claim 1.

With specific regard to moiety Y, Petitioner argues that Singh's "cross linkers include a reactive functionality on each end of the linker," namely a maleimide, iodo- or bromo-acetamide, or NHS ester group. Pet. 45 (citing Ex. 1008 ¶¶ 134, 136, Figures 4, 8, 10, 13, 15, 16A). Petitioner asserts that "[t]hese functional groups 'enable reaction of the hydrophilic linker with a cell-binding agent' and therefore meet the definition of Y in formula (I)," as claim 1 recites. *Id.* (citing Ex. 1008 ¶ 136; Ex. 1003 ¶ 119).

Petitioner also contends that the reactive functionality at the other end of Singh's cross-linkers (a pyridyldisulfide, maleimide, iodo- or bromoacetamide, or NHS ester group) enables linkage to a cytotoxic drug via a disulfide, thioether, or amide bond, as claim 1 recites for moiety Z. *Id.* at 45–46 (citing Ex. 1003 ¶¶ 120, 136, Figures 4, 6B, 8, 12–13, 15, 16B).

Petitioner argues that Harris discloses a basic structure encompassing hydrophilic PEG derivatives comprising "one or two sulfone moieties that are useful for conjugating two biologically-active molecules (e.g., proteins, pharmaceuticals), where at least one of the biologically-active molecules has a reactive thiol moiety." Pet. 41–42, 49 (citing Ex. 1007, claims 33, 34, 3:28–35, 16:34–17:5, 18:5–30, 19:10–15, 24–30, Abstract; Ex. 1003, ¶126).

In view of this teaching, Petitioner alleges that the ordinarily skilled artisan "would have been motivated to replace one or both of the reactive functionalities in Singh's bifunctional PEG cross-linkers with a vinyl sulfone group, resulting in Q or Q and T each being a sulfone group, and Y, or Y and Z, each being a vinyl group." *Id.* at 48–49 (citing Ex. 1003 ¶ 125).

Petitioner argues that the ordinarily skilled artisan would have found it obvious to modify Singh's linker in view of Harris "to incorporate" vinyl

sulfones and that the artisan would have appreciated advantages provided by Harris' sulfonyl-containing PEG derivatives, including their high selectivity for coupling with thiol moieties on molecules, their high solubility and stability in water. *Id.* at 49–51 (citing Ex. 1007, 6:8–15, 19:37–37, 26:11–15, 28:29–34; Ex. 1003 ¶¶ 128–129). Petitioner further contends that one of ordinary skill in the art would have expected such a combination to successfully yield hydrophilic linkers with desirable functional properties. *Id.* at 51 (citing Ex. 1008 ¶ 134, Figures 50–51; Ex. 1007, 21:26–28:28; Ex. 1003 ¶ 130). According to Petitioner:

Thus, modifying the PEG-containing ADC linkers of Singh to *include* vinyl sulfones or related sulfonyl derivatives as a reactive functionality that can form a thioether bond with a cell-binding agent or drug would be expected to have comparable, if not higher, hydrophilicity, and such conjugates would be expected to exhibit the same advantageous properties (enhanced potency, less precipitation) already recognized by Singh for its ADC linkers.

Id. at 52 (citing Ex. 1003 ¶ 131) (emphasis omitted). Petitioner argues that Singh “expressly suggests the use of vinyl sulfones as a thiol-reactive functionality and teaches their equivalence to maleimide and haloacetamides for this purpose.” *Id.* at 48 (citing Ex. 1008 ¶ 134; Ex. 1003 ¶ 124). These modifications would provide the Q and/or T moieties of claim 1.

On this preliminary record, Petitioner has established a reasonable likelihood that claim 1 would have been unpatentable in view of Singh's compound 4, as modified in view of Harris. As noted above, the DRP determined that, when the hydrophilic linker contains a vinyl sulfone group, the vinyl group should be mapped to moiety Y or Z, and the vinyl meets the “enables reaction” function for Y and the “enables linkage” function for Z. DRP Dec. 16. Furthermore, Singh relates to linkers that link drugs, such as

cytotoxic agents, to cell-binding agents and describes how thiol-containing maytansinoid drugs may be linked via a thioether bond. Ex. 1008 ¶¶ 2, 136. Singh also teaches that vinyl sulfone is a thiol-reactive functionality that provides a thioether bond. *Id.* ¶ 134. Therefore, at this stage, according to our understanding of Petitioner’s challenge, Singh’s disclosure further supports the vinyl of a vinyl sulfone group providing the enabling reaction function of Y and the cytotoxic drug linkage function of Z recited in claim 1. Petitioner’s mapping of Singh’s compound 4, as modified in view of Harris, to the R₂ and R₄ moieties of claim 1 satisfies those limitations on this record. Pet. 48. We address Patent Owner’s arguments in opposition below.

Patent Owner first argues that Harris is non-analogous art, stating that “Harris is not from the same field of endeavor as the ’682 Patent’s inventions as Harris does not relate to the field of therapeutic protein-drug conjugates.” Prelim. Resp. 20 (citing Ex. 2001 ¶ 63). According to Patent Owner, “Harris ‘relates to active derivatives of poly(ethylene glycol) and related hydrophilic polymers and to methods for their synthesis for use in modifying the characteristics of surfaces and molecules.’” *Id.* (citing Ex. 1007, 1:2–6, 18:34–19:2; Ex. 2001 ¶¶ 63–68) (emphases omitted). Patent Owner further argues that “Harris [is not] reasonably pertinent to the problem facing the ’682 Patent inventors” because “Harris does not teach therapeutic linkers, much less linkers that solve the identified need . . . it is not reasonably pertinent to this problem.” *Id.* (citing Ex. 1001, 2:45–49; Ex. 2001 ¶ 63).

Petitioner responds that Patent Owner’s argument regarding the relevant field relies upon an intended use of the claimed structures, not whether Harris discloses the claim limitation. Pet. Prelim. Reply 9–10. According to Petitioner, the ’682 patent focuses on hydrophilic linkers that

can be used to conjugate drugs and cell-binding agents. *Id.* at 10 (citing Ex. 1001, 1:7–9, 14:45–15:11). Petitioner asserts that Harris “is within the same field of endeavor: ‘PEG/sulfone derivatives as useful for conjugating two different biologically-active moieties such as proteins [and] pharmaceuticals’” and “is pertinent to the problem addressed via its teaching of sulfone linkers having infinite water solubility that bring otherwise insoluble molecules into solution.” *Id.* (citing Pet. 6) (alternation in original).

Patent Owner argues that “Harris is non-analogous art to the ’682 Patent with respect to Grounds 3-5.” PO Sur-reply 9. Patent Owner contends that Petitioner does not dispute Patent Owner’s argument that “Harris does not relate to the field of therapeutic protein-drug conjugates and does not teach conjugation of a drug to an antibody or other protein for use in therapeutic targeting.” *Id.* at 9–10 (emphases omitted). According to Patent Owner, “[t]he field of the ’682 Patent relates to novel linkers that are desirable for the targeted treating of specific cell populations, such as cancer cells, using a selective cell-binding agent such as an antibody attached to a drug compound.” *Id.* at 10 (citing Ex. 1001, 1:6–15). Patent Owner contends that Harris “instead is focused on the use of PEG derivatives for ‘modifying the characteristics of surfaces and molecules . . . not for therapeutic targeting.” *Id.* (citing Ex. 1007, 3:2–6). Patent Owner also argues that “[t]he inventors of the ’682 Patent were focused on developing therapeutic linkers that addressed the potency, selectivity, and pharmacokinetics of the resulting conjugates,” whereas “Harris does not disclose linkers designed to address these properties of therapeutic drug conjugates.” *Id.* (citing Prelim. Resp. 7).

The field of endeavor test involves identifying explanations of the invention's subject matter in the patent, "including the embodiments, function, and structure of the claimed invention." *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004). The '682 patent relates to hydrophilic linkers for the conjugation of a drug, such as a cytotoxic agent to a biological molecule. Ex. 1001, 1:7–9. Harris relates to water soluble and hydrolytically stable derivatives of PEG polymers and related hydrophilic polymers having one or more active sulfone moieties, which are "highly selective for coupling with thiol moieties instead of amino moieties on molecules and on surfaces." Ex. 1007, 6:8–14. Harris further teaches that "[p]harmaceuticals from aspirin to penicillin can be usefully modified by attachment of active sulfone polymer derivatives if these pharmaceuticals are modified to contain thiol moieties." *Id.* at 6:28–31. Harris also describes attachment of its PEG vinyl sulfone to a protein. *Id.* at 28:17–21. On this record, Petitioner sufficiently demonstrates that Harris is in the same field of endeavor as the '682 patent.

Patent Owner next argues that Petitioner's allegations incorrectly map the independent function of the Y group to the combined Q-Y vinyl sulfone group because Y is an independent moiety not reliant on the function of Q. Prelim. Resp. 54–58. As we understand Petitioner's challenge for claim 1, incorporating vinyl sulfone into Singh's linker, in view of Harris's teachings, would provide moieties that satisfy Q and/or T. Pet. 49. For compound 4, Petitioner argues the existing maleimide groups in Singh's linkers function as moieties Y and Z for claim 1, as shown in Petitioner's Table C1. *Id.* at 45–46, 48. This comports with Petitioner's argument for claim 2, which appears to rely on the existing maleimide or haloacetamide groups in the compounds shown in Petitioner's Tables A1 and C1. *Id.* at 53.

However, Petitioner also argues that the ordinarily skilled artisan would have modified Singh's linker "to *include* vinyl sulfones or related sulfonyl derivatives as a reactive functionality that can form a thioether bond with a cell-binding agent or drug." *Id.* at 52. This mapping appears to treat the "included" vinyl sulfones as also functioning as the Y and Z moieties of claim 1. We highlight these concerns and encourage the parties to further address them at trial. For purposes of institution, we treat Petitioner's challenge for claim 1 as incorporating vinyl sulfone into Singh's linker, in view of Harris's teachings, which would provide moieties that satisfy moieties Q and/or T recited in claim 1. *See* Pet. 49. For compound 4 shown in Petitioner's Tables A1 and C1, this modification would appear to leave the maleimide groups to function as Y and Z. From this standpoint, Petitioner does not argue that the added vinyl sulfones function as Y, as Patent Owner contends. Prelim. Resp. 54–58.

Patent Owner also cites its arguments against Harris's disclosures as discussed in the second ground above and further contends that Petitioner has not identified sufficient motivation to add vinyl alone to Singh's linker. Prelim. Resp. 56–58. We disagree. Petitioner articulates that modifying Singh's linker to incorporate vinyl sulfones in view of Harris's teachings would provide Singh's linkers hydrophilicity and other advantages of vinyl sulfones. *See* Pet. 49–52. As discussed above, Petitioner's proposed modification would appear to leave the maleimide groups of Singh's compound 4 intact and able to function as the Y and Z moieties of claim 1. *Id.* at 45–46. On this record, Petitioner has demonstrated a reasonable likelihood that these maleimide groups would function 1) as moiety Y because Singh describes a maleimide group reacting with a cell binding agent (Ex. 1008 ¶ 136); and 2) as moiety Z because Singh describes a

maleimide group as a reactive functionality that forms a thioether bond, which Singh teaches to be a bond that can be formed with a maytansinoid drug (*id.* ¶¶ 134, 136). Dr. Chari states that maytansinoids are used as cytotoxic anti-tumor drugs. Ex. 1003 ¶ 9.

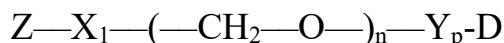
For the same reasons, compounds 1–3 and 5 of Petitioner’s Table C1 would also appear on this record to demonstrate a reasonable likelihood that claim 1 is unpatentable. *See* Pet. 48. As discussed above, Petitioner appears to sufficiently explain at this preliminary stage why the ordinarily skilled artisan would have found it obvious to modify the linkers of compounds 1–3 and 5 with the maleimide, haloacetimide, and/or NHS ester group of these linkers. In doing so, the resulting compound would satisfy the Q, T, Y and Z moieties of claim 1. *See* Pet. 45–58.

c) Claim 2

For dependent claim 2, Petitioner argues that “[b]oth Singh and Harris teach that Z can be maleimide or haloacetyl, as set forth in Table C1.” Pet. 53 (citing Ex. 1003 ¶¶ 133–134). Based on our understanding that Petitioner’s modification of Singh in view of Harris incorporates vinyl sulfones in Singh’s compound 4 to function as Q and T and leave maleimides groups to function as Y and Z (*see* Pet. 45–46, 48–49), Petitioner appears at this stage to demonstrate a reasonable likelihood that the proposed modification of Singh in view of Harris would render claim 2 unpatentable.

d) Claims 20, 29, and 30

Regarding claims 20 and 29–31, Petitioner argues that Singh discloses formula (1), reproduced below, as a PEG drug linker that may be attached to a cell binding agent.



Pet. 54 (citing Ex. 1008 ¶¶ 14, 80; Ex. 1003 ¶¶ 137–151). According to Petitioner, formula (1) overlaps with and suggests the claimed compounds. *Id.*

Petitioner asserts that Singh teaches Z to be “a reactive functionality that can form an amide or a thioether bond with a cell-binding agent,” which satisfies moiety Y for claims 20, 29, and 30. *Id.* at 54 (citing Ex. 1003 ¶ 138) (emphasis omitted). According to Petitioner, Singh teaches that the reactive functionality may be vinyl sulfone, which also satisfies moiety Q in claims 20, 29, and 30. *Id.* at 54–55 (citing Ex. 1008 ¶ 134; Ex. 1003 ¶ 138).

Petitioner further contends that the formula’s PEG group satisfies R₂, addresses how R₃ would be satisfied, that Singh’s formula includes “D” for drug, and that the last limitation of claims 20 and 29 may be satisfied when Singh’s formula includes a single sulfonyl group (i.e., Q or T is sulfone because Singh’s linker includes vinyl sulfone, one of m and n is 0, and Singh’s Z is an NHS ester). *Id.* at 55–57 (citing Ex. 1003 ¶¶ 140–141, 143; Ex. 1008 ¶¶ 80, 134).

With regard to R₄ of claims 20, 29, and 30, which connects the claimed Drug to the linker, Petitioner argues that moiety Y in Singh’s formula is an aliphatic or heterocyclic group attached to Singh’s Drug via a thioether or amide bond, a carbamate bond, an ether bond, or an amine bond. *Id.* at 56 (citing Ex. 1003 ¶ 141). Petitioner further argues that Singh’s Y in formula (1) can provide a single sulfonyl group, per claims 20 and 29, or can provide first and second sulfone groups because Singh discloses the use of vinyl sulfones as thiol reactive moieties. *Id.*

Patent Owner cites its argument for claims 1 and 2. Prelim. Resp. 58.

For the reasons discussed above with regard to claim 1, we do not agree with Patent Owner’s arguments. On this record, Petitioner has

demonstrated a reasonable likelihood that claims 20, 29, and 30 would have been unpatentable over Singh and Harris.

Singh's formula (1) ($Z-X_1-(CH_2-O)_n-Y_p-D$) includes a PEG group that would satisfy R_2 , including when both Q and T are a sulfone group, as claim 30 recites. Singh further teaches that "D represents a drug," which satisfies the Drug of claims 20, 29, and 30. Ex. 1008 ¶ 15.

With respect to R_4 of claims 20 and 29, Petitioner argues that "when Y of Singh's formula (1) is sulfonyl ethyl with a thioether link to the drug, Singh's Z may be reactive functionalities that form a thioether or amide bond." Pet. 57 (emphasis omitted). Singh teaches that formula (1)'s Y "represents an aliphatic, an aromatic or a heterocyclic group attached to the drug via a covalent bond selected from the group consisting of a thioether bond, an amide bond, a carbamate bond, an ether bond, an amine bond, a carbon-carbon bond and a hydrazone bond." Ex. 1008 ¶ 14. Singh further teaches that vinyl sulfone will form a thioether bond. *Id.* ¶ 134. Therefore, on this record, Petitioner has demonstrated a reasonable likelihood that Singh suggests the use of vinyl sulfone as Y in Singh's formula (1). In such a situation, the sulfone group of the vinyl sulfone would function as moiety T in claims 20 and 29 and the vinyl (an aliphatic group) of the vinyl sulfone would function as R_4 in claims 20 and 29, which may be a linear alkyl of 1–6 carbon atoms. Pet. 56. This would also provide the type of bond that claims 20 and 29 recite for how the Drug is linked (e.g., via a thioether bond due to the vinyl sulfone group). Further, on this record, we agree with Petitioner's contention that R_3 in this circumstance can be absent or Singh's X in formula (1) may function as R_3 . *Id.*

As noted above, Petitioner argues that "when Y of Singh's formula (1) is sulfonyl ethyl with a thioether link to the drug, Singh's Z may be reactive

functionalities that form a thioether or amide bond.” Pet. 57 (emphasis omitted). Petitioner further asserts that Singh teaches an NHS ester forms an amide bond. *Id.* (citing Ex. 1008 ¶¶ 134). On this record, we agree that Singh discloses Z in formula (1) as “a reactive functionality that can form an amide or a thioether bond with a cell-binding agent” and further teaches that an NHS ester is an amine-reactive functionality that can form an amide bond. Ex. 1008 ¶¶ 14, 134. On this record, Petitioner’s allegations satisfy moiety Y of claims 20 and 29 for the circumstance in which T is sulfone, m is 0, and Y is an NHS ester (the last limitation of claims 20 and 29).

Claim 30 differs from claims 20 and 29 by requiring that m and n are integers from 1 to 5. In other words, claim 30 requires a Q and a T, which are each either a phosphinate, sulfone, or sulfoxide. On this record, Petitioner demonstrates that Singh’s formula (1) suggests claim 30. Petitioner argues that Z of Singh’s formula (1) may be vinyl sulfone and that the sulfone would function as Q. Pet. 54–55. At this stage, we agree that Singh teaches that Z of formula (1) may be a reactive functionality that forms a thioether bond with a cell-binding agent and that vinyl sulfone is a thiol-reactive functionality that forms a thioether bond. Ex. 1008 ¶¶ 14, 134. Petitioner also argues that Y of Singh’s formula (1) can provide a second vinyl sulfone group to provide a thioether bond to a drug. Pet. 56. As discussed above with regard to claims 20 and 29, Petitioner has demonstrated a reasonable likelihood on this record that Singh suggests the use of vinyl sulfone as Y for Singh’s formula (1). This use would provide a sulfone that functions as T and a vinyl group that functions as R₄ and would provide a thioether bond, as claim 30 requires for its drug linkage.

Petitioner also provides a Table C2 to diagram how specific examples taught by Singh in Figures 4, 5, 6A, 13, and 16A would map to claims 29,

30, and 31. Pet. 57–59. Petitioner further argues that it would have been obvious to substitute a thiol reactive group (maleimide) or an amide bond forming group (e.g., NHS ester) with vinyl sulfone. *Id.* at 60. We have concerns about Petitioner’s allegations with respect to Table C2. For entries 1, 2, and 4, Petitioner indicates that the NHS ester would be replaced with vinyl sulfone. *Id.* at 57–59. Singh teaches that NHS ester is an amine-reactive functionality that provides an amide bond, not a thiol-reactive functionality like maleimide and vinyl sulfone that forms a thioether bond. Ex. 1008 ¶ 134. In other words, although Singh teaches various reactive functionalities, Singh groups these functionalities according to what type of bond they form. *Id.* On this record, we have concerns whether Petitioner has demonstrated a reasonable likelihood that a thioether bond forming reactive functionality (e.g., maleimide or vinyl sulfone) would bond with the same cell-binding agent or drug as an amide bonding forming reactive functionality (e.g., an NHS ester). Therefore, we have concerns whether Petitioner has demonstrated a reasonable likelihood that an ordinarily skilled artisan would have found it obvious to replace an NHS ester group with a vinyl sulfone group as alleged. In addition, Petitioner indicates that entry 3 would include a substitution of vinyl sulfone for the maleimide group on the right-hand side, providing moieties Q or T and Y in the claims, but does not address how entry 3 would satisfy the other of Q and T (e.g., as a phosphinate, sulfone, or sulfoxide), as claim 30 recites.

Petitioner also argues that one of ordinary skill in the art “would have been motivated to incorporate vinyl sulfones as the Z group in formula (I) of Singh and/or attach the drug using a vinyl sulfone in view of Harris and would have had a reasonable expectation of success in doing so.” Pet. 56 (citing Ex. 1003 ¶ 142). As discussed above with regard to claim 1,

Petitioner has sufficiently articulated a rationale to modify Singh's linker "to incorporate" vinyl sulfones, as Petitioner asserts at this preliminary stage. However, for claim 1, Petitioner asserted that the existing maleimide groups in Singh's linkers function as moieties Y and Z, not the vinyl sulfones. *See, e.g.*, Pet. 45–46, 48. We suggest the parties address this disparity at trial.

Again citing its arguments for claim 1 under this ground, Petitioner asserts that it would have been obvious to *substitute* with vinyl sulfone in view of Harris. *Id.* at 60. Petitioner's rationales argued for claim 1 (*id.* at 49–52) appear to demonstrate a reasonable likelihood of success on this record that one of ordinary skill in the art would have had a reason to modify Singh's linker by substituting vinyl sulfone for thiol reactive groups that can react with a cell-binding agent or form a thioether bond to a drug, as Petitioner argues. *Id.* For the reasons discussed above with regard to claims 20, 29, and 30, vinyl sulfone would function as moieties T and R₄ of claims 20, 29, and 30 and as Q and Y of claim 30. Petitioner also argues it would have been obvious to replace an amide bond forming group, such as an NHS ester, with vinyl sulfone in view of Singh's teachings or in view of Harris. *Id.* For the reasons discussed above with regard to entries 1, 2, and 4 in Petitioner's Table C2 (Pet. 57–59), Petitioner demonstrates a reasonable likelihood on this record that it would have been obvious to replace an NHS ester group with a vinyl sulfone group in view of Harris (Pet. 49–52).

e) Claims 21 and 31

Petitioner contends that claim 21 would have been obvious over the teachings of Singh and Harris. *Id.* at 61 (citing Ex. 1007, 6:28–31; Ex. 1008 ¶¶ 136, 139; Ex. 1003 ¶¶ 151, 153). For claim 31, Petitioner argues that, as discussed with respect to claims 20 and 29, Singh's PEG group functions as R₂ and/or R₃. Pet. 61.

Patent Owner does not present separate arguments for claims 21 and 31. Prelim. Resp. 58.

On this record, Petitioner has demonstrated a reasonable likelihood that claims 21 and 31 would have been unpatentable over the teachings of Singh and Harris. For claim 21, Singh teaches that a maytansinoid drug may be linked via a thioether bond. Ex. 1008 ¶ 136. As discussed above with regard to claim 1 and claims 20, 29, and 30, maleimides and vinyl sulfone may form a thioether bond. *Id.* ¶ 134. With regard to claim 31, Singh's PEG group corresponds to moiety R₂ of claim 30 and Singh suggests the use of two vinyl sulfone groups that would provide two sulfone groups that correspond to Q and T in claim 30, as discussed above with regard to claims 20, 29, and 30.

f) Claims 3, 24, and 26

As an initial matter, Petitioner contends that the preambles (reciting “cell-binding agent-drug conjugate”) of claims 3, 24, and 26 are not limiting, or, alternatively, would have been taught by Singh in view of Harris. Pet. 62. Because we agree, and Patent Owner does not dispute that, these references disclose the preamble, we do not further address whether the preamble is limiting.

Petitioner argues that Singh teaches formulas (2)/(2') and (4)/(4'). Pet. at 62 (citing Ex. 1008 ¶¶ 15, 17, 84, 93, 136–138, 214, 218–221, Figs. 1–3, 7–12, 14–15, 17–18, 20–21). According to Petitioner, Singh's disclosures for D, Y, p, n, and X for formulas (2)/(2') are identical to those for formula (1). *Id.* at 63 (citing Ex. 1003 ¶ 157). In view of this, Petitioner cites its arguments for claim 1 and claims 20, 29, and 30, including why “sulfonyl groups [meet] the definition of Q and T,” for claims 3, 24, and 26. *Id.* Petitioner further asserts that one of ordinary skill in the art would have

understood that the cell-binding agent of Singh's formulas teaches the cell-binding agent of claims 3, 24, and 26. *Id.* (citing Ex. 1003 ¶ 158).

For claims 3, 24, and 26, Patent Owner cites its arguments provided earlier in their Preliminary Response. Prelim. Resp. 59.

Singh teaches for formula (2) that Z represents a reactive functionality that can form an amide or thioether bond with a cell-binding agent and Y represents an aliphatic, aromatic, or heterocyclic group attached to a drug via a thioether or amide bond. Ex. 1008 ¶ 15. In other words, Z and Y of Singh's formula (2) are similar to Z and Y of Singh's formula (1). Further, as noted above, Petitioner asserts for claims 3, 24, and 26 and that one would include vinyl sulfonyl to satisfy Q and T. Therefore, for the reasons discussed above with regard to claim 30, Petitioner has demonstrated a reasonable likelihood that claims 3, 24, and 26 would have been unpatentable as alleged.

g) Claims 4–8, 10–12, and 14–17

Petitioner provides arguments asserting why claims 4–8, 10–12, and 14–17 would have been obvious over Singh and Harris. Pet. 67–70. Claims 4–8, 10–12, and 14–17 depend from claim 3. Patent Owner does not provide separate arguments for these dependent claims. Prelim. Resp. 59.

On this record, Petitioner has demonstrated a reasonable likelihood of demonstrating that claims 4–8, 10–12, and 14–17 would have been obvious in view of the teachings of Singh and Harris cited in the Petition and for the reasons argued by Petitioner.

4. Ground 4: Obviousness Based on Singh, Harris, and Bhakta

Petitioner argues that claims 9 and 13 would have been obvious in view of Singh, Harris, and Bhakta. Pet. 70–72.

a) Bhakta (Ex. 1011)

Bhakta is titled “Cysteine Engineered Antibodies and Conjugates).”

Ex. 1011, code (54). Bhakta discloses antibody-drug conjugates comprising:

a cysteine engineered antibody (Ab), and a drug moiety (D) wherein the antibody has one or more free cysteine amino acids, and the antibody is attached through the one or more free cysteine amino acids by a linker moiety (L) to D; the composition having formula I: Ab-(L-D)_p, where p is 1, 2, 3, or 4.

Id., ¶¶ 211–0212. Bhakta discloses that its antibody drug conjugates may form dipeptides or longer peptides using naturally or non-naturally occurring amino acid analogs, including citrulline. *Id.*, ¶¶ 244–245.

b) Analysis

Petitioner asserts that Bhakta shows that valine-citrulline was a well-known cleavable dipeptide used to link drugs in ADCs, similar to how disulfide bonds were used. Pet. 71. Specifically, Petitioner argues that “Bhakta expressly teaches ADCs comprising a cysteine engineered antibody and a drug moiety, wherein the antibody has one or more free cysteine amino acids that attach via a linker to the drug moiety” and “may further comprise amino acid residues linking the antibody to the drug moiety of the cysteine engineered ADC, where the amino acid residues can be ‘optimized in their selectivity for enzymatic cleavage by...for example, a tumor-associated protease to liberate an active drug moiety.’” *Id.* (citing Ex. 1011 ¶¶ 244–245). According to Petitioner, “[t]he valine-citrulline (‘val-cit’) dipeptide is highlighted and can be cleaved by cathepsin B, C and D, or a plasmin protease.” *Id.*

Petitioner argues that “ADCs utilizing the disulfide linkages of Singh were previously found to exhibit reduced efficacy, greater off target toxicity

and poor serum stability.” Pet. 72 (citing Ex. 1049, Abstract). Petitioner contends that one of ordinary skill in the art:

would have been motivated to use the well-known val-cit-PAB linker of Bhakta to replace, *e.g.*, the disulfide linkage of Singh, in order to obtain more selective and efficient release of the Drug at target cancer cells because, for example, when the val-cit dipeptide is cleaved from the PAB by cathepsins associated with the target cancer cell, the ester linkage to the drug subsequently hydrolyzes as well and releases the drug within the cancer cell.

Id. (citing Ex. 1017, 101:1–104:43; Ex. 1003 ¶¶ 181–182).

Patent Owner argues that this ground fails for the same reasons as in the Ground based on Singh and Harris because claims 9 and 13 depend from claim 3. Prelim. Resp. 59.

On this record, we have concerns whether Petitioner has demonstrated a reasonable likelihood that claims 9 and 13, which depend from claim 3, would have been obvious over Singh, Harris, and Bhakta. In particular, Petitioner argues that one of ordinary skill in the art would have replaced disulfide linkages in Singh’s compound or formula. Petitioner cites Singh’s formulas (2) and (4) in its arguments for claim 3. Pet. 61–63. Singh’s formula (2) does not include a disulfide bond whereas Singh’s formula (4) includes a disulfide bond to link to a drug. Ex. 1008 ¶¶ 15, 17.

Petitioner’s arguments for claim 3 regarding Singh’s formulae, however, focus more on formula (2) (which lacks a disulfide bond). Pet. 61–63. Petitioner did not adequately explain its arguments based on formula (4). Therefore, we have concerns whether Petitioner has sufficiently demonstrated a reasonable likelihood that Singh’s formula (4) would render claim 3 unpatentable. We suggest the parties further address this issue at trial.

5. *Ground 5: Based on Singh, Harris, and Snow*

Petitioner asserts that claims 2, 25, and 32–34 would have been rendered obvious by the combination of Singh, Harris, and Snow. Pet. 73–76.

a) *Snow (Ex. 1010)*

Snow is titled “Vinyl Sulfone Coupling of Polyoxyalkylenes to Proteins.” Ex. 1010, code (54). Snow discloses polyalkylene oxide vinyl sulfone reagents and a method for using them in hydrated media for the modification of proteins. *Id.* at code (57, Abstract).

b) *Analysis*

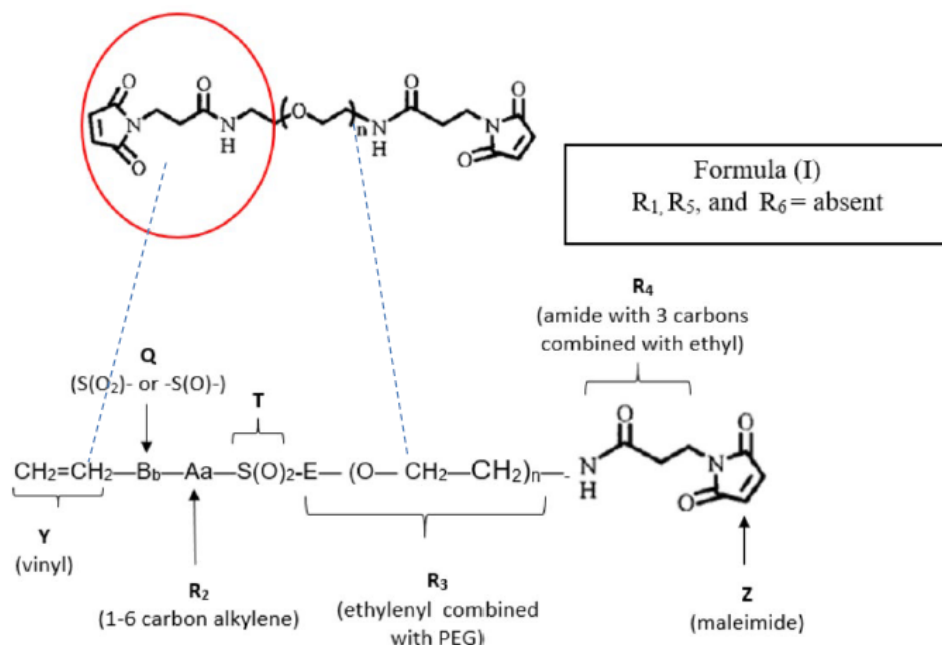
Petitioner relies on Singh and Harris for the alleged disclosures of Y and Z as discussed above in regards to the Ground 3 based on Singh and Harris. Pet. 73. Specifically, Petitioner cites the compounds of Singh that Petitioner provides in Table A1 (relied upon for claim 1) and in Table C2 (relied upon for claims 20, 29, and 30), asserting that “Singh discloses a bifunctional bismaleimide PEG crosslinker that can be conjugated to a thiol-bearing maytansinoid drug.” *Id.* at 74.

According to Petitioner, one of ordinary skill in the art “would be motivated to further improve the solubility of ADC linkers that are conjugated to exceptionally hydrophobic drugs like maytansinoids, at high drug loads, where they are prone to aggregation/precipitation.” *Id.* (citing Ex. 1050, 2:19–25, 10:20–25, 64:59–67; Ex. 1003 ¶ 186). Petitioner argues that the ordinarily skilled artisan would have been “motivated to replace at least one of the maleimide-containing arms in Singh’s bifunctional bismaleimide PEG crosslinking agent with the bis-vinyl sulfone group of Snow” to enhance hydrophilicity of the PEG linkers, and would have had a reasonable expectation of success in doing so. Pet. 74. Petitioner provides

diagrams to reflect the proposed substitutions that Petitioner identifies as Formulas (I), (IV), and (III). *Id.* at 75–76.

Patent Owner argues that this ground fails for the same reasons as in the Ground based on Singh and Harris because each of the alleged claims depends from a claim challenged in that ground. Prelim. Resp. 59.

As noted above, Petitioner argues that it would have been obvious to modify Singh's compound by replacing "at least one of the maleimide-containing arms" in Singh's compound. Pet. 74–75. Petitioner's proposed substitution for Formula (I), reproduced below, demonstrates what Petitioner means by this.



Petitioner's annotated substitution for Formula (IV) is reproduced above. *Id.* Petitioner shows the same substitution for Formula (IV) except that it is performed at both ends of the compound. *Id.* at 76.

As shown in Petitioner's Formula (I) above, these proposed substitutions involve more than replacing the maleimide group alone because the amide group to the right of the maleimide group is also being

replaced (as indicated in the area enclosed by the red circle). We have concerns at this stage whether Petitioner has sufficiently articulated a reason why one of ordinary skill in the art would have replaced both the maleimide group and the amide group, as Petitioner proposes. We suggest the parties further address this issue at trial.

III. CONCLUSION

As discussed above, we have determined that Petitioner has established a reasonable likelihood of prevailing with respect to at least one of the challenged claims.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that *inter partes* review of claims 1–17, 20–21, 24–26, and 29–34 of the '682 patent is instituted on all grounds stated in the Petition; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is given of the institution of a trial; the trial will commence on the entry date of this decision.

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Patent 10,131,682 C1

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