

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ONCUSP THERAPEUTICS, INC.,

Petitioner,

v.

DAIICHI SANKYO COMPANY, LTD.,

Patent Owner.

PGR2023-00037
U.S. Patent No. 11,446,386

**PATENT OWNER'S PRELIMINARY RESPONSE TO PETITION FOR
POST-GRANT REVIEW OF U.S. PATENT NO. 11,446,386**

TABLE OF CONTENTS

	Page
I. INTRODUCTION.....	1
II. BACKGROUND	4
A. Requirements for the Petition.....	4
B. Overview of The '386 Patent	6
C. Antibody Structure and Function	7
D. The Level of Ordinary Skill in the Art.....	15
E. The Prior Art	15
1. Novartis	15
2. Urano.....	16
3. Sato.....	16
III. CLAIM CONSTRUCTION	16
IV. Reasons why the petition should be denied.....	17
A. Petitioner's Arguments for Ground 1: Lack of Written Description of Claims 1-18 of the '386 Patent are Insufficient	18
1. Claim 1	21
2. Claim 2	21
3. Claims 5 and 13-18	21
4. Claim 3	22
5. Claim 4	23
6. Claim 6	24
7. Claims 7-12	25

8.	Additional Written Description Arguments.....	26
B.	Petitioner’s Arguments for Ground 2: Lack of Enablement of Claims 1-18 of the ’386 Patent are Insufficient	27
1.	The Nature of the Invention and Breadth of the Claims.....	30
2.	The State of the Art, Predictability in the Field, and the Level of Ordinary Skill	30
3.	The Knowledge of One of Ordinary Skill	30
4.	The Amount of Direction or Guidance Provided and the Lack of Representative Examples.....	30
5.	The Quantity of Experimentation Required To Practice The Full Scope of the Claims.....	31
C.	Petitioner’s Arguments for Ground 3: Anticipation of Claims 1, 5, 13-16, and 18 By Novartis are Insufficient and Likewise Should be Rejected under 35 U.S.C. § 325(d)	32
D.	Petitioner’s Arguments for Ground 4: Obviousness of Claims 1, 5, and 13-18 Over Novartis or Novartis in Combination with Urano and or Sato as to Claims 14-17 are Insufficient and Likewise Should be Rejected under 35 U.S.C. § 325(d)	35
E.	Petitioner’s Arguments for Ground 5: At Least Claims 1-5 and 14-18 Are Patent-Ineligible Under 35 U.S.C. § 101 are Insufficient.....	37
V.	CONCLUSION.....	39
	CERTIFICATE OF COMPLIANCE.....	41
	CERTIFICATE OF SERVICE	42

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>Adaptics Ltd. v. Perfect Co.</i> , IPR2018-01596, Paper 20 (P.T.A.B. Mar. 6, 2019)	5
<i>Agarwal v. Jhunjunwala</i> , PGR2021-00071, Paper 10 (P.T.A.B. Sept. 17, 2021).....	6
<i>Alice Corp. v. CLS Bank Int’l</i> , 573 U.S. 208 (2014)	37, 38, 39
<i>Ariad Pharm., Inc. v. Eli Lilly & Co.</i> , 598 F.3d 1336 (Fed. Cir. 2010).....	18
<i>Xerox Corp. v. Bytemark, Inc.</i> , IPR2022-00624, Paper No. 9 (P.T.A.B. Aug. 24, 2022)	18
Statutes	
35 U.S.C. § 101.....	2, 37
35 U.S.C. § 112(a)	18
35 U.S.C. § 322(a)(3)	4, 5
35 U.S.C. § 325(d)	32, 34, 35, 36
Other Authorities	
37 C.F.R. § 42.204(b)(4)	4, 5
37 C.F.R. § 42.204(b)(5)	4, 5

PATENT OWNER'S EXHIBIT LIST

Exhibit No.	Description
2001	Peter Parham, “ <i>The Immune System</i> ”, 2nd Ed. (Garland Science Publishing 2005)
2002	U.S. Patent & Trademark Office presentation entitled “ <i>Antibodies and the written description requirement of 35 U.S.C 112(a)</i> ,” dated Sept. 27, 2020
2003	Keith A. Charlton, “Expression and Isolation of Recombinant Antibody Fragments in <i>E. coli</i> ”, Methods in Molecular Biology, Vol. 248: Antibody Engineering: Methods and Protocols (Humana Press 2004), pp.245-254.

Patent Owner Daiichi Sankyo Company, Ltd. (“Daiichi” or “Patent Owner”) submits this Preliminary Response to Petitioner OnCusp Therapeutics, Inc.’s (“OnCusp” or “Petitioner”) Petition for Post-Grant Review (“PGR”) of U.S. Patent No. 11,446,386 (the “’386 Patent”) (“Petition”). For the reasons stated below, the Board should not institute review.

I. INTRODUCTION

The ’386 Patent is directed to novel antibodies that specifically bind to the EC3 domain (extracellular domain 3) of cadherin-6 (“CDH6”)—a transmembrane protein that is overexpressed in tumor cells of certain human cancers, including renal cell carcinoma, ovarian cancer, thyroid cancer, bile duct cancer, and small cell lung cancer. The antibodies of the ’386 Patent allow for the targeted treatment of CDH6-expressing tumor cells.

Patent Owner discovered that specific recognition and binding to the EC3 domain of CDH6 is key to the ability of the antibody:CDH6 complex to be internalized by the CDH6-expressing cell. This discovery led Patent Owner to develop the claimed novel antibodies to CDH6 that specifically bind this portion of the target protein. Patent Owner discovered and patented the claimed novel antibodies, not previously found in nature, with specific structural features that allow for these important properties. The ’386 Patent claims these antibodies by reciting these specific structural features and describes these antibodies such that a person of

ordinary skill in the art (“POSITA”) could make and use these antibodies. The ’386 Patent claims these novel antibodies and discloses CDH6-targeted therapeutics encompassing such antibodies.

The Petition asks the Board to institute PGR proceedings on the following grounds: (1) Section 112 alleging that the claims lacks enablement and written description support; (2) Section 102 and 103 anticipation or obviousness grounds based on asserted prior art; and (3) Section 101 grounds alleging non-patentable subject matter. As explained in detail below, the Petition is facially deficient under the governing rules, as it fails on each of the asserted grounds to provide even the basic arguments and evidentiary support to address each of the challenged claims. The Petition fails to specifically confront and address the large amounts of structure that is disclosed and claimed in the ’386 Patent, as well as the robust disclosure and teachings as to the structure/function relationship that enables EC3 binding and internalization.

The governing rules for PGR institution impose specific requirements for institution. The petition must identify, in writing and with particularity, each claim challenged, the grounds on which the challenge to each claim is based, and the evidence that supports the grounds for the challenge to each claim. Petitioner fails to do so.

Where the grounds presented in the petition are based on prior art, the petitioner must specify where each element of the claim is found in the prior art. For other grounds, the petitioner must identify the specific part of the claim that fails to comply with the statutory grounds and state how the identified subject matter fails to comply with the statute. Here, instead, the Petitioner lumps the claims together, making arguments throughout the Petition about the "challenged claims" as a whole instead of the individual claims. When the individual claims are referenced, Petitioner fails to address the actual claim language and makes conclusory statements about the claims without citing evidence.

Petitioner fails to support its arguments with evidence throughout. Instead, Petitioner repeatedly makes statements that cite no supporting evidence, cites conclusory statements from its expert, and glosses over important aspects of the technology at issue, such as the well-understood aspects of antibody structure-function relationships. For example, Petitioner fails to acknowledge that the six complementarity determining regions ("CDRs") of an antibody are the structural feature known in the art to largely determine antigen binding of an antibody. Rather, Petitioner barely acknowledges their existence, and essentially ignores them as features recited in the claims.

Institution of a PGR by the Board is all-or-nothing. Given that Petitioner has failed to meet the requirements to identify each Ground and each claim with

particularity, it is fundamentally unfair to force the Patent Owner to address such a large number of arguments when such arguments are not articulated clearly, are not addressed to specific claims and claim limitations, fail to acknowledge key teachings of the art, and cite little to no supporting evidence. Accordingly, and for the reasons further set forth below, Patent Owner asks that institution be denied.

II. BACKGROUND

A. Requirements for the Petition

Under 35 U.S.C. § 322(a)(3), a petition for post-grant review must “identif[y], in writing and with particularity, each claim challenged, the grounds on which the challenge to each claim is based, and the evidence that supports the grounds for the challenge to each claim.” The petition must also meet several specific requirements for content under 37 C.F.R. § 42.204(b)(4), which provides: “Where the grounds for unpatentability are based on prior art, the petition must specify where each element of the claim is found in the prior art” and “[f]or all other grounds of unpatentability, the petition must identify the specific part of the claim that fails to comply with the statutory grounds raised and state how the identified subject matter fails to comply with the statute.” 37 C.F.R. § 42.204(b)(4). Section 42.204(b)(5) further requires the “exhibit number of the supporting evidence relied upon to support the challenge and the relevance of the evidence to the challenge raised, including identifying specific portions of the evidence that support the challenge.” That provision further

provides that the “Board may exclude or give no weight to the evidence where a party has *failed to state its relevance or to identify specific portions of the evidence* that support the challenge.” *Id.* § 42.204(b)(5). (emphasis added).

Patent Owner submits that each of the grounds asserted by the Petitioner fails to meet the requirements under 35 U.S.C. § 322(a)(3) and 37 C.F.R. §§ 42.204(b)(4) and (5). Petitioner fails to express the reasons for the asserted Grounds of unpatentability with sufficient particularity for the reasons described below. For prior art grounds, the location where each element of the claim is found in the prior art is not provided, and, for other grounds, the specific parts of each claim that fail to comply with the statute are not identified. Petitioner fails to provide evidence supporting each Ground, and where evidence *is* provided, Petitioner fails to state its relevance or point to specific portions thereof.

Moreover, Patent Owner submits that the lack of particularity § 322(a)(3) as to one or more asserted grounds of the petition justifies denial of the *entire* petition, due to the all-or-nothing practice of institution under *SAS*. “Because the Board’s practice, in light of *SAS*, is to institute on all grounds asserted in a petition, the Board may consider whether a lack of particular[ity] as to one or more of the asserted grounds justifies denial of an entire petition.” *Adaptics Ltd. v. Perfect Co.*, IPR2018-01596, Paper 20 at 17 (P.T.A.B. Mar. 6, 2019) (designated informative). Patent Owner submits that, not only is the Petition insufficient on all grounds, but each

ground below that lacks sufficient particularity justifies denial of the entire Petition. Institution of the Petition would be unfair to Patent Owner and reward Petitioner's lack of particularity and insufficient evidentiary support. *See Agarwal v. Jhunjhunwala*, PGR2021-00071, Paper 10 at 14 (P.T.A.B. Sept. 17, 2021) ("because, if we institute review, *SAS* requires that we do so on all grounds asserted in the Petition, we cannot limit this proceeding to a subset of those asserted and thereby remedy the Petition's failure to identify and set forth the grounds with particularity").

B. Overview of The '386 Patent

The '386 Patent relates to novel antibodies that specifically bind to the EC3 domain of CDH6 and have internalization activity. Ex. 1001 at 3:47-53. The ability to bind to this target on the surface of a tumor cell and internalize enables these antibodies to be used in antibody drug conjugates to allow for targeted deliver of cytotoxins to the tumor cells. That is, by recognizing and binding to CDH6 on cells where it is overexpressed in tumor cells of certain human cancers, including renal cell carcinoma, ovarian cancer, thyroid cancer, bile duct cancer, and small cell lung cancer. *Id.* at 1:60-2:6. The antibodies of the '386 Patent allow for the targeted treatment of these CDH6-overexpressing tumor cells. *Id.* at 3:35-58.

The '386 Patent describes the discovery that specific recognition and binding to the EC3 domain of CDH6 was an important aspect for internalization ability,

allowing for the design of novel antibodies, not previously found in nature, with specific structural features that had these important properties. *Id.* at 3:47-58. The '386 Patent claims the novel antibodies by their specific structural features, and describes these antibodies such that a person of ordinary skill in the art could make and use them.

C. Antibody Structure and Function

Antibodies, also known as immunoglobulins, are a key component of the mammalian immune response and are a class of large protein molecules that bind with varying levels of affinity to particular targets known as “antigens.” Ex. 2001 at 37. Antigens are substances that are capable of inducing an immune response and can be of various types, including small molecules, proteins, pieces of a protein, and viruses. *Id.* at 37.

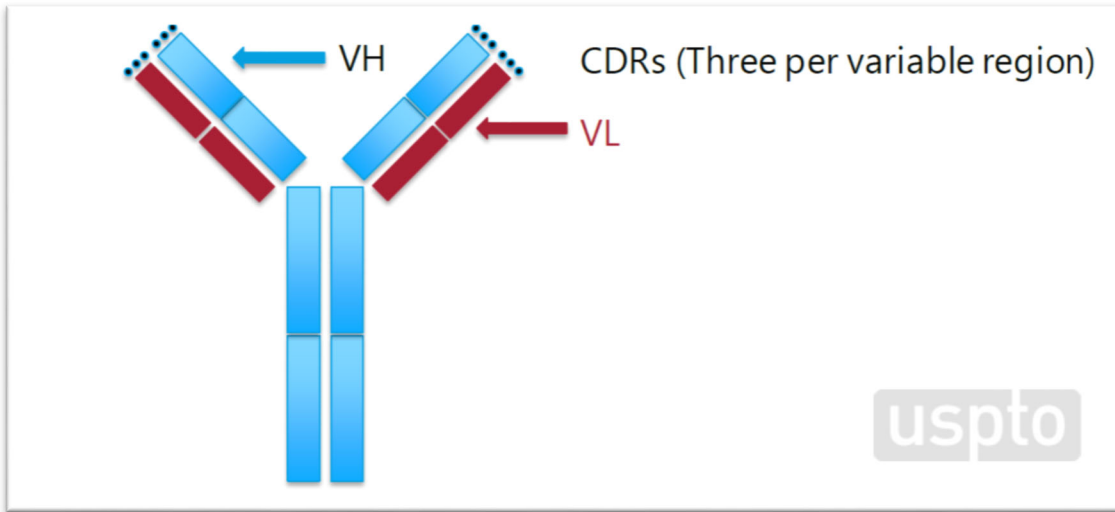
At the time of filing, the structure of a monoclonal antibody was well known. Antibodies are generally described as “Y-shaped immunoglobulin molecule” that consist of two identical heavy chains and two identical light chains that are bound together by disulfide bonds. *Id.* at 21. The chains are further subdivided into variable regions (VH, VL for the heavy and light chains, respectively) and constant regions (CH1, CH2, and CH3 for the heavy chain and CL for the light chain). *Id.* at 21-22. An antibody’s binding characteristics (e.g., specificity and affinity) are primarily determined by the sequence of amino acids within its variable regions, while the

constant regions mediate how the immune system responds to an antibody/antigen complex. *Id.* at 22.

The variable region for each heavy and light chain is further subdivided into four framework regions (FRs) and three interspersed complementarity determining regions (CDRs). *Id.* at 21-22. CDRs, also referred to as hypervariable regions, have a particularly highly variable primary structure and are separated into three sites on the primary structure of the polypeptide chain in each of the heavy chain and light chain. The '386 Patent explains that these "sites are located close to one another on the three-dimensional structure, and determine the specificity of the antibody to an antigen to which the antibody binds." Ex. 1001 at 18:57-59. *See also* Ex. 2001 at 22. The site on the antigen to which the antibody binds is called the epitope of the antigen. Ex. 2001 at 21. In the context of the '386 Patent, CDH6 is an antigen for CDH6 antibodies and the epitope is within the EC3 domain. Ex. 1001 at 3:47-53, 17:57-60. Although Petitioner's expert, Dr. Bournazos, acknowledges the primacy of CDRs in determining binding, the petition fails to even cite his opinions on this subject, as required. *See* Ex. 1003 at ¶ 48 ("It is these six variable regions (three light chain CDRs and three heavy chain CDRs) that largely determine whether an antibody will bind to a particular antigen, as well as how tightly the antibody will interact with the complementary segment of that antigen.")

Antibodies may be used as therapeutics on their own or as a component of an antibody-drug conjugate, or ADC. The goal of antibody-drug conjugates is to deliver and release a toxin to specific targeted cells such as tumor cells. Thus, it is useful for the antibody portion of the antibody-drug conjugate to be able to internalize into the cell, enabling delivery of the toxin inside the target cell to kill the target cell. Ex. 1001 at 2:42-49. It was one of the goals of the '386 Patent to provide antibodies specific to CDH6 that had high internalization activity. *Id.* at 3:35-43. In response to that goal, the inventors of the '386 Patent discovered and disclosed that antibodies specifically binding to extracellular domain 3 (EC3) of the CDH6 antigen have strong internalization activity. Likewise, the '386 Patent explains that when a first antibody and a second antibody bind to the same epitope and the first antibody has special effects such as antitumor activity or internalization activity, the second antibody can be expected to have the *same activity* as that of the first antibody. *Id.* at 18:35-40. Because the CDR sequences determine the binding specificity of the antibody, it can be expected that antibodies that share CDR sequences, and thus have common sites for epitope-binding, would likewise share internalization activity.

A September 17, 2020 slide presentation from the USPTO confirms the USPTO's understanding of antibody structure: the antigen-binding region is highly variable, with the constant regions coming from a small number of known sequences. Ex. 2002 at 4.

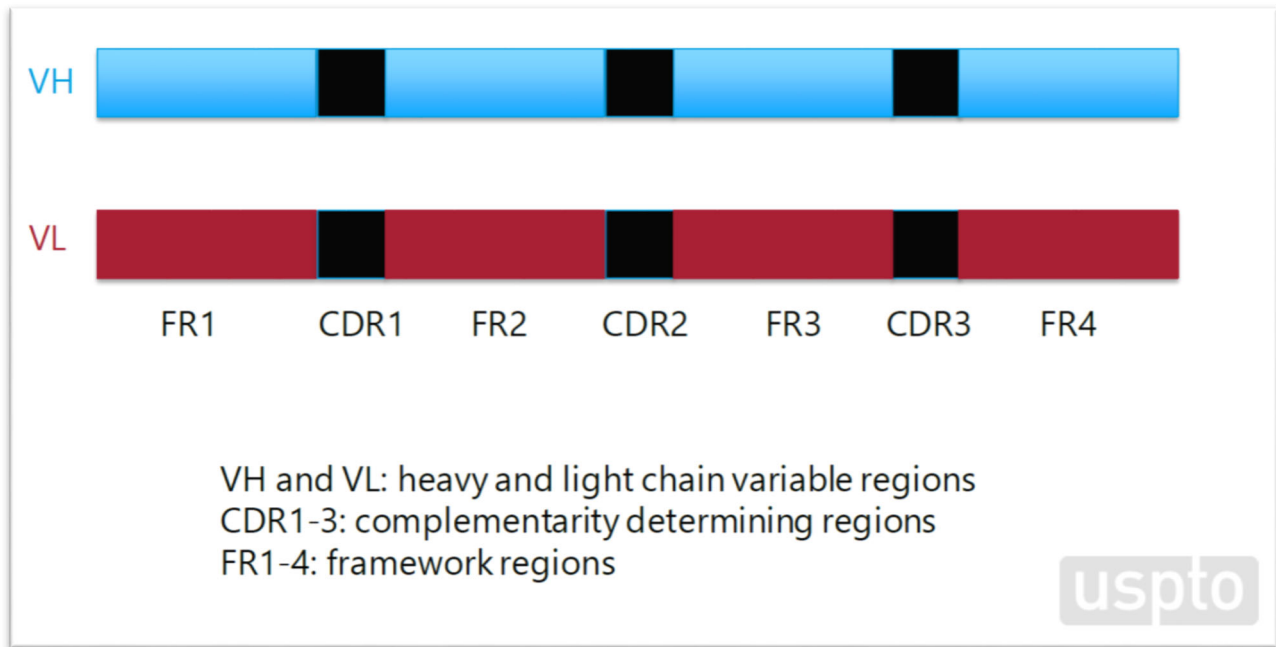


Ex. 2002 at 4.

Most of the variability comes from the CDRs, with less variability in the framework portions of the variable regions. *Id.* at 5. CDRs are generally considered to the region of contact between the antibody and the antigen. *Id.* at 7.

As of the priority date of the '386 Patent,¹ a POSITA would have understood that fragments of antibodies capable of binding that antibody's target were well known. The '386 Patent lists a number of examples such as Fab, F(ab')₂, scFv, a diabody, and Fab' fragments. Ex. 1001 at 17:40-56. The types of fragments and the smallest derivatives of antibodies that could maintain antigen-binding activity, and how to make such fragments, were known in the art well before the priority date. *See generally* Ex. 2003.

¹ Petitioner does not challenge the earliest priority date of May 15, 2017.



Ex. 2002 at 6.

The 2020 USPTO presentation provides guidance on the written description compliance of antibody claims. The presentation clearly conveys that recitation in the claims of an antibody *or antigen-binding fragment thereof* comprising heavy chain variable region sequence and a light chain variable region sequence (VH and VL, respectively) that bind to a particular antigen would satisfy the written description requirement, even if constant regions were not defined by the claim language and could be varied. Ex. 2002 at 22. In such an instance, the function (*e.g.*, binding) is correlated to the structure (the sequences of the VL and VH domains). The USPTO presentation also confirms that recitation of an antibody *or antigen-binding fragment thereof* comprising three light chain and three heavy chain CDRs

meets the written description requirement, stating that “[t]he art recognizes that frameworks can influence binding to some degree, but *most of the binding is determined by the CDRs.*” *Id.* at 23 (emphasis added). In one such example provided by the USPTO that meets the written description requirement, only a single antibody is disclosed in the hypothetical application. *Id.* Once again, function (binding) is correlated to structure (CDRs). *Id.* at 24. The presentation states that “[o]ne skilled in the art [presented with the three heavy chain CDRs and three light chain CDRs] would be able to immediately envision other antibodies which have different framework and constant regions yet which retain binding as claimed.” *Id.* Another such example confirms that written description support is met, even if only a single mouse antibody is generated in the application and a humanized antibody or antigen-binding fragment thereof is claimed. *Id.* at 25.

The guidance of the USPTO for written description with respect to CDRs and antibody structure is similar to and consistent with the Examiner’s statements regarding the enablement of claim 8 in the prosecution history. The Examiner pointed out that no enablement rejection for claim 8 was made since the Examiner “believed that the recited regions of the light and heavy chains comprise *all 6, full-length, CDRs*” Ex. 1002 at 13344 (emphasis added). At the time, claim 8 was similar to the current version of the claim, which recites the sequences of full heavy and light chain regions.

The claims of the '386 Patent recite a number of sequences that confer structural features upon the antibodies claimed therein. The Petition fails to even refer to these specific sequences that structurally define the claimed inventions. For example, Table 1 of the '386 Patent specifically sets out the disclosed sequences by description and the SEQ ID NO. Table 1, below, summarizes the sequences of Table 1 in the '386 Patent that are recited in the '386 Patent claims, including a description of the structure the SEQ ID NO represents and where in the claims the SEQ ID NO is recited as a structural feature.

Table 1. The sequences conferring structural features of the claims.

SEQ ID NO:	Description	Claims
12	rG019 CDRL1	3, 4
13	rG019 CDRL2	3, 4
14	rG019 CDRL3	3, 4
17	rG019 CDRH1	3, 4
18	rG019 CDRH2	3, 4
19	rG019 CDRH3	3, 4
22	rG055 CDRL1	3, 4
23	rG055 CDRL2	3, 4
24	rG055 CDRL3	3, 4
27	rG055 CDRH1	3, 4
28	rG055 CDRH2	3, 4
29	rG055 CDRH3	3, 4
32	rG056 CDRL1	3, 4

SEQ ID NO:	Description	Claims
33	rG056 CDRL2	3, 4
34	rG056 CDRL3	3, 4
37	rG056 CDRH1	3, 4
38	rG056 CDRH2	3, 4
39	rG056 CDRH3	3, 4
42	rG061 CDRL1	3, 4
43	rG061 CDRL2	3, 4
44	rG061 CDRL3	3, 4
47	rG061 CDRH1	3, 4
48	rG061 CDRH2	3, 4
49	rG061 CDRH3	3, 4
60	chG019 CDRH2	3, 4
61	hL02 full light chain	8, 9, 10, 12
63	hL02 light chain variable region	6, 7
65	hL03 full light chain	8, 11
67	hL03 light chain variable region	6, 7
69	hH01 full heavy chain	8, 9
71	hH01 heavy chain variable region	6, 7
73	hH02 full heavy chain	8, 10, 11
75	hH02 heavy chain variable region	6, 7
77	hH04 full heavy chain	8, 12
79	hH04 heavy chain variable region	6, 7

D. The Level of Ordinary Skill in the Art

For the limited purpose of this Preliminary Response, Patent Owner does not challenge the definition of a POSA set forth in the Petition. Patent Owner reserves the right to challenge this definition should the Petition be instituted.

E. The Prior Art

The Petitioner asserts the following prior art in its anticipation and obviousness grounds:

- Int'l Patent Application Publication No. WO 2016/024195 A1 (“Novartis”) (Ex. 1005)
- US 2016/0317656A1 to Urano et al. (“Urano”) (Ex. 1006)
- US 2016/0046720A1 to Sato et al. (“Sato”) (Ex. 1007)

Each of these references is summarized and addressed in turn below:

1. Novartis

As explained by Petitioner, the Novartis reference discloses a number of human or humanized anti-human CDH6 antibodies. Petition at 63. The Novartis reference is focused on antibodies that bind to the EC5 region of the human CDH6 protein, particularly at an epitope described as SEQ ID NO: 534. Ex. 1005 at [0009], Table 11.

2. Urano

The Urano reference relates to antibodies that bind to the fibroblastic growth factor receptor (FGFR). According to Petitioner, Urano discloses “a modified form of the antibody or functional fragment thereof having post-translational modification (e.g., N-linked or O-linked glycosylation, N-terminal or C-terminal processing, deamidation, isomerization of aspartic acid, or oxidation of methionine), or a methionine residue added to the N-terminus by expression using prokaryotic host cells” and “the advantages of some of the modification, such as glycosylation in enhancing the antibody-dependent cellular cytotoxic activity.” Petition at 70. Urano does not disclose CDH6 antibodies.

3. Sato

The Sato reference relates to antibodies that bind to the human thymic stromal lymphopoietin (TSLP) receptor. According to Petitioner, Sato discloses “a modified antibody or fragment ‘in which glutamine or glutamic acid of the N terminal of the heavy chain is modified to pyroglutamic acid due to pyroglutamylation.’” *Id.* Sato does not disclose CDH6 antibodies.

III. CLAIM CONSTRUCTION

Petitioner proposes constructions for three terms: “specifically binds to the amino acid sequence shown of SEQ ID NO: 4,” “humanized antibody,” and “functional fragment.” Petitioner largely takes the proposed constructions from the

text of the patent, with some variations. For the limited purpose of this Preliminary Response, Patent Owner does not challenge the claim constructions set forth in the Petition. Patent Owner reserves the right to challenge these claim constructions should the Petition be instituted.

IV. REASONS WHY THE PETITION SHOULD BE DENIED

Throughout the Petition, it is impossible to reasonably determine exactly what grounds Petitioner is asserting, because Petitioner fails to address the claim language with particularity. Petitioner presents arguments to multiple claims at once without addressing their differences and ignores recited claim limitations and the teachings of the patent and the art regarding those limitations. For example, the complete text of claims 2-4 and 6-12 cannot be found *anywhere* within the Petition, and yet these claims are challenged on multiple grounds. The Petition fails to even mention—let alone fully address—the numerous sequence-specific structural elements described in the specification and recited in the claims as to the claimed antibodies. These structural elements, such as CDRs, variable regions, and full heavy and light chains—identified in the claims by SEQ ID NO—are not explained anywhere in the Petition and are essentially ignored. Furthermore, Petitioner fails to provide evidentiary support throughout the Petition. This includes both a failure to cite the expert declaration or any other source, as well as instances where the expert declaration repeats the Petition verbatim and is not supported by further sources.

Such naked expert assertion is entitled to little or no weight. *See Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Paper No. 9 at 15 (P.T.A.B. Aug. 24, 2022) (designated precedential Feb. 10, 2023) (declaration that “merely repeats, *verbatim*, the conclusory assertion for which it is offered to support” is entitled to little weight) (emphasis in original). For these reasons and the further reasons laid out below, institution of the Petition should be denied.

A. Petitioner’s Arguments for Ground 1: Lack of Written Description of Claims 1-18 of the ’386 Patent are Insufficient

Petitioner lays out the statutory standard for written description under 35 U.S.C. § 112(a), explaining that the patent specification

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

Petition at 29-30. Petitioner further explains that a patent’s written description “must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.” *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (internal quotations omitted). With regard to antibodies, Petitioner claims that the patent claims must either disclose a “representative number of species falling within the scope of the genus” or

“structural features common to the members of the genus.” Petition at 32. Petitioner alleges that the claims of the ’386 Patent fail *both* prongs of this test, but Petitioner fails to support this allegation.

Petitioner begins its arguments related to written description with a heading saying “The Very Broad Claims (Claims 1-6 and 13-18) Cover A Vast Number of Antibodies That Are Not Supported By Any Common Structural Features.” *Id.* Thereafter, Petitioner makes arguments that apparently address all of claims 1-6 and 13-18 at the same time, without making individual arguments. *Id.* at 32-42. Repeatedly, Petitioner refers to “the very broad claims,” “the claims,” and “these claims.” *See, e.g., id.* at 32, 34, 36, and 40.

For example, Petitioner argues that “[t]he main reason, however, that *these claims* cover so many potential antibodies is because they are not defined by any structure, but rather by their functional capacity to bind to EC3 and internalize.” *Id.* at 34 (emphasis added). Petitioner puts forth the argument that the claims *in general* are not defined by any structure. However, a POSITA can clearly see that there are structural limitations such as recited CDRs and heavy and light chain variable regions identified by SEQ ID NO within the claims classified in the heading as “very broad.” Petitioner follows up with the statement that there is “nothing in *these claims* that limits the various ways a POSA could undertake in identifying and assembling the claimed antibodies.” *Id.* (emphasis added). Petitioner makes

arguments that hybridomas would have to be used to screen for billions of antibody candidates. *Id.* And yet, Petitioner does not address the structural limitations recited in the claims that would necessarily limit the ways a POSITA would identify and assemble those antibodies.

Petitioner also alleges that “the specification of the Challenged Claims makes *no attempt to identify any structural features* that contribute to an antibody’s possession of an ability to internalize that permits cellular intake,” (*Id.* at 37 (emphasis added)) and Petitioner’s expert claims that “no such correlation exists between the structure of the antibody and its ability to internalize” (*Id.*) (the expert declaration (Ex. 1003) at ¶ 190 provides no citations to the art to support this statement). Petitioner ignores what the specification, its own expert, and the guidance of the United States Patent and Trademark Office teaches about the complementarity determining regions (CDRs) of an antibody and their centrality to the structure and function of an antibody, as explained above in Section II.C.

Furthermore, Petitioner does not identify with particularity the grounds to which the challenge to each claim is based, nor does Petitioner provide the evidence that supports the grounds. At most, Petitioner submits brief attorney argument or unsupported expert assertions for certain claims that fail to meet the particularity requirements of the statute.

1. Claim 1

Claim 1 is not directly addressed in the Petitioner's arguments regarding written description. In fact, Petitioner only mentions claim 1 in the context of an antibody that allegedly anticipates the claim, and Petitioner does not recite the language of claim 1 in the entire section on written description.

2. Claim 2

With regard to claim 2, Petitioner points out that claim 2 recites an additional functional feature, a competitive inhibitory activity relative to the five reference antibodies (*i.e.*, chG019, H01L02, H02L02, H02L03, and H04L02). Petition at 38-39. Because this claim is still defined by a further functional element, Petitioner argues that the claim still suffers from a lack of written description, because “the specification does not identify any common structural features that would allow for this competitive inhibitory activity with the recited antibodies.” *Id.* However, Petitioner does not recite the full language of claim 2 to explain the “five reference antibodies” (which antibody names are not recited in the claim). Importantly, Petitioner cites no evidence to support its specific arguments regarding claim 2.

3. Claims 5 and 13-18

For claims 5 and 13-18, Petitioner only states that “none of the[] features specified in claims 5 and 13-18 are identified by the '386 Patent as the common structural features for binding to EC3 and internalization recited by the Challenged

Claims” and that “[a]s such, these dependent claims are also invalid for lack of written description because the specification still fails to disclose structural features common to members of the broad genus of these claims.” *Id.* at 39-40. However, Petitioner has previously stated that *none* of the claims recite structural features common to the broad genus of the claims, even though, as explained above in Section II.C, many of the claims specifically *do* recite structural elements, such as CDRs, variable regions, and entire heavy and light chains. Petitioner recites the additional claim limitations of claims 5 and 13-18 in turn, but does not explain how these structural features are inadequate, let alone cite any evidence supporting their argument for a lack of written description support for these claims as a whole.

4. Claim 3

Petitioner explains that claim 3 “specifies six CDR sequences obtained through a mix-and-match approach by combining light chain CDRs . . . of the four rat antibodies (*i.e.*, rG019, rG055, rG056, and rG061) with heavy chain CDRs . . . of the four rat or chimeric antibodies (*i.e.*, rG019/chG019, rG055, rG056, and rG061).” *Id.* at 40. However, Petitioner does not explain what sequences recited in the claims correspond to which rat antibodies disclosed in the specification, nor does the Petitioner explain why the CDRs recited are not sufficient to describe the structure of the antibody, in view of the USPTO presentation indicating six CDRs

may be used to define a genus of antibodies in a claim and still meet the written description requirement.

For claim 3, Petitioner goes on to refer to a binding assay detailed in the specification, stating it cannot “rule out the possibility that rG019, rG055, rG056, or rG061 binds to a joint region between EC3 and EC2 or between EC3 and EC4—rather than binding to EC3—which could lead to the same results as depicted in Figure 2 of the ’386 Patent.” *Id.* However, Petitioner does not explain the support for this statement or why this is relevant to the written description support for claim 3. All Petitioner’s expert, Dr. Bournazos, contributes is the explanation that “there is no definitive evidence that the anti-CDH6 antibodies having these CDR sequences would internalize into cells, because claim 3 does not specify any additional common structural features required for internalization.” Petition at 40, citing Ex. 1004 (sic, 1003), ¶¶168-170. Petitioner does not explain why the recited CDRs do not count as structural features.

Thus, Petitioner’s conclusions ignore what the ’386 Patent, the USPTO, and what its own expert states about the CDRs and the role of CDRs in defining structure and function of an antibody.

5. Claim 4

Petitioner simply states that “Claim 4 specifies six CDR sequences of four antibody clones, *i.e.*, rG019/chG019, rG055, rG056, and rG061,” without explaining

how the claim language relates to the CDR sequences recited therein (*i.e.*, which SEQ ID NO refers to which antibody, *etc.*), or how the four antibody clones are defined by the SEQ ID NOs throughout. With regard to claim 4 meeting the written description requirement, Petitioner simply says “claim 4 also fails to provide sufficient common structural features required for both binding and internalization functions of the human or humanized antibodies and their functional fragments.” Petition at 40-41. Petitioner does not explain how claim 4 is similar to or differs from claim 3, and Petitioner does not cite evidence supporting why claim 4 allegedly does not meet the written description requirement.

6. Claim 6

With regard to claim 6, the Petitioner states that “Claim 6 specifies the heavy chain and light chain variable region sequences, again through a mix-and-match approach by combining the light chain variable region of L02 or L03 with the heavy chain variable region of H01, H02, or H04.” *Id.* at 41. Petitioner states that claim 6, “covers variants of these combinations with ‘an amino acid sequence having at least 95% or more to the sequence of a framework region.’” *Id.* Petitioner does not explain why claim 6 does not recite sufficient structural information when, at the very least, CDRs are recited, and the variable regions are subject to very strict

conditions. Furthermore, Petitioner does not cite any evidence supporting its lack of written description arguments for claim 6.

7. Claims 7-12

Despite not falling under the heading of “very broad claims” found in Section IX.A.1 of the petition, claims 7-12 are included in Petitioner’s arguments on written description under the heading addressing these “very broad” claims.

Petitioner states that “Claim 7 specifies the heavy chain and light chain variable region sequences of H01L02, H02L02, H02L03, and H04L02” and alleges that it “fail[s] to specify any common structural features required for both binding and internalization functions of the human or humanized antibodies and their functional fragments.” *Id.* No explanation is provided about why the full heavy chain and light chain variable regions are not enough to convey common structural features. No evidence is cited to support these arguments.

Petitioner states that “Claim 8 specifies the heavy chain and light chain amino acid sequences of H01L02, H02L02, H02L03, or H04L02” and that “Claims 9-12 specify the heavy chain and light chain amino acid sequences of H01L02, H02L02, H02L03, and H04L02, respectively.” *Id.* Petitioner goes on to state that “Claims 8-12 also cover functional fragments of the claimed antibodies as well as antibody variants having various modifications,” alleging that “there is no evidence indicating that the functional fragments or antibody variants would retain common structures

required for both binding and internalization functions.” *Id.* For this, Petitioner cites Dr. Bournazos, who states that “functional fragments or antibody variants often exhibit different activities compared to intact, full-length antibodies.” *Id.* at 41-42. However, Petitioner never lays out the portions of the antibody or how they relate to structure and function, and fails to point out how antibodies comprising *full heavy and light chain regions*, such as those claimed in claims 8-12, would be unable to perform the claimed functions, even if only a “fragment” of an antibody, given that these claims comprise all the defined sequences of an antibody.

8. Additional Written Description Arguments

Petitioner includes a section detailing how the working examples of the '386 Patent are not representative of what is in the claims, but does not directly compare the working examples to the antibodies disclosed in the claims. Furthermore, Petitioner does not address, for example, the USPTO guidance that a single mouse antibody with defined CDRs can support a claim to a humanized antibody defined by such CDRs. *See* Section II.C, above.

The conclusory statements closing the section on written description, like “the limited disclosure of the '386 Patent would not allow the POSA to visualize the genus of antibodies covered by the Challenged Claims” (Petition at 47) and “[t]here is simply no way to predict the amino acid sequences of the antibodies claimed purely by function in the Challenged Claims,” (*Id.*) likewise do not distinguish the

claims from one another, are unsupported by evidence, and ignore the structural features recited in the claims.

B. Petitioner’s Arguments for Ground 2: Lack of Enablement of Claims 1-18 of the ’386 Patent are Insufficient

Petitioner explains that Section 112 requires that a patent specification enable those skilled in the art to make and use the full scope of the invention without “undue experimentation.” *Id.* at 50. Likewise, Petitioner explains that “[w]hether undue experimentation is needed” is *not* a single, simple factual determination, but “a conclusion reached by weighing many factual considerations.” *Id.* Petitioner specifically points to the Supreme Court’s recent holding in *Amgen* as support for the lack of enablement of the Challenged Claims, because “there are a large number of potential embodiments based on broad functional claims, relatively few working examples disclosed in the patent that are all structurally similar, and little guidance in the patent as to how to practice the full scope of the claims except through random trial and error.” *Id.* at 51. Petitioner alleges that the facts in *Amgen* are “*remarkably similar*” to those presented in the ’386 Patent, and then states that “the claims in *Amgen I* were directed to a genus of antibodies claimed broadly in terms of functional ability to bind to an antigen.” *Id.* at 52 (emphasis in original). Petitioner then relates the facts of *Amgen* and does not further compare with the Challenged

Claims. Instead, Petitioner refers to the '386 Patent claims generally and does not point to specific claims when comparing to the facts of *Amgen*. *Id.* at 52-56.

Petitioner argues that the Supreme Court's holding in *Amgen* applies doubly in this case, because the "Challenged Claims are directed to not one but at least two functional requirements: (1) binding to EC3; and (2) possessing an ability to internalize that permits cellular uptake." *Id.* at 53. However, Petitioner does not address the further limitations of the claims that lend structure to the functional claim language. In fact, Petitioner, in the section regarding enablement, does not refer to the language of the claims *at all*. Petitioner only mentions a handful of claims (7-12) by number, and these claims are the narrowest claims with the most extensive structural limitations.

Petitioner's expert opines that "the only way the POSA could create human or humanized monoclonal antibodies that function as claimed would be to randomly screen and test millions of different antibodies," but the Petition fails to address the structural features recited in the claims, stating only that the claims are "extremely broad," but not explaining how the recited CDRs, variable regions, and heavy and light chains of the claims are *not* common structural features predicted to be required for internalization. *Id.* at 53-54. Petitioner points to the specification relating the difficulty of predicting an antigen-binding site suitable for internalization and the

difficulty of predicting an antibody having high internalization ability from binding strength, physical properties and the like. *Id.* at 54.

But Petitioner fails to point to the portion of the specification stating that antibodies that bind to the same epitope are expected to have the same activity, such as internalization (*see* Section II.C), and fails to explain why the structural features recited in the claims, which determine the location of epitope binding on CDH6, are not sufficient to enable a person of ordinary skill in the art to make and use the invention. Petitioner makes broad, sweeping statements about the Challenged Claims without looking at the language of any one claim.

Petitioner purports to walk through the *Wands* factors for the “Challenged Claims,” with headers addressing, in turn, “The Nature of the Invention and Breadth of the Claims,” “The State of the Art, Predictability in the Field, and the Level of Ordinary Skill,” “The Knowledge Of One Of Ordinary Skill,” “The Amount of Direction or Guidance Provided And The Lack of Representative Examples,” and “The Quantity of Experimentation Required To Practice The Full Scope of the Claims.” *Id.* at 56-62. These sections, however, utilize minimal citation to evidence, including minimal citation to the report of their expert, Dr. Bournazos, and only address claims 7-12 specifically.

1. The Nature of the Invention and Breadth of the Claims

Petitioner cites no evidence regarding the nature of the invention and the breadth of the claims.

2. The State of the Art, Predictability in the Field, and the Level of Ordinary Skill

Petitioner cites Dr. Bournazos as supporting the statement that “[w]hile basic techniques for generating and screening antibodies existed in 2017, these are still inherently unpredictable today.” Petition at 57, citing Ex. 1003 at ¶ 195 (citing no additional sources). The only other evidence cited is the quote from the specification of the ’386 Patent regarding the difficulty of predicting an antigen-binding site and antibody suitable for internalization, which Petitioner quotes liberally throughout the Petition without addressing how the ’386 Patent relates the discovery of such an antigen-binding site on CDH6 along with antibodies that bind thereto.

3. The Knowledge of One of Ordinary Skill

Petitioner does not cite any evidence to support the arguments presented in this section.

4. The Amount of Direction or Guidance Provided and the Lack of Representative Examples

Petitioner does not cite any evidence to support the arguments presented in this section.

5. The Quantity of Experimentation Required To Practice The Full Scope of the Claims

Petitioner argues, including citation to the declaration of Dr. Bournazos, that the “skilled artisan would . . . need to screen numerous antibody sequences to make and use antibodies across the broad genus of the claims.” *Id.* at 61.

Petitioner admits, however, that “the inventors of the ’386 patent” carried out
a

significant amount of work . . . in producing, identifying, purifying, and characterizing . . . the four rat anti-CDH6 antibodies used as starting material for the claimed antibodies, as well as the additional work required to obtain cDNAs of antibodies, determine their sequences, construct and generate humanized versions of the antibodies, and characterize binding and internalization functions of the humanized antibodies and their functional fragments.

Id. at 61-62. Petitioner argues that the “skilled artisan still likely would not have arrived at sequences with sufficient diversity to represent the broad scope of the claimed invention,” (*id.* at 62) but fails to explain why the CDRs, variable regions, and heavy and light chain regions recited in the challenged claims do not provide enough structure.

Finally, Petitioner makes a number of arguments—throughout the section addressing the enablement ground—that claims 7-12 have the same issues as the

“Challenged Claims” in general because the “functional fragment” limitation is an “impermissibly broad element,” which would “increase the unpredictability of screening for these fragments.” *Id.* at 58. Petitioner further argues that there are “no examples of any functional fragments that satisfy the elements of these claims,” and “the sheer breadth of having to screen not just full antibodies, but any number of partial fragments that could bind and EC3 and internalize would be staggering.” *Id.* at 61-62 (emphasis in original). However, Petitioner fails to address the fact that claims 7-12 recite at least the heavy and light chain variable regions and, in the case of claims 8-12, the heavy and light chain regions in their entirety, resulting in “fragments” that must necessarily comprise these portions of the antibody. Furthermore, Petitioner fails to address the knowledge of a POSITA related to antibody fragments, as explained in Section II.C, above.

The arguments presented in the Petition regarding enablement fail to meet the particularity requirement and do not support institution of the Petition.

C. Petitioner’s Arguments for Ground 3: Anticipation of Claims 1, 5, 13-16, and 18 By Novartis are Insufficient and Likewise Should be Rejected under 35 U.S.C. § 325(d)

Petitioner alleges that claims 1, 5, 13-16, and 18 are anticipated by the Novartis reference. Petitioner cites the Novartis reference with regard to disclosing the limitations of claim 1, but does not cite its expert declaration in support. Thus, the conclusions presented are nothing more than attorney argument.

With regard to anticipation, Petitioner only cites the expert declaration of Dr. Bournazos for claims 15 and 16, which address only the deletion of the two amino acids from the carboxyl terminus of a heavy chain, and do not address the limitations of claim 1. Petition at 66-67.

Specifically, without citing to their own expert, Petitioner alleges that NOV0719 and NOV0710, disclosed in the Novartis reference, are shown to “bind strongly to hCDH6 EC3.” *Id.* at 63-64. The Novartis reference notes, however, with regard to its epitope mapping studies, that “[i]t is important to note that changes in deuterium uptake are sensitive to both direct binding and allosteric events; in order to precisely determine the epitope HDx has to be combined with orthogonal technologies (e.g. X-ray crystallography).” Ex. 1005 at [00391]. The data from the Novartis reference also discloses that the decreases in deuterium uptake are exhibited in peptides of EC2 and EC4 for NOV0719 and in peptides of EC5 for NOV0710. *Id.* at [00396], [00398]-[00399].

With regard to internalization, the Novartis reference states the following regarding the antibodies disclosed therein:

To allow for the functional characterization, the Fab antibody clones were converted into the IgG format, yielding 47 unique IgG clones of which 44 were successfully expressed at screening scale. The purified, unique IgGs were subjected to a series of characterization assays including human/cyno/rat/mouse cross-

reactivity by FACS, affinity ranking by Octet, cellular internalization assays as well as surrogate ADC assays using an anti-human IgG Fab-SMCC-DM1 secondary reagent. Based on these assays, human IgGs were selected for scaled up production, subsequent direct conjugation to ADC linker/pay loads and testing as ADCs in *in vitro* and *in vivo* experiments.

Id. at [00379] (emphasis in original). Petitioner claims that his passage supports the argument that “all the NOV anti-hCDH6 antibodies as listed in Table 5, including NOV0710 and NOV0719, possess an ability to internalize that permits cellular uptake.” Petition at 64. However, the Novartis reference does not provide any teachings with regard to whether the antibodies that specifically bind to EC3 possess an ability to internalize that permits cellular uptake.

Regardless of whether such attorney argument should be given any weight, the alleged disclosures that Petitioner argues are anticipatory are not supported by the portions of the Novartis reference cited by Petitioner.

Furthermore, a counterpart of the Novartis reference was in front of the Examiner during the prosecution of the application that became the '386 Patent. Petitioner argues with respect to 35 U.S.C. § 325(d), that the Examiner should not have allowed the Patent to issue because Patent Owner allegedly made false arguments. *Id.* at 81. Specifically, Patent Owner made the statement that “there is no indication in the record [of the Novartis reference] that binding to any or all of

the various extracellular domains will always necessarily result in internalization of an antibody.” Ex. 1002 at 13665-13666. Petitioner does not explain why the statement is allegedly false, nor does Petitioner provide evidence for the falsity of the statement beyond the arguments presented in the anticipation and obviousness grounds. As shown in Sections IV.C and IV.D of this response, Petitioner does not cite evidence beyond a single line in the Novartis reference for the falsity of Patent Owner’s statement, and the Petition does not cite Petitioner’s expert in support thereof. Thus, not only are Petitioner’s arguments insufficient, they should be rejected under 35 U.S.C. § 325(d) because substantially the same arguments and art were already presented to the Patent Office.

D. Petitioner’s Arguments for Ground 4: Obviousness of Claims 1, 5, and 13-18 Over Novartis or Novartis in Combination with Urano and or Sato as to Claims 14-17 are Insufficient and Likewise Should be Rejected under 35 U.S.C. § 325(d)

Although Petitioner cites to the declaration of Dr. Bournazos with respect to the obviousness arguments for claims 1, 5, and 13-18, nothing in this section remedies the deficiencies of Section IX.C of the Petition, wherein the anticipation arguments for claim 1 and the dependent claims amount to attorney argument with no evidentiary support and thus are entitled to little or no weight.

With regard to the asserted obviousness of claims 14 to 17, the additional limitations of the claims are addressed by citations to the expert declaration, but the

arguments of Dr. Bournazos do not address the claim limitations of independent claim 1.

Furthermore, Petitioner fails to identify the required motivation to combine and reasonable expectation of success necessary for a finding of obviousness. All that Petitioner submits on this subject is as follows:

In view of the disclosures of Novartis, Urano, and Sato, it would have been obvious for the POSA to be motivated, who would also motivated, to generate a human or humanized monoclonal antibody or functional fragment thereof with the heavy chain or the light chain that has undergone one or two or more modifications as claimed.

Id. at 71. Petitioner cites paragraphs from the declaration of its expert, Dr. Bournazos, but does not identify the motivation itself or the specific evidentiary support for such motivation.

Likewise, because the Examiner considered and rejected the anticipation arguments above during prosecution (*See* Ex. 1002 at 13665-13666), and the obviousness arguments rely on the anticipation arguments in view of the Novartis reference, the obviousness arguments should also be rejected under 35 U.S.C. § 325(d).

Thus, Petitioner's arguments fail on multiple fronts and do not support institution.

E. Petitioner’s Arguments for Ground 5: At Least Claims 1-5 and 14-18 Are Patent-Ineligible Under 35 U.S.C. § 101 are Insufficient

Petitioner argues that claims 1-5 and 14-18 are patent-ineligible under 35 U.S.C. § 101. As Petitioner explains, the test for patent eligibility is dictated by the Supreme Court’s instructions in *Alice*, which provide a two-part framework for evaluating the patent eligibility of a claim. Petition at 73. In step 1 of the *Alice* framework, one must "first determine whether the claims at issue are directed to a patent-ineligible concept." *Alice Corp. v. CLS Bank Int’l*, 573 U.S. 208, 218 (2014). If the claims are directed to a patent-ineligible concept, then, in step 2 of the *Alice* framework, one must “examine the elements of the claims to determine whether it contains an ‘inventive concept’ sufficient to ‘transform’ the claimed [patent-ineligible concept] into a patent-eligible application.” *Id.* at 221.

With regard to claim 1, Petitioner argues that “the sheer breadth of claim 1 would cover antibodies that bind to EC3 and internalize that are isolated from a human subject without any further modification,” and cite the expert declaration of Dr. Bournazos. Petition at 76. By way of further explanation, Petitioner argues that “[t]he human CDH6 protein is a tumor-associated antigen and therefore, in cancer patients, the human body will produce naturally occurring antibodies that bind to CDH6 (including its EC3 region) in cancer cells expressing this protein,” and once again cites the expert declaration. *Id.* Why the human body should make antibodies

to a human protein is not explained. However, Dr. Bournazos does not claim that such antibodies exist in nature. The most Dr. Bournazos alleges is that “one cannot exclude the high likelihood that at least one of these naturally occurring antibodies will also internalize and therefore satisfy all the elements of claim 1.” *Id.*

Petitioner implies that the above allegation is enough to satisfy step 1 of the *Alice* framework. However, step 1 of the *Alice* framework asks whether the claim is directed to a patent ineligible concept such as a law of nature, a natural phenomenon, or an abstract idea. Petitioner argues that the antibodies recited in claim 1 are a product of nature, but offers no proof that such antibodies actually exist in nature, only a blank statement that their expert believes that the high likelihood ***cannot be excluded***. *Id.* Petitioner’s expert does not even state that any likelihood ***exists***, only that a high one “cannot [be] exclude[d].” This argument is insufficient to meet step 1 of the *Alice* framework.

Even if claim 1 and the dependent claims were to meet step 1 of the *Alice* framework, it does not meet step 2 of the *Alice* framework. Petitioner argues that claim 1 “does not include any additional features that are markedly different from the naturally occurring product.” Petition at 77. However, Petitioner never points to an actual naturally occurring product to which such a comparison can be made. Petitioner, at best, has speculated that such a product *might* exist, and thus, it is

impossible to evaluate step 2 of the *Alice* framework, since there is no natural product against which to make a comparison.

Petitioner does not remedy the deficiencies of the argument with respect to claim 1 regarding claims 2-5 and 13-18. At no point can Petitioner point to evidence that there is a naturally occurring product that meets the limitations of claim 1 or any of the dependent claims.

Petitioner's arguments regarding patent ineligibility are insufficient and do not support institution.

V. CONCLUSION

For the reasons set forth above, OnCusp's Petition for Post-Grant Review should be denied in its entirety.

Respectfully submitted,

WEIL, GOTSHAL AND MANGES LLP

Dated: October 12, 2023

By: /Elizabeth S. Weiswasser/
Elizabeth S. Weiswasser (Reg. No. 55,721)
Lead Counsel for Patent Owner
Anish R. Desai (Reg. No. 73,760)
Natalie C. Kennedy (Reg. No. 68,511)
Weil, Gotshal & Manges LLP
767 Fifth Avenue
New York, NY 10153
Phone: 212-310-8000
Fax: 212-310-8007
elizabeth.weiswasser@weil.com
anish.desai@weil.com
natalie.kennedy@weil.com

Christopher M. Pepe (Reg. No. 73,851)
Weil, Gotshal & Manges LLP
2001 M Street, N.W., Suite 600
Washington, D.C. 20036
Phone: 202-682-7153
Fax: 202-857-0940
christopher.pepe@weil.com

CERTIFICATE OF COMPLIANCE

The undersigned certifies that this brief complies with the type-volume limitations of 37 CFR § 42.24(a)(1)(ii). This brief contains 8,452 words as calculated by the “Word Count” feature of Microsoft Word 2016, the word processing program used to create it.

The undersigned further certifies that this brief complies with the typeface requirements of 37 CFR § 42.6(a)(2)(ii) and typestyle requirements of 37 CFR § 42.6(a)(2)(iii). This brief has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in Times New Roman 14 point font.

Respectfully submitted,

WEIL, GOTSHAL AND MANGES LLP

Dated: October 12, 2023

By: /Elizabeth S. Weiswasser/
Elizabeth S. Weiswasser
Reg. No. 55,721
Lead Counsel for Patent Owner

CERTIFICATE OF SERVICE

The undersigned hereby certifies that on October 12, 2023, the foregoing **PATENT OWNER'S PRELIMINARY RESPONSE TO PETITION FOR POST-GRANT REVIEW OF U.S. PATENT NO. 11,446,386** was served via electronic mail, upon the following:

Gerard P. Norton, Ph.D.
FOX ROTHSCHILD LLP
Princeton Pike Corporate Center
997 Lenox Drive
Lawrenceville, NJ 08648-2311
gnorton@foxrothschild.com

Ryan N. Miller
FOX ROTHSCHILD LLP
2000 Market St., 20th Floor
Philadelphia, PA 19103-3222
rmiller@foxrothschild.com

Howard S. Suh
FOX ROTHSCHILD LLP
101 Park Avenue, 17th Floor
New York, NY 10178
hsuh@foxrothschild.com

Jianming Jimmy Hao
Fox Rothschild LLP
997 Lenox Drive
Lawrenceville, NJ 08648
jhao@foxrothschild.com

Joe G. Chen
Fox Rothschild LLP
997 Lenox Drive
Lawrenceville, NJ 08648
joechen@foxrothschild.com

/Timothy J. Andersen/

Timothy J. Andersen

IP Paralegal

Weil, Gotshal & Manges LLP

2001 M Street, NW, Suite 600

Washington, DC 20036

timothy.andersen@weil.com