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Paper 12
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,
Petitioner,

v.

HALOZYME, INC.,
Patent Owner.

PGR2025-00052
Patent 12,264,345 B1

Before SUSAN L. C. MITCHELL, CYNTHIA M. HARDMAN, and MICHAEL A. VALEK, *Administrative Patent Judges*.

HARDMAN, *Administrative Patent Judge*.

DECISION
Granting Institution of Post Grant Review
35 U.S.C. § 324

I. INTRODUCTION

Petitioner Merck Sharp & Dohme LLC filed a Petition requesting post grant review of claims 1–17 of U.S. Patent No. 12,264,345 B1 (Ex. 1001, "the '345 patent"). *See* Paper 1 ("Pet."). Patent Owner Halozyme, Inc. did not file a Preliminary Response.[1]

We have authority to determine whether to institute a post grant review. *See* 35 U.S.C. § 324; 37 C.F.R. § 42.4(a). Considering the arguments and evidence presented, we institute a post grant review because Petitioner demonstrates "that it is more likely than not that at least 1 of the claims challenged in the petition is unpatentable." 35 U.S.C. § 324(a).

The following preliminary findings of fact and conclusions of law are made solely to determine whether to institute review. Any final decision will be based on the full trial record.

A. Real Parties in Interest

Petitioner identifies Merck Sharp & Dohme LLC as the real party in interest. Pet. 6. Patent Owner identifies Halozyme, Inc. and Halozyme Therapeutics, Inc. as the real parties in interest. Paper 4, 1.

B. Related Matters

The parties collectively identify the following thirteen post grant review proceedings:

U.S. Patent 11,952,600 (PGR2025-00003)

U.S. Patent 12,018,298 (PGR2025-00004)

[1] Patent Owner also did not file a brief directed to discretionary denial issues. The case was referred to this panel to consider the merits and non-discretionary considerations. *See* Paper 11, 1–2.

U.S. Patent No. 12,152,262 (PGR2025-00006)

U.S. Patent No. 12,123,035 (PGR2025-00009)

U.S. Patent No. 12,110,520 (PGR2025-00017)

U.S. Patent No. 12,060,590 (PGR2025-00024)

U.S. Patent No. 12,054,758 (PGR2025-00030)

U.S. Patent No. 12,049,652 (PGR2025-00033)

U.S. Patent No. 12,104,185 (PGR2025-00039)

U.S. Patent No. 12,037,618 (PGR2025-00042)

U.S. Patent No. 12,091,692 (PGR2025-00046)

U.S. Patent No. 12,077,791 (PGR2025-00050)

U.S. Patent No. 12,195,773 (PGR2025-00053)

See Pet. 6; Paper 4, 2.

The parties also identify *Halozyme, Inc. v. Merck Sharp & Dohme LLC*, 2:25-cv-03179 (D.N.J.) as a related matter in which Patent Owner alleges infringement of, *inter alia*, the '345 patent. Pet. 6; Paper 4, 1.

Patent Owner states that the '345 patent is related to the following pending U.S. Patent Applications and patents: 18/759,577; 18/922,889; 18/069,651; 18/340,786; 19/071,005; 19/071,055; 19/075,092; 19/071,264; 19/071,345; and U.S. Patent No. 12,195,773. Paper 4, 2.

C. The '345 Patent

The '345 patent issued on April 1, 2025, from U.S. Application 18/778,554, filed on July 19, 2024. Ex. 1001, codes (45), (21), (22). The '345 patent is a continuation of a lengthy set of applications claiming continuity to U.S. Application 13/694,731 (the "'731 Application"), filed December 28, 2012, which claims the priority benefit of provisional

applications U.S. 61/796,208, filed November 1, 2012, and U.S. 61/631,313, filed December 30, 2011. *Id.* at code (60).

The '345 patent is drawn to "[m]odified PH20 hyaluronidase polypeptides, including modified polypeptides that exhibit increased stability and/or increased activity." Ex. 1001, 2:43–45. The '345 patent teaches "[h]yaluronan (hyaluronic acid; HA) is a polypeptide that is found in the extracellular matrix of many cells, especially in soft connective tissues." *Id.* at 2:50–52. The '345 patent teaches "[c]ertain diseases are associated with expression and/or production of hyaluronan. Hyaluronan-degrading enzymes, such as hyaluronidases, are enzymes that degrade hyaluronan. By catalyzing HA degradation, hyaluronan-degrading enzymes (e.g., hyaluronidases) can be used to treat diseases or disorders associated with accumulation of HA or other glycosaminoglycans." *Id.* at 2:57–63. The '345 patent teaches that "[v]arious hyaluronidases have been used therapeutically . . . . Many of these are ovine or bovine forms, which can be immunogenic for treatment of humans." *Id.* at 3:1–7.

With regard to modified PH20 hyaluronidase polypeptides, the '345 patent teaches:

> Single amino acid abbreviations for amino acid residues are well known to a skilled artisan . . . and are used herein throughout the description and examples. For example, replacement with P at a position corresponding to position 204 in a PH20 polypeptide with reference to amino acid residue positions set forth in SEQ ID NO:3 means that the replacement encompasses F204P in a PH20 polypeptide set forth in SEQ ID NO:3.

Id. at 3:33–42. The '345 patent teaches that the "modified PH20 polypeptides provided herein exhibit altered activities or properties

compared to a wildtype, native or reference PH20 polypeptide." *Id.* at 73:66–74:1.

D. Illustrative Claims

Claim 1 is illustrative of the challenged claims in the '345 patent, and is reproduced below.

> 1. A modified PH20 polypeptide, comprising:
>
> (i) a hyaluronidase domain that corresponds to amino acid residues 3-339 with reference to numbering in SEQ ID NO:7; and
>
> (ii) an amino acid replacement at the residue corresponding to M313 with reference to numbering in SEQ ID NO:7,
>
> wherein the hyaluronidase domain contains up to 20 modifications.

Ex. 1001, 301:37–44.

E. Asserted Grounds of Unpatentability

Petitioner contends that the challenged claims are unpatentable based on the following four grounds:

Ground	Reference(s)/Basis	35 U.S.C. §	Claim(s) Challenged
1	Written Description	§ 112(a)	1–17
2	Enablement	§ 112(a)	1–17
3	Indefiniteness	§ 112(b)	1–17
4	'429 patent,[2] Chao[3]	§ 103	1–17

[2] Bookbinder et al., U.S. Patent No. 7,767,429 B2, issued Aug. 3, 2010 (Ex. 1005) (the "'429 patent").

[3] Chao et al., *Structure of Human Hyaluronidase-1, a Hyaluronan Hydrolyzing Enzyme Involved in Tumor Growth and Angiogenesis*, 46 Biochemistry 6911–20 (2007) (Ex. 1006) ("Chao").

Petitioner relies on the Declarations of Michael Hecht, Ph.D. (Ex. 1003) and Sheldon Park, Ph.D. (Ex. 1004), among other evidence.

II. ANALYSIS

A. Post Grant Review Eligibility

As a threshold issue, we must determine whether the '345 patent is eligible for post grant review. There are two requirements for post grant review eligibility. First, the petition must be filed within nine months of the issuance of the challenged patent. 35 U.S.C. § 321(c). Here, Petitioner adequately demonstrates, and Patent Owner does not dispute, that the Petition was timely filed. Pet. 4.

Second, the challenged patent must have issued from an application that at one point contained at least one claim with an effective filing date of March 16, 2013, or later. *See* Pub. L. No. 112-29, §§ 3(n)(1), 6(f)(2)(A). Here, the priority dates recited for the '345 patent include three filings prior to March 16, 2013, i.e., (i) the '731 Application, filed December 28, 2012; (ii) U.S. Provisional Application 61/796,208, filed November 1, 2012; and (iii) U.S. Provisional Application 61/631,313, filed December 30, 2011. Ex. 1001, code (60).

Petitioner asserts that the disclosure of "[t]he '731 Application (including subject matter incorporated by reference) does not provide written description support for and does not enable any claim of the '345 Patent." Pet. 5–6.

Because the analysis of priority and PGR-eligibility in this Institution Decision relies on substantially the same analysis relevant to Petitioner's challenge based on alleged lack of written description (Ground 1), we address post grant review eligibility and written description together below.

See infra Section II.D.1. As discussed below, we determine that the '345 patent is eligible for post grant review. *See id.*

B. Level of Ordinary Skill in the Art

We consider the grounds of unpatentability in view of the understanding of a person of ordinary skill in the art (sometimes referred to herein as "POSA") as of the effective filing date of the challenged claims. Petitioner contends that one of ordinary skill in the art would

> have had an undergraduate degree, a Ph.D., and post-doctoral experience in scientific fields relevant to [the] study of protein structure and function (*e.g.*, chemistry, biochemistry, biology, biophysics). From training and experience, the person would have been familiar with factors influencing protein structure, folding and activity, production of modified proteins using recombinant DNA techniques, and use of biological assays to characterize protein function, as well with techniques used to analyze protein structure (*i.e.*, sequence searching and alignments, protein modeling software, etc.).

Pet. 16–17 (citing Ex. 1003 ¶¶ 13, 35–36).

At this stage of the proceeding and on the record before us, we apply Petitioner's proposed POSA level, which is presently undisputed and appears consistent with the level of skill shown in the prior art references of record. *See Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007).

C. Claim Construction

In a post grant review, we interpret a claim "using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b)." 37 C.F.R. § 42.200(b). Under this standard, we construe the 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." *Id.*

Petitioner asserts that the "terms used in the claims are either expressly defined in the common disclosure[4] or are used with their common and ordinary meaning. Consequently, no term requires a special construction to assess the grounds." Pet. 18.

Regarding terms that are expressly defined in the '345 patent, we note that the Specification specifically defines the terms "PH20," "modified PH20 polypeptide," and "hyaluronidase domain," among other terms. These definitions "control[] the claim interpretation." *Southwall Tech., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1578 (Fed. Cir. 1995).

The '345 patent defines "PH20" as "a type of hyaluronidase that occurs in sperm and is neutral-active,"[5] and "includes those of any origin including, but not limited to, human, chimpanzee, Cynomolgus monkey, Rhesus monkey, murine, bovine, ovine, guinea pig, rabbit and rat origin." Ex. 1001, 44:20–26. The '345 patent further explains that "[r]eference to PH20 includes precursor PH20 polypeptides and mature PH20 polypeptides (such as those in which a signal sequence has been removed), truncated forms thereof that have activity, and includes allelic variants and species variants, variants encoded by splice variants, and other variants." *Id.* at

[4] Petitioner uses the term "common disclosure" to refer to the "shared disclosure of the '345 Patent and the '731 Application." *See* Pet. 6 n.5. Petitioner asserts that these "disclosures are substantively identical." *Id.*

[5] "Neutral-active" means that PH20 is able "to enzymatically catalyze the cleavage of hyaluronic acid at neutral pH, such as at a pH between or about between pH 6.0 to pH 7.8." Ex. 1001, 49:4–7.

44:37–46. The '345 patent states that "PH20 polypeptides also include those that contain chemical or posttranslational modifications and those that do not contain chemical or posttranslational modifications." *Id.* at 44:46–49.

The '345 patent provides a specific definition of the term "modified PH20 polypeptide," stating that the term

> refers to a PH20 polypeptide that contains at least one amino acid modification, such as at least one amino acid replacement as described herein, in its sequence of amino acids compared to a reference unmodified PH20 polypeptide. A modified PH20 polypeptide can have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide ***exhibits hyaluronidase activity***. Typically, a modified PH20 polypeptide contains 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 amino acid replacements. It is understood that a modified PH20 polypeptide also can include any one or more other modifications, in addition to at least one amino acid replacement as described herein.

Id. at 47:3–18 (emphasis added).

Thus, the evidence of record shows the '345 patent recognizes a broad understanding of a "modified PH20 polypeptide" as encompassing PH20 sequences from a variety of different mammalian species, with or without precursor or signal sequences, with or without post-translational modifications, and with up to 150 amino acid replacements.

The definition of "modified PH20 polypeptide" in the '345 patent permits up to 150 amino acid replacements but ***only*** "so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity." Ex. 1001, 47:8–11. That is, the definition of "modified PH20 polypeptide" in the '345 patent expressly requires some hyaluronidase activity. On the current

record, we therefore adopt the definition for "modified PH20 polypeptide" as recited in the '345 patent to encompass polypeptides with some hyaluronidase activity.

The '345 patent provides a specific definition of the term "hyaluronidase domain," i.e., a "region of about 340 amino acids in length that corresponds to amino acid residues 38-374 of the precursor human PH20 sequence set forth in SEQ ID NO:6."[6] Ex. 1001, 68:19–24.

We determine that we need not expressly construe any other claim terms for the purpose of deciding whether to institute post grant review. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

Any final written decision entered in this case may include final claim constructions that differ from the preliminary understanding of the claims set forth above. Any final claim constructions will be based on the full trial record.

D. Unpatentability Grounds

In a post grant review, "the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016).

[6] According to Petitioner's declarant Dr. Hecht, "[p]ositions 38-374 of SEQ ID NO:6 correspond to positions 3-339 in SEQ ID NO:3 and in SEQ ID NO:7, which omit the 35 amino acid signal sequence." Ex. 1003 n.135.

The petitioner ultimately bears the burden of persuasion to prove unpatentability of each challenged claim by a preponderance of the evidence. 35 U.S.C. § 326(e). This burden never shifts to the patent owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). The Board may authorize a post grant review if we determine that the information presented in the record shows that it is more likely than not that the petitioner will prevail with respect to at least one of the claims challenged in the petition. 35 U.S.C. § 324(a).

We now turn to analyzing each of Petitioner's asserted grounds of unpatentability.

1. Written Description (Ground 1)

a) Principles of Law

"A specification that 'reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date' has adequate written description of the claimed invention." *Novartis Pharm. Corp. v. Accord Healthcare, Inc.*, 21 F.4th 1362, 1368 (Fed. Cir. 2022) (citing *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010)). "[T]he test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Id.* at 1368–69.

We analyze the asserted grounds of unpatentability in accordance with these principles to determine whether Petitioner has met its burden to establish that it would more likely than not prevail at trial.

b) Petitioner's Position

Petitioner asserts that claims 1–7 capture a large, unpredictable, and diverse genus, comprising more than 10^{43} different modified PH20

polypeptides comprising a mutated hyaluronidase domain. *See* Pet. 40, 72–73. According to Petitioner, "[t]he claim language permits any combination of modifications (up to 15 or 20 total), including one substitution at 313 and any modification at 336 other positions within the 'hyaluronidase domain.'" *Id*. at 41. According to Petitioner, "[c]onsidering only substitutions within the mutated 'hyaluronidase domain' yields immense numbers of distinct modified PH20 polypeptides," including 1.85×10^{56} distinct amino acid sequences for claim 1 and 3.10×10^{43} distinct amino acid sequences for dependent claims 3 and 17. *Id.* at 20; Ex. 1003 ¶ 126 (citing Ex. 1004 ¶ 176).

Petitioner asserts that the claims also "permit ***additional*** variability outside the mutated 'hyaluronidase domain,'" including inactive and/or insoluble truncated polypeptide sequences. Pet. 41–42 (citing, e.g., Ex. 1001, 70:49–67 (glycosyl phosphatidylinositol (GPI) anchor sequence at 456–474 of SEQ ID NO:7), 134:33–42 (truncation of GPI anchor sequence can produce a soluble polypeptide); Ex. 1003 ¶¶ 178, 201–02); *id.* at 30 (citing Ex. 1001, 68:23–32 (explaining that "contiguous ***unmodified*** sequence of human PH20 extending to least position 429 (***not 339***) of SEQ ID NO:7 is the 'minimal sequence required for ***hyaluronidase activity***"'); Ex. 1003 ¶ 97). The claim language, Petitioner contends, "also permits modified PH20 polypeptides to combine ***non-human*** PH20 sequences with the human 'hyaluronidase domain' segment." *Id.* at 42 (citing Ex. 1003 ¶¶ 128–30).

Petitioner contends that "[t]he 10^{43}+ different PH20 polypeptide sequences being claimed can give rise to myriad protein structures," which

"structures could not have been reliably predicted before 2020 (or even if the sequences will fold)." *Id.* at 43.

Despite the enormous breadth and variety captured by these claims, Petitioner asserts that

> the common disclosure describes ***no single*** modified PH20 polypeptide (actual or prophetic) that combines (i) a position 313 substitution ***plus*** (ii) one or more insertions, deletions, or substitutions restricted to the "hyaluronidase domain" (much less demonstrates possession of ***all*** of them). And it certainly does not demonstrate possession of the unidentified and unknown numbers of the claimed modified PH20 polypeptides within those genera with credible utility ("active mutants") or even those with implausible contraceptive utility ("inactive mutants").

Id. at 40.

Petitioner argues that the claims lack adequate written description support because the common disclosure lacks blaze marks indicating possession of "modified PH20 polypeptides with multiple modifications ***restricted within*** positions 3-339 of SEQ ID NO: 7 [i.e., the hyaluronidase domain], much less one with a position 313 replacement." Pet. 45 (citing Ex. 1003 ¶¶ 154, 167, 180–81); *see also id.* at 43–45. According to Petitioner, "[t]he common disclosure makes only passing reference to a conserved 'hyaluronidase domain' in its discussion of the prior art, and attaches no particular significance to it for making 'modified PH20 polypeptides.'" *Id.* at 45 (citing Ex. 1001, 68:14–57, 3:60–4:17, 79:16–80:3, Table 8; Ex. 1003 ¶¶ 155–58). Petitioner also argues that the common disclosure does not describe incorporating a mutated human hyaluronidase domain into a non-human PH20 polypeptide. *Id.* at 46. Petitioner asserts that "[t]he omissions in the common disclosure cannot be rectified by

'piecing together' disparate and generic portions of the disclosure," and "[b]ecause the 'hyaluronidase domain' is not used in the common disclosure's description of the claimed genera of ***modified*** PH20 polypeptides, all claims lack written description." *Id.* at 49.

Petitioner further argues that the claims lack written description support because they include "modified PH20 polypeptides" that did not exist as of the December 28, 2012, filing date of the '731 Application, such as the "283 new non-human PH20 sequences [that] were discovered and published" between January 2013 and July 2024. Pet. 49–50. Petitioner also argues that "the common disclosure does not identify which . . . mutated starting PH20 polypeptides are 'neutral active,' and determining which are would require an impossible amount of experimentation." *Id.* at 51 (citing Ex. 1003 ¶¶ 131, 133) (emphasis omitted).

Petitioner also asserts that the common disclosure provides only "a 'research plan' that instructs skilled artisans 'to generate a modified PH20 polypeptide containing any one or more of the described mutation[s], and test each" for hyaluronidase activity (or perhaps contraceptive activity, which Petitioner contends is a "scientifically implausible" utility). Pet. 52–53.

Petitioner argues that the claims "capture modified PH20 polypeptides with modifications that the common disclosure instructs should not be made," including mutations and truncations that are taught to eliminate hyaluronidase activity. Pet. 53–57. According to Petitioner, the common disclosure does not demonstrate possession of any active, multiply-modified PH20 polypeptides as claimed, and the claims are impermissibly broader

than "the unambiguously limited examples of enzymatically active modified PH20 polypeptides in the common disclosure." *Id.* at 55, 57, 58.

Petitioner further argues that "the common disclosure do[es] not describe to a skilled artisan the structural features of ***multiply***-modified PH20 polypeptides having 2 to 15 or 20 modifications restricted to positions 3-339 of SEQ ID NO:7, much less ones that are enzymatically active." Pet. 58. Petitioner argues that the "[e]mpirical results reported in the common disclosure" are "not analyzed," and thus "[n]o attempt is made to assess the impact of any single substitution on the protein's structure, much less extrapolate these results to PH20 polypeptides with multiple substitutions." *Id.* at 58, 59–60. Petitioner asserts, for example, that based on the common disclosure, skilled artisans cannot determine "***which*** of ~ 4,180 'inactive' or unclassified mutants were (i) properly folded and enzymatically inactive, (ii) were not successfully produced within or secreted from the transfected cells, or (iii) were secreted but could not fold or remain folded." *Id.* at 61–62 (citing Ex. 1003 ¶¶ 110–11, 113, 114).

Petitioner argues that "[t]he common disclosure describes ***no*** enzymatically active multiply-modified PH20 polypeptides—it only presents ***the idea*** of making them." Pet. 63 (citing Ex. 1003 ¶ 184). According to Petitioner, the '345 patent "proposes a prophetic research plan requiring 'iterative' make-and-test experiments that ***might discover*** enzymatically active, multiply-modified PH20 polypeptides." *Id.* at 64 (citing Ex. 1001, 140:44–56, 41:8–15, 133:11–45, 133:62–67, 134:3–135:43, 138:45–58, 136:4–140:43; Ex. 1003 ¶ 207).

Petitioner further argues that the common disclosure "does not identify to a skilled artisan ***any structural features*** shared by all 'active

mutant' (or all putatively useful 'inactive mutant') modified PH20 polypeptides being claimed." Pet. 69. It also asserts that the common disclosure lacks a representative number of examples of multiply-modified PH20 polypeptides, given the unpredictable effects of multiple modifications and the fact that "[t]he examples are restricted to ***one type of change*** (a single amino acid replacement) in ***one type of PH20 polypeptide*** (SEQ ID NO: 3)," whereas "the claims encompass multiply modified mutants with myriad structures within the 'hyaluronidase domain' in addition to one replacement at position 313." *Id.* at 69, 72.

c) Analysis

On the current record, we find the evidence taken as a whole supports Petitioner's position.

"Every patent must describe an invention. It is part of the *quid pro quo* of a patent." *Ariad*, 598 F.3d at 1345. *Ariad* explains that for generic claims,

> the question may still remain whether the specification, including original claim language, demonstrates that the applicant has invented species sufficient to support a claim to a genus. The problem is especially acute with genus claims that use functional language to define the boundaries of a claimed genus. In such a case, the functional claim may simply claim a desired result, and may do so without describing species that achieve that result. But the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus.

Id. at 1349. *Ariad* "explained that an adequate written description requires a precise definition, such as by structure, formula, chemical name, physical

properties, or other properties, of species falling within the genus sufficient to distinguish the genus from other materials." *Id.* at 1350. *Ariad*

> also held that functional claim language can meet the written description requirement when the art has established a correlation between structure and function. . . . But merely drawing a fence around the outer limits of a purported genus is not an adequate substitute for describing a variety of materials constituting the genus and showing that one has invented a genus and not just a species.

Id.

As discussed above (*supra* Section II.C), claim 1 is reasonably interpreted to encompass multiply-modified PH20 polypeptides with some hyaluronidase activity. Petitioner adequately demonstrates for purposes of institution that despite the enormous breadth of the claimed genus, the common disclosure lacks a representative number of species or an identified structure-function relationship to support the claimed genus. *See, e.g.*, Pet. 63–72. For example, as Dr. Hecht demonstrates, "[t]he common disclosure provides a report on a random mutagenesis experiment that generated a large number of single substitutions within the human $PH20_{1-447}$ sequence," but fails to include any analysis "to understand why the results were observed, and to determine what changes influenced discrete structures within the protein." Ex. 1003 ¶ 179. Dr. Hecht also demonstrates that

> [t]he common disclosure does not suggest that incorporating one of the substitutions that has a single mutation caused the human $PH20_{1-447}$ to exhibit increased activity will ensure that any multiply-modified PH20 protein with that mutation will be enzymatically active or will have a similarly increased activity, regardless of the number, location, or identity of the additional modifications. The common disclosure also did not draw any distinction between

> substitutions made within or outside the "hyaluronidase domain" in the $PH20_{1-447}$ single-substitution mutants that were tested. It would not have been scientifically plausible to suggest, before the advances in computational prediction of protein structure around 2020, that a skilled artisan could have predicted the effects of making the myriad possible sets of 2-14 or 2-19 additional changes (plus one substitution at position 313) on the enzymatic activity or other characteristics of a PH20 polypeptide.

Id. ¶ 180. Dr. Hecht further demonstrates that "[t]he examples of single-replacement human $PH20_{1-447}$ mutants are not representative of the incredible diversity of possible modified PH20 polypeptides having different sets of 1 to 14 or 1 to 19 *additional* substitutions within the common hyaluronidase domain that meet the parameters of the claims." *Id.* ¶ 184.

Petitioner also demonstrates that "there are ***no examples*** (prophetic or actual) of modified PH20 polypeptides with multiple modifications ***restricted within*** positions 3-339 of SEQ ID NO:7, much less one with a position 313 replacement," and indeed the common disclosure "attaches no particular significance" to a "conserved 'hyaluronidase domain'" for making modified PH20 polypeptides. Pet. 45. For this reason too, it is not clear that the inventors "possessed a genus of modified PH20 polypeptides with a position 313 replacement and up to 14 or 19 additional modifications restricted within the 'hyaluronidase domain.'" *Id.*

We also agree with Petitioner that use of the claimed multiply-modified polypeptides as contraceptive antigens lacks credibility. *See, e.g.*, Pet. 52. But even if immunization using PH20 polypeptide as a contraceptive antigen serves to satisfy the utility requirement for the instant claims, there is a similar concern as to whether multiply-modified PH20

polypeptides as encompassed by claim 1 would maintain the antigenic determinants necessary to function as contraceptives. *See* Ex. 1003 ¶ 123.

The '345 patent discloses synthesis of 6,753 single amino acid mutations in residues 1–447 of SEQ ID NO: 3, which were expressed and screened for hyaluronidase activity. *See* Ex. 1001, 200:9:–14, 200:29–31, 232:32–36. The '345 patent teaches that just under 10% of these mutations, i.e., over 600, "exhibit activity that is increased compared to wildtype." *Id.* at 232:57–58. Dr. Hecht, reviewing the '345 patent, states that Table 10 lists 3,380 tested "inactive mutants." Ex. 1003 ¶ 112. While Dr. Hecht notes some inconsistencies in the data in the '345 patent, he states that the '345 patent data shows that approximately "57.1% were inactive, and 29.4% had activity <100%." *Id.* ¶ 115. Thus, the '345 patent evidences that even when only a single mutation is made in the PH20 polypeptide, that single mutation is more likely than not to alter the structure in such a way as to inactivate the hyaluronidase activity found in the native PH20 polypeptide.

On this record, Dr. Hecht persuasively demonstrates that when the full scope of claim 1 is addressed, which includes not just single mutations in the PH20 polypeptide but also multiple mutations, there is no expectation of structural homogeneity, stating that "multiple substitutions can disrupt the sequence patterns necessary for certain secondary structures, while insertions or deletions can alter or completely remove interactions with other residues by shifting the residue positioning." Ex. 1003 ¶ 182. "These types of effects can . . . impair or eliminate functional characteristics associated with those lost or altered structures." *Id.*

On the current record, the evidence shows it is more likely than not that the claims of the '345 patent fail to satisfy the written description

requirement because they "recite a description of the problem to be solved while claiming all solutions to it and . . . cover any compound later actually invented and determined to fall within the claim's functional boundaries—leaving it to the pharmaceutical industry to complete an unfinished invention." *Ariad*, 598 F.3d at 1353.

Accordingly, on the current record, we find that Petitioner has demonstrated that it is more likely than not that the challenged claims do not comply with the written description requirement. For similar reasons, the current record does not appear to provide evidence of possession of the full scope of the claims of the '345 patent in the '731 Application or any of the subsequent divisional or continuation applications leading to the '345 patent that claim priority to the '731 Application (which appear to all have the same specification), for the reasons given above. Therefore the '345 patent might not receive the benefit of priority to the '731 Application, and based on this preliminary determination, is eligible for post grant review because the effective filing date is no earlier than the '345 patent's filing date of July 19, 2024. *See* Ex. 1001, code (22).

2. Enablement (Ground 2)

a) Principles of Law

"[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *Trustees of Boston Univ. v. Everlight Elecs. Co.*, 896 F.3d 1357, 1362 (Fed. Cir. 2018) (internal quotations omitted). That is, "there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill [in the

art] how to make and how to use the invention as broadly as it is claimed."

In re Vaeck, 947 F.2d 488, 496 (Fed. Cir. 1991).

> Factors to be considered in determining whether a disclosure would require undue experimentation . . . include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

b) Analysis

Petitioner asserts that

> Enabling the full scope of the present claims requires enabling the sub-genus of enzymatically active ***multiply***-modified PH20 polypeptides that satisfy the claim parameters—because that subgenus is not enabled, the full scope of the claims cannot be. The only method the common disclosure describes for making such multiply-modified "active mutant" PH20 polypeptides requires a skilled artisan to make and test the 10^{43}+ different modified PH20 polypeptides being claimed to determine which possess hyaluronidase activity—an impossible scale of experimentation. . . .
>
> [T]he same impossible scale of experimentation is necessary to discovery which multiply-modified PH20 polypeptides might have the implausible "contraceptive" utility.

Pet. 75–76 (citing Ex. 1003 ¶¶ 114, 123–24).

We analyze Petitioner's more detailed arguments in view of the *Wands* factors.

(1) Breadth of the Claims

Petitioner's declarant Dr. Hecht explains that the limitations recited in claim 1 "only govern the 'hyaluronidase domain' portion of the polypeptide (positions 3-339 of SEQ ID NO:7)," and "[c]onsidering only the parameters governing this mutated 'hyaluronidase domain' portion captures an immense number of distinct PH20 polypeptide sequences." Ex. 1003 ¶ 139.

Petitioner's declarant Dr. Park "calculated the number of distinct polypeptides that exist" in the genera covered by claims 1–7 and 15–17 that meet certain specified criteria. Ex. 1004 ¶ 176. Dr. Hecht summarizes Dr. Park's calculations in the table below:

Claims	*Positions w/in 3-339 That Can Be Changed*	*# of Total Changes w/in 3-339*	*Pos. 313 Choices*	*# of Distinct Polypeptides*
1, 4, 8-16	337	20	19	1.85×10^{56}
2	327	20	19	1.02×10^{56}
3, 17	337	15	19	3.10×10^{43}
5	327	15	19	2.01×10^{43}
6	337	20	8	7.78×10^{55}
7	337	20	1	9.72×10^{54}

The table above shows the "numbers of distinct modified PH20 polypeptides based on the different sets of parameters used in the claims." Ex. 1003 ¶ 141. The "number of distinct polypeptides is extremely large by all accounts, ranging from 10^{43} to 10^{56}," "even without accounting for variability permitted outside the mutated 'hyaluronidase domain.'" Ex. 1004 ¶ 176; Pet. 76. To illustrate how large these numbers are, Dr. Hecht states

that an "aggregate weight of one set of these mutants from the '345 Patent claims, where one assumes one molecule of each mutant is in the set," would be approximately 1.80×10^{21} kg, whereas "[t]he weight of the Earth is 'only' ~ 5.97×10^{24} kg." Ex. 1003 ¶ 142. That is, "just to make the possible variants that have the 'hyaluronidase domain' in one base human PH20 sequence (and not accounting for the variations outside of that region) would consume mass equal to nearly ~5% of the mass of Earth." *Id.* ¶¶ 142, 226.

On the current record, we find that the breadth of claim 1 and the dependent claims is immense.

(2) Skill in the Art

Petitioner addressed the skill in the art, as discussed *supra* Section II.B. On the current record, we agree with Petitioner that a person of ordinary skill in the art "was highly skilled." Pet. 91.

(3) State of the Prior Art

Dr. Hecht acknowledges protein expression is routine, stating that the "conventional procedures relating to production of the wild-type human $PH20_{1-447}$ protein that are described in the '429 Patent could be applied to produce forms of $PH20_{1-447}$ that incorporate a single amino acid substitution . . . with little effort." Ex. 1003 ¶ 239. Dr. Hecht further states that the "first experimentally determined structure of a hyaluronidase was of bvH, both alone and in complex with HA (published in 2007)" and that "Markovic-Housley identified the catalytic site and residues involved in catalytic activity using this structure." Ex. 1003 ¶ 81 (citing Ex. 1033, 1028–31).

However, Dr. Hecht states that data in the '429 patent and a 2007 paper by Frost (Ex. 1013) showed that "truncations of varying length at the

C-terminus of PH20 caused significant variations in hyaluronidase activity." *Id.* ¶ 94. Dr. Hecht states that a 2009 paper by Zhang et al. (Ex. 1010, "Zhang") "reported that a truncation just upstream of the start of the Hyal-EGF domain in HYAL1 reduced its activity to ~6%." *Id.* ¶ 96. Dr. Hecht states that "[n]either the scientific literature existing by 2011 nor the common disclosure provides an explanation why these PH20 truncation mutations that differ by one residue (*i.e.*, $PH20_{1-446}$ vs. $PH20_{1-447}$ vs. $PH20_{1-448}$) exhibit variability in their activity." *Id.* ¶ 98.

Dr. Hecht states that "[t]here were limits to using rational design techniques in the 2011-timeframe." *Id.* ¶ 51 (citing Ex. 1018, 378 ("The complexity of the structure/function relationship in enzymes has proven to be the factor limiting the general application of rational design."); Ex. 1059, 1225–26). Dr. Hecht states, regarding another approach to protein modification termed directed evolution, that the "challenge with directed evolution is scale. One has to identify the successful mutant out of an immense number of possibilities, which presents different kinds of challenges." *Id.* ¶ 53 (footnote omitted). Dr. Hecht states that "changing many amino acids simultaneously risks disrupting the pattern necessary to induce formation of the original secondary structure . . . and [can] be highly destabilizing to the overall protein structure." Ex. 1003 ¶ 56. Dr. Hecht states that in a smaller, ten amino acid substitution situation, "[t]here are approximately 6×10^{12} different scenarios of 10 substitutions." *Id.* ¶ 59.

On the current record, we find that the evidence shows that simply making and expressing modified PH20 polypeptides was well within the state of the prior art. However, the evidence of record also demonstrates that one of ordinary skill in the art would have been aware that mutations,

whether conservative or non-conservative, may impact protein function and physical shape. *See, e.g.*, Ex. 1003 ¶¶ 96, 101, 123, 195–97. The evidence of record demonstrates that identifying which of the 10^{43} to 10^{56} members of the PH20 polypeptide genus would either retain functional hyaluronidase activity or contraceptive activity was not established as known in the prior art.

(4) Presence of Working Examples

Dr. Hecht acknowledges that Table 8 of the '345 patent lists 6,753 $PH20_{1-447}$ mutants produced by the inventors. Ex. 1003 ¶ 107. Each mutant contains a single amino acid change. *See id.* Dr. Hecht notes that Table 10 lists 3,380 "inactive mutants." *Id.* ¶ 112. Dr. Hecht calculates that based on the data in the '345 patent, "57.1% were inactive, and 29.4% others had activity <100%." *Id.* ¶ 115.

Dr. Hecht states that the '345 patent "does not identify any ***mutated*** PH20 polypeptides that were effective when used in a contraceptive vaccine. *Id.* ¶ 123.

On the current record, we find that the evidence demonstrates the presence of a limited set of working examples relative to the genera recited in the claims, though the evidence also shows that more than half of these working examples would not be encompassed by the claims because they were enzymatically inactive and no mutated PH20 protein was shown to be an effective contraceptive.

(5) Amount of Direction or Guidance Presented

The '345 patent states that "[p]roteins, such as modified PH20 polypeptides, can be purified using standard protein purification techniques known in the art." Ex. 1001, 151:4–6.

Dr. Hecht states that the '345 patent "uses the >40% activity threshold to classify a mutant as an 'active mutant'" and that "'inactive mutants' are mutants with 20% or less of the activity of unmodified PH20." Ex. 1003 ¶¶ 104–05. Dr. Hecht states that the data in the '345 patent shows "most of the single-replacement $PH20_{1-447}$ mutants exhibited less activity than the unmodified $PH20_{1-447}$ (*i.e.*, 57.1% were inactive, and 29.4% others had activity <100%)." *Id.* ¶ 115.

Dr. Hecht states that the '345 patent

> does not identify any ***mutated*** PH20 polypeptides that were effective when used in a contraceptive vaccine. . . . The common disclosure does not provide any guidance that would allow a skilled artisan to determine whether any active or inactive mutants are useful as contraceptive vaccines (such as by identifying common structural or functional characteristics shared by those inactive mutants), without making and testing all ~10^{43} (or more) modified PH20 polypeptides within the parameters of each claim.

Id. ¶ 123. Dr. Hecht states that "the data for testing the 409 mutants reported in Tables 11 and 12 [of the '345 patent] does not provide any meaningful guidance to a skilled artisan about the types of mutations that would improve the stability of PH20 polypeptides generally, or for the human $PH20_{1-447}$ form specifically." *Id.* ¶ 77. Dr. Hecht states that the '345 patent

> identifies no examples of PH20 polypeptides with multiple amino acid substitutions at different positions (*i.e.*, specific

> amino acids being inserted at two or more different positions of the same PH20 polypeptide), including any that were enzymatically active proteins. . . . There are also no examples of multiply-modified PH20 polypeptides that have incorporated insertions or deletions within the common hyaluronidase domain (or any other internal region of the human PH20 sequence). This appears to be the case because no multiply-modified PH20 polypeptides appear to have actually been made or tested.

Id. ¶ 206. Dr. Hecht characterizes the disclosure of the '345 patent as "best described as a research plan, as it generally outlines the types of steps one might take to carry out a mutagenesis and screening research program." *Id.* ¶ 207.

On the current record, we find that the evidence demonstrates significant guidance on synthesis and expression of modified PH20 polypeptides. However, the evidence also shows that the '345 patent provides minimal guidance regarding effective methods to identify which members of the immense modified PH20 polypeptide genus function to retain either hyaluronidase activity or contraceptive activity.

(6) Quantity of Experimentation

Dr. Hecht states that

> the effects on the local structure of a protein at the site of a single amino acid substitution will not necessarily be observed when multiple modifications are made at or near that position (or even when they are made remote from the site of the first substitution). Consequently, even if one had insights on the effects of a single substitution on the local structure of a PH20 polypeptide at the site of that substitution, that information would not provide insights into the effects on the protein structure that might result when different combinations of 5, 10, 15, or more modifications are made to the protein. Consequently, the results observed for the single-replacement

> human $PH20_{1-447}$ polypeptides reported in the common disclosure would not be considered to be representative of all mutated forms of human $PH20_{1-447}$ polypeptides with that substitution (*e.g.*, at position 313) plus between 1 to 19 *additional* substitutions at any of hundreds of positions within the "hyaluronidase domain" of the PH20 protein. Instead, a skilled artisan would have had to discover which combinations of substitutions to the PH20 protein would result in mutants that exhibit hyaluronidase activity by making and testing all of them, which is an ***impossibly large undertaking***.

Ex. 1003 ¶ 197 (last emphasis added).

Dr. Hecht states that "[m]aking and identifying all of the multiply-modified PH20 polypeptides within the immense set of polypeptides (between at least 10^{43} and 10^{56} distinct mutants) defined by the claims' parameters and that are enzymatically active would require not only an undue amount of experimentation, it likely is impossible." *Id.* ¶ 204. Dr. Hecht states the directed evolution methods of the '345 patent are "the quintessential 'make and test' trial and error technique. By definition, the scientist carrying out a directed evolution protocol does not know which of the potentially trillions of possible mutants might incorporate a substitution that causes the protein to exhibit a particular characteristic, whether that is measured as increased stability, activity or something else." *Id.* ¶ 223.

We find the facts here similar to those in *Idenix Pharmaceuticals LLC v. Gilead Sciences Inc.*, 941 F.3d 1149, 1156 (Fed. Cir. 2019) where, in a genus of billions, the "key enablement question is whether a person of ordinary skill in the art would know, without undue experimentation, which [species] would be effective." *Idenix* states that because of the "many thousands of [species] which need to be screened for . . . efficacy, the

quantity of experimentation needed is large and weighs in favor of non-enablement." *Id.* at 1159.

On the current record, we find that the evidence demonstrates that a very large amount of experimentation would be necessary to enable the full scope of the claims of the '345 patent.

(7) Predictability of the Art

Dr. Hecht states that the

> effects caused by one substitution in a protein like PH20 . . . cannot predict the effects on a modified form of that protein that incorporates 5, 10, 15 (or more) changes (including additional substitutions). A skilled artisan would not view the first, single amino acid substituted PH20 [as] representative of all modified PH20 proteins having that one substitution, along with 5, 10, or 15, or more additional substitutions or other changes.

Ex. 1003 ¶ 62. Dr. Hecht states, citing the '429 patent, that the "varying effects of changing residues in the Hyal-EGF region of PH20 show that a skilled artisan's belief that changes in this region would be unpredictable were warranted and would be more so if multiple changes were made concurrently." *Id.* ¶ 100. Dr. Hecht states that "the effects on the structure of a PH20 polypeptide that result from making combinations of substitutions or other modifications within the amino acid sequence of the PH20 polypeptide could not have been accurately predicted by a skilled artisan in the 2011 timeframe using the tools that were available then." *Id.* ¶ 196.

Dr. Hecht states that the artisan following the '345 patent's "iterative mutagenesis and screening research plan cannot know in advance of conducting multiple rounds of experiments, whether multiply-modified

PH20 polypeptides will be produced that retain sufficient activity will be selected for the next round of the process." *Id.* ¶ 220.

On the current record, we credit Dr. Hecht's testimony as showing it is highly unpredictable which polypeptides would have hyaluronidase or contraceptive activity. *See, e.g., id.* ¶¶ 185, 189, 202–222. We find that the evidence shows it is highly unpredictable which modified PH20 polypeptides within the scope of the claims of the '345 patent would have any functional utility.

c) Conclusion

As we weigh the *Wands* factors, we find that the totality of the evidence shown in the current record as discussed above supports Petitioner's position. Accordingly, Petitioner has demonstrated that it is more likely than not that undue experimentation would have been required to enable the broad scope of the claims, and that the claims therefore fail to comply with the enablement requirement of 35 U.S.C. § 112(a).

3. Indefiniteness (Ground 3)

a) Principles of Law

"[A] patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014).

b) Petitioner's Position

Petitioner argues that "[t]he claims define only a portion of the claimed modified PH20 polypeptides—a mutated 'hyaluronidase domain'

within each" modified PH20 polypeptide. Pet. 97. According to Petitioner, "[p]er the common disclosure's definitions, the remainder of the modified PH20 polypeptide must derive from the starting PH20 polypeptide sequence that is modified to yield it. The claims, however, do not identify with reasonable certainty what those sequences are." *Id.* at 98 (footnote omitted).

Petitioner argues that the term "PH20" requires polypeptides that are "'neutral-active' (*i.e.*, enzymatically active at pH 6.0-7.8)," and can include "***non-human*** PH20 polypeptides" and truncated forms. *Id.* at 98. Petitioner further argues that "[t]he claims and common disclosure also provide no indication how much (or little) of a 'starting PH20' must be included in the modified PH20 polypeptide that contains the mutated 'hyaluronidase domain,' where the mutated 'hyaluronidase domain' may/must be positioned within it, or what 'chemical or posttranslational modifications' can be made (and where)." *Id.* at 99 (footnotes omitted). Petitioner argues:

> Given these shortcomings, a skilled artisan could not have reasonably determined from the claim language and/or the common disclosure what the full identity of the claimed modified PH20 polypeptides are, as they may include sequences outside the 'hyaluronidase domain' that were unknown as of December 28, 2012, or unknowable without testing. Any of these shortcomings prevents a skilled artisan from being able to reasonably determine which modified PH20 polypeptides are within the scope of the claims; collectively they make those boundaries undecipherable. Every claim is indefinite, and thus unpatentable.

Id. at 99–100 (footnote omitted).

c) Analysis

On the current record, we find that Petitioner has not demonstrated that it is more likely than not that the challenged claims are indefinite.

The claim term Petitioner takes issue with recites: "A modified PH20 polypeptide." *See* Pet. 97–98. Elsewhere in the Petition, Petitioner asserts that this entire term, as well as its component "PH20," are defined in the Specification, stating:

> According to the common disclosure, a "modified PH20 polypeptide" is "a PH20 polypeptide that contains at least one amino acid modification, such as at least one amino acid replacement . . . in its sequence of amino acids . . . " In turn, the common disclosure defines "PH20" as ". . . a type of hyaluronidase that occurs in sperm and is neutral-active." Neutral-active means that PH20 is able to ". . . ***to enzymatically catalyze*** the cleavage of hyaluronic acid ***at neutral pH***, such as at a pH between or about between pH 6.0 to pH 7.8.

Pet. 21 (footnotes omitted) (citing Ex. 1001, 47:3–8, 44:20–21, 49:4–7); *see also id.* 98 (conceding that the Specification defines "PH20").

These definitions undercut Petitioner's argument regarding indefiniteness. Indeed, Petitioner's complaints—including that the claims embrace "***non-human*** PH20 polypeptides," truncated forms, and "starting PH20" polypeptides of varying length—go more to the breadth of the claims, rather than to indefiniteness. *See, e.g.*, *In re Miller*, 441 F.2d 689, 693 (CCPA 1971) ("breadth is not . . . indefiniteness"). For this reason, we find on this record that Petitioner has not demonstrated that the challenged claims are more likely than not indefinite.

4. Obviousness (Ground 4)

a) Principles of Law

Under 35 U.S.C. § 103, a claim is unpatentable as obvious if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective

filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. 35 U.S.C. § 103; *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved based on underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) any objective indicia of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

An obviousness determination requires finding a reason to combine accompanied by a reasonable expectation of achieving what is claimed in the challenged patent. *See Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016). "[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *KSR*, 550 U.S. at 419–20.

b) Overview of the Asserted Prior Art

(1) The '429 Patent (Ex. 1005)

The '429 patent was filed on March 5, 2004 and issued on August 3, 2010. Ex. 1005, codes (22), (45). The '429 patent is drawn to "members of the soluble, neutral active Hyaluronidase Glycoprotein family, particularly the human soluble PH-20 Hyaluronidase Glycoproteins (also referred to herein as sHASEGPs)." *Id.* at 3:51–54.

The '429 patent teaches "a substantially purified glycoprotein including a sequence of amino acids that has at least . . . 95% . . . identity to the sHASEGP." *Id.* at 6:15–20. The '429 patent states:

> Suitable conservative substitutions of amino acids are known to those of skill in this art and can be made generally without altering the biological activity, for example enzymatic activity, of the resulting molecule. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity.

Id. at 16:14–20. The '429 patent claims a specific truncated version of the hyaluronidase glycoprotein composed of positions 36–482 of SEQ ID NO:1. *See id.* at 153:39.

(2) Chao (Ex. 1006)

Chao is a publication in the journal Biochemistry that was published in 2007. Ex. 1006, 6911.

Chao states that "[t]here are five homologous hyaluronidases encoded in the human genome: hHyal-1 through -4 and the sperm adhesion molecule 1 (termed PH-20)." *Id.* Chao states that "[i]n humans, eight alternative splice transcripts of *HYAL1* encode the full-length enzyme and five splice variants. Variants 1-5 (designated v1 through v5) are each truncated to a different extent. They lack enzymatic activity." *Id.* at 6912 (citation omitted). Chao "report[s] the crystal structure of the enzyme showing that it contains an EGF-like domain not seen previously, and examine[s] the impact of alternative splicing on the enzyme structure and function." *Id.*

Chao states that "[h]uman hyaluronidases exhibit 33-42% sequence identities and even higher conservation of active site residues. Yet, the enzymes differ in their catalytic efficiencies and pH profiles." *Id.* at 6914.

Figure 3 of Chao is reproduced below:

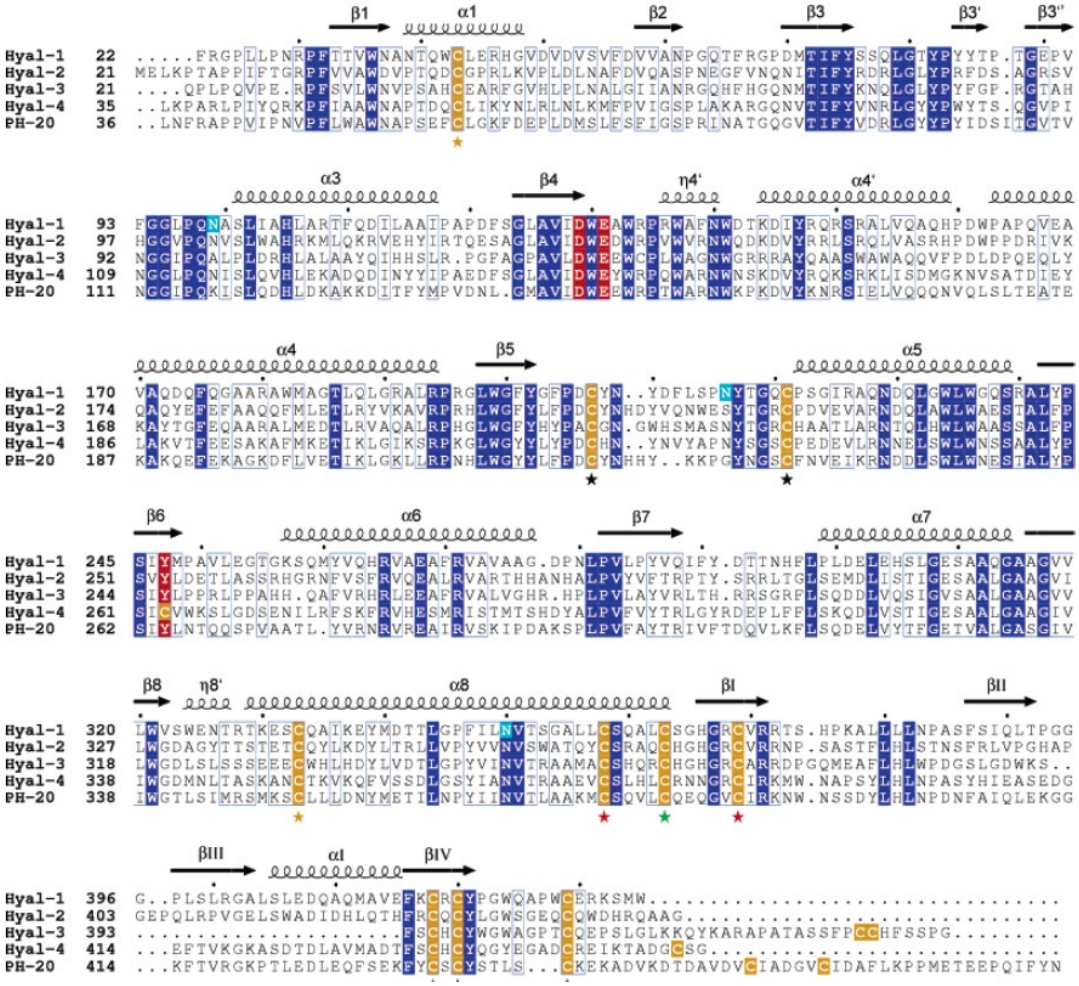

Figure 3 shows a

> [s]tructure-based sequence alignment of human hyaluronidases. Invariant residues are shown in blue except for three key catalytic residues that are colored red. Cysteine residues are colored yellow. The hHyal-1 N-glycosylated asparagines residues are colored turquoise. Residues exhibiting conservative replacements are blocked in blue. Pairs of cysteine residues that form disulfide bonds are indicated by stars with matching colors. Secondary structure units are labeled.

Id. at 6916.

c) Asserted Obviousness Over the '429 Patent and Chao

(1) Petitioner's Position

Petitioner asserts that the '429 patent "teaches making a ***particular*** type of modification (a single amino acid substitution) in ***particular*** locations (all of the non-essential regions of PH20) in a ***particular*** PH20 sequence ($PH20_{1–447}$) to yield equivalents of $PH20_{1–447}$ (*i.e.*, those that do not substantially alter the activity or function of $PH20_{1-447}$)." Pet. 103 (citing Ex. 1003 ¶ 242; Ex. 1004 ¶ 33). Petitioner asserts that Chao "described 'a novel, EGF-like domain' in the C-terminal region of human hyaluronidases 'closely associated' with the catalytic domain (in PH20 at 337-409), with a characteristic pattern of residues." Pet. 105 (internal cross-reference omitted) (citing Ex. 1006, 6911; Ex. 1004 ¶¶ 98–99; Ex. 1003 ¶¶ 85, 88).

Petitioner asserts that "a skilled artisan looking to implement the '429 Patent's teachings would have (i) identified all of the non-essential regions in $PH20_{1-447}$, and (ii) determined which substitutions to make within those non-essential regions." Pet. 104 (citing Ex. 1003 ¶¶ 287–89). Petitioner asserts that Dr. Park performed such an analysis and, consistent with Chao's Figure 3, identified "position 313 as being within a non-essential region [in] $PH20_{1-447}$." *Id.* at 107–08 (citing Ex. 1003 ¶¶ 252, 256; Ex. 1004 ¶¶ 32–33, 104, Appx. D-2; Ex. 1006, 6916; Ex. 1005, 16:14–22, 16:24–36).

Petitioner asserts that in Dr. Park's alignment, "[m]ethionine (M) occurs at position 313 in human PH20 and at positions corresponding to position 313 in ~14% of homologous proteins, while lysine (K) is the most prevalent amino acid found at those positions (~40%) (*i.e.*, 35 different proteins)." *Id.* at 110 (citing Ex. 1004 ¶¶ 106–07, 114; Ex. 1003 ¶ 253).

Petitioner asserts that a "skilled artisan would have viewed lysine (K) as an obvious single substitution at position 313 in $PH20_{1-447}$." *Id.* at 110. Petitioner asserts: "First, the '429 Patent explicitly identifies lysine as being one of the conservative substitutions for methionine as a single amino acid substitution in PH20 proteins." *Id.* (citing Ex. 1005, 16:4–32, Table 1, 10:9–13). Petitioner asserts that, "[s]econd, lysine occurs at this position in many homologous proteins and in 2 of 5 human hyaluronidases." *Id.* (citing Ex. 1004 ¶¶ 44, 107, 114; Ex. 1003 ¶ 253, 256–57). Petitioner asserts: "Third, lysine has a high helix propensity, meaning it is favored in sequences that form α-helix structures, while Chao reports position 313 as being in an α-helix sequence ('α8')." *Id.* at 111 (citing Ex. 1050, 422–24, Table 2; Ex. 1004 ¶¶ 32, 70–71, 109, 118; Ex. 1003 ¶¶ 43, 254; Ex. 1006, 6916, Figure 3).

Petitioner asserts that in prosecuting the '429 patent, Patent Owner relied on "its statements that a skilled artisan would have expected ***any*** single amino acid substitution in ***any*** non-essential position of $PH20_{1-447}$ to not substantially affect the activity of the enzyme." *Id.* at 112. Petitioner also asserts that "a skilled artisan would have reasonably expected the M313K substitution to not substantially alter the hyaluronidase activity of $PH20_{1-447}$." *Id.* at 112.

(2) Analysis

On the current record, we find that Petitioner has not provided any persuasive reason to particularly target the methionine at position 313 of a PH20 polypeptide for modification with lysine. Neither the '429 patent nor Chao specifically identifies or discusses position 313 of the PH20 polypeptide.

On this record, we are not persuaded by Petitioner's arguments that multiple sequence alignments identify amino acids that are tolerated at particular positions or that the '429 patent identifies lysine as a conservative substitution for methionine (*see, e.g.*, Pet. 108–10), because tolerance is not a positive reason to make a substitution. "It is not enough, even after *KSR*, to support a determination of obviousness that a reference includes a broad generic disclosure and a common utility to that in the claims and other prior art references—there must be some reason to select a species from the genus." *Knauf Insulation, Inc. v. Rockwool Int'l A/S*, 788 Fed. App'x 728, 733 (Fed. Cir. 2019).

Dr. Park identified 379 positions in PH20 with evolutionary variation, that is, where "homologous proteins have tolerated different amino acids at those positions." Ex. 1004 ¶ 32. Dr. Park distributes the twenty standard amino acids into four categories depending on their roles in forming secondary structure such as alpha helices or beta sheets, with each category having a minimum of six members. *See id.* ¶ 71. Nothing in the prior art or Dr. Park's analysis directs the ordinary artisan to position 313 itself, and Dr. Park notes that Chao did not identify position 313 of PH20 as part of the catalytic active site, unlike positions 146, 148, and 219, nor was position 313 one of the residues identified as being in the cleft where ligand binds. *See id.* ¶ 92. Dr. Park indicates that position 313 was not identified by Chao as part of the Hyal-EGF domain, was not identified by Stern in the active site, and was not identified by Arming as impacting PH20 activity. *See id.* ¶¶ 99–102 (citing Ex. 1006, 6912, 6916; Ex. 1008, 825; Ex. 1011, 811–813).

Indeed, Dr. Hecht states that "[r]eplacing, inserting or deleting amino acids indiscriminately in this [α8] region could disrupt that [alpha helical]

pattern, which could have a range of effects in this region of the helical structure." Ex. 1003 ¶ 229. And while Dr. Hecht asserts that the '429 patent suggests conservative mutations—including substituting lysine for methionine—Petitioner did not point us to any specific teaching or suggestion to modify position 313 of PH20. *See*, *e.g.*, *id.* ¶¶ 242–244. On this record, Petitioner did not point us to anything in Dr. Hecht's Declaration that explained why position 313 was of interest in any way, versus position 316 or 318 or any other position within the PH20 polypeptide.

We are also not persuaded by Petitioner's arguments that a person of ordinary skill in the art would have substituted methionine with lysine at position 313 because "lysine has a high helix propensity, meaning it is favored in sequences that form α-helix structures." Pet. 111. This statement is not a reason for the substitution, but rather a statement as to the properties of lysine. Dr. Park identified seven different amino acids that favor alpha helix formation. *See* Ex. 1004 ¶ 71. Figure 3 of Chao shows a number of different alpha helical regions, α1, α3, η4', α4', α4, α5, α6, α7, and α8, each composed of multiple amino acids, many of which appear to be non-conserved. *See* Ex. 1006, 6916 Table 1. Each of these large number of amino acids found within alpha helices might be subject to substitution by one of the seven preferred amino acids identified by Dr. Park, but it is Petitioner's "burden to show that the 'prior art would have suggested making the *specific molecular modifications* necessary to achieve the claimed invention.'" *Amerigen Pharm. Ltd. v. UCB Pharma GmBH*, 913 F.3d 1076, 1089 (Fed. Cir. 2019) (citing *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007)). Petitioner has not satisfied this

burden of showing specific reasons to modify position 313 of the PH20 polypeptide.

Accordingly, on the current record, we find that Petitioner has not demonstrated that it is more likely than not that the combination of the '429 patent and Chao would have rendered challenged claims 1–17 obvious.

III. CONCLUSION

On the current record, Petitioner sufficiently shows that least one of the challenged claims is more likely than not unpatentable. Accordingly, we institute a post grant review.

At this stage of the proceeding, the Board has not made a final determination regarding the patentability of any challenged claim. Thus, any conclusion reached in the foregoing analysis could change upon completion of the record.

The Board will deem forfeited any issue not raised in a timely response to the Petition, or as permitted in another manner during trial.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 324(a), post grant review of claims 1–17 of the '345 patent is hereby instituted on the grounds set forth in the Petition; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 324(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial commencing on the entry date of this Decision.

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