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Paper 24
Entered: October 1, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,
Petitioner,

v.

HALOZYME, INC.,
Patent Owner.

PGR2025-00033
Patent 12,049,652 B2

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

VALEK, *Administrative Patent Judge*.

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

I. INTRODUCTION

Merck Sharp & Dohme LLC ("Petitioner") filed a Petition (Paper 1, "Pet.") requesting post-grant review of claims 1–40 of U.S. Patent No. 12,049,652 B2 (Ex. 1001, "the '652 patent"). Halozyme, Inc. ("Patent Owner") filed a Preliminary Response. Paper 18 ("Prelim. Resp."). Petitioner also filed an authorized reply. Paper 22 ("Reply").[1]

Concurrent with filing its Preliminary Response, Patent Owner filed a statutory disclaimer of claims 3–5 and 30–40 of the '652 patent, leaving only claims 1, 2 and 6–29 at issue here. *See* Ex. 2003.

We have authority to determine whether to institute a post-grant review under 35 U.S.C. § 324. Institution of a post-grant review is authorized by statute when "the information presented in the petition . . . would demonstrate 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). Applying that standard in view of the current record, we determine that Petitioner has shown it is more likely than not that claims 1, 2 and 6–29 of the '652 patent are unpatentable and therefore institute post-grant review for the reasons articulated below.

We note, however, this decision is not a final determination regarding the patentability of claims for which post-grant review is instituted. Our final decision will be based on the full record developed during trial.

[1] Although authorized, Patent Owner elected not to file a sur-reply. The parties also filed briefs addressing discretionary denial issues. *See* Papers 15, 17. The Director denied Patent Owner's request for discretionary denial and referred the Petition to the Board. Paper 23.

II. 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 real parties-in-interest. Paper 4, 1.

III. RELATED PROCEEDINGS

The parties collectively identify the following post grant review proceedings:

U.S. Patent 11,952,600 (PGR2025-00003); U.S. Patent 12,018,298 (PGR2025-00004); 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. 12,104,185 (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. 12,264,345 (PGR2025-00052); and U.S. Patent No. 12,195,773 (PGR2025-00053). *See* Paper 18, 1; Paper 19, 2.

The Parties also identify *Halozyme, Inc. v. Merck Sharp & Dohme Corp.*, 2:25-cv-03179 (D.N.J.) as a related matter in which Patent Owner alleges infringement of the ’652 patent. Paper 18, 1; Paper 19, 1.

Patent Owner states that the ’652 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. Paper 19. 2.

IV. THE ’652 PATENT

A. Background

The ’652 patent issued July 30, 2024, from U.S. Application 18/064,886, filed December 12, 2022. Ex. 1001, codes (21), (22), (45). The ’652 patent is a division of application of U.S. Application 17,327,568, filed on May 21, 2021, which is a continuation in a lengthy set of applications claiming continuity to U.S. Application 13/694,731 (“the ’731 application”), filed on Dec. 28, 2012, now U.S. Patent No. 9,447,401 B2. *Id*. at code (60). The ’731 application claims the priority benefit of provisional applications U.S. 61/796,208, filed November 1, 2012, and U.S. 61/631,313, filed Dec. 30, 2011. *Id.*

The ’652 patent is drawn to “[m]odified PH20 hyaluronidase polypeptides, including modified polypeptides that exhibit increased stability and/or increased activity.” Ex. 1001, 4:20–22. The ’652 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 4:27–29. The ’652 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 4:34–40. In addition, the ’652 patent teaches that “since HA is a major component of the interstitial barrier, hyaluronan-degrading enzymes (e.g., hyaluronidase) increase tissue permeability and therefor can be used to increase the dispersion and delivery of therapeutic agents.” *Id.* at 4:41–44. According to

the ’652 patent, “[v]arious hyaluronidases have been used therapeutically,” but “[m]any of these are ovine or bovine forms, which can be immunogenic for treatment of humans” and therefore improved hyaluronan-degrading enzymes “that can be used for treatment are needed.” *Id.* at 4:45–54.

The ’652 patent purports to describe modified PH20 hyaluronidase polypeptides that have been modified with “amino acid replacement, deletion an/or insertions.” Ex. 1001, 4:58–62. For instance, the ’652 patent states as follows:

> [P]rovided are modified PH20 polypeptides that contain one or more amino acid replacements that result in a PH20 polypeptide that retains activity and/or exhibits increased or altered stability under a variety of conditions. . . . Exemplary modifications are amino acid replacements. For purposes herein . . . amino acid replacements are denoted by the single amino acid letter followed by the corresponding amino acid position in SEQ ID NO:3 in which the replacement occurs. 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, or the same replacement at the corresponding position in another PH20 polypeptide.

Id. at 4:66–5:19.

The ’652 patent states that the “modified PH20 polypeptides provided herein exhibit altered activities or properties compared to a wildtype, native or reference PH20 polypeptide.” Ex. 1001, 75:45–47. The ’652 patent further provides:

> Included among the modified PH20 polypeptides provided herein are PH20 polypeptide that are active mutants, whereby the polypeptides exhibit at least 40% of the hyaluronidase activity of

> the corresponding PH20 polypeptide not containing the amino acid modification (e.g., amino acid replacement). In particular, provided herein are PH20 polypeptides that exhibit hyaluronidase activity and that exhibit increased stability compared to the PH20 not containing the amino acid modification. Also provided are modified PH20 polypeptides that are inactive, and that can be used, for example, as antigens in contraception vaccines.

Id. at 75:47–58.

B. Post-Grant Review Eligibility

As a threshold issue, we must determine whether the '652 patent is eligible for post-grant review. There are two requirements that must be met for post-grant review to be available. First, post-grant review is only available if the petition is filed within nine months of the issuance of the challenged patent. 35 U.S.C. § 321(c). Petitioner certifies that the Petition, filed on March 7, 2025, is within nine months of the '652 patent's July 30, 2024, issue date. Pet. 4; Ex. 1001, code (45).

Second, post-grant review is available only for patents that issue from applications 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 listed on the face of the '652 patent include three filings prior to March 16, 2013. These prior filings are the '731 application, filed December 28, 2012, U.S. Provisional Application 61/796,208, filed Nov. 1, 2012, and U.S. Provisional Application 61/631,313, filed December 30, 2011. *See* Ex. 1001, code (60).

Petitioner asserts the disclosure of the "'731 Application (including subject matter incorporated by reference) does not provide written description support for and does not enable any claim of the '652 Patent." Pet. 5. According to Petitioner, "[t]he '652 Patent is PGR eligible as at least

one of its claims does not comply with § 112(a) based on the '731 Application," and therefore has an effective filing date after March 16, 2013. *See id.* at 6.

Patent Owner asserts that Petitioner has failed to meet its burden of demonstrating that the challenged patent is eligible for PGR, because Petitioner used the wrong date in its written description analysis. *See* Prelim. Resp. 10–12. Specifically, Patent Owner contends that "rather than assess the '731 application as of its *2012* filing date, [Petitioner]'s analysis consistently *and only* applied a *2011* date, while fatally ignoring the '731 Application's *December 28, 2012* filing date." *Id.* at 11 (emphasis in original).

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 IX. As discussed below, we determine that the '652 patent is eligible for post grant review. *See id.*

V. ILLUSTRATIVE CLAIM

Claim 1 is illustrative of the challenged claims in the '652 patent, and is reproduced below.

> 1. A modified PH20 polypeptide, comprising one or more amino acid modifications in an unmodified PH20 polypeptide, wherein:
>
> the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID Nos: 3, 7 and 32–66;

> amino acid modifications are selected from the group consisting of amino acid replacements(s), deletion(s), and/or insertion(s);
>
> the modified PH20 polypeptide comprises an amino acid replacement at a position corresponding to residue 320, with reference to amino acid positions set forth in SEQ ID NO:3;
>
> the replacement at the position corresponding to residue 320 is selected from the group consisting of H, K, R, and S;
>
> corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the amino acid sequence of SEQ ID NO:3; and
>
> the modified PH20 polypeptide has at least 91 % sequence identity to a polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7 and 32–66.

Ex. 1001, 309:18–43. Claim 2 further limits the modified PH20 polypeptide of claim 1 to one having "at least 95% sequence identity." *Id.* at 309:44–47.

VI. ASSERTED GROUNDS

Petitioner contends that the challenged claims are unpatentable based on several grounds that are presented below.

Ground	Reference(s)/Basis	35 U.S.C. §	Claim(s) Challenged[2]
1	Written Description	§ 112	1, 2, 6–29
2	Enablement	§ 112	1, 2, 6–29
3	'429 patent,[3] Chao[4]	§ 103	1, 2, 6–29

See Pet. 7. Petitioner also relies on the Declarations of Michael Hecht, Ph.D. and Sheldon Park, Ph.D. *See* Exs. 1003, 1004, respectively. Patent Owner relies on the Declaration of Barbara Triggs-Raine, Ph.D. *See* Ex. 2055.

VII. 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 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. 15–16 (citing Ex. 1003 ¶ 13).

[2] We have adjusted the claims challenged in the Petition to only those that remain in effect following Patent Owner's disclaimer.
[3] US 7,767,429 B2, issued Aug. 3, 2010 (the "'429 patent") (Ex. 1005).
[4] Chao et al., *Structure of Human Hyaluronidase-1, a Hyaluronan Hydrolyzing Enzyme Involved in Tumor Growth and Angiogenesis*, 46 Biochemistry 6911–20 (2007) ("Chao") (Ex. 1006).

Patent Owner contends that this definition is incomplete "[b]ecause the patent relates to modified PH20 polypeptides and the prior art [Petitioner] cites (e.g., the '429 Patent and Chao) relates to hyaluronidases, a POSA or a member of a multi-disciplinary team that includes the POSA would have *at least two years of practical experience with hyaluronidases*." Prelim. Resp. 12 (emphasis in original) (citing Ex. 2055 ¶¶ 23–46; Ex. 2004; Ex. 2005). Patent Owner contends the "practical experience with hyaluronidases must come from either the POSA's own experience or through collaborations with a member of a multidisciplinary team having experience studying and characterizing hyaluronidases." *Id*. at 13 (citing Ex. 2055 ¶¶ 45–46).

Patent Owner's contentions are, at this stage, unavailing because Patent Owner's proffered definition of a POSA is too restrictive. Petitioner's proposal is sufficiently comprehensive to encompass the level of skill reflected in prior art relevant to the '652 patent. It is reasonably clear that, in indicating that a POSA would have an advanced degree (like a Ph.D.) and years of experience in analysis of protein structure, Petitioner is asserting that knowledge of proteins generally is sufficient to understand the types of problems encountered in the art and the prior art solutions to those problems, and the ordinary artisan need not have expertise specifically in hyaluronidases. *See* Pet. 15–16. Petitioner requires that the POSA would be able to apply key scientific concepts (e.g., biochemistry, recombinant biology, sequence analysis and protein modeling) to enzymes such as hyaluronidases. *See id*.

Moreover, Patent Owner fails to persuasively explain why Petitioner's definition that includes a person with expertise in other enzymes is

insufficient. Even if we were to apply Patent Owner's POSA definition, it is not clear on the record before us that Petitioner's experts lack relevant expertise or qualifications of at least a POSA.

Patent Owner will have the chance to cross-examine Dr. Hecht and Dr. Park in this proceeding to develop a full record for us to determine the weight that each expert's testimony should be given. Patent Owner will have further opportunity on a full record to assert that we should discount either experts' testimony due to lack of appropriate qualifications.

At this stage of the proceeding and on the record before us now, we apply Petitioner's proposed POSA level, which 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).

VIII. 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.*

A. Petitioner's Position

Petitioner asserts the "claim terms are either expressly defined in the common disclosure[5] or are used with their common and ordinary meaning.

[5] Petitioner uses the term "common disclosure" to refer to the specifications of both "the '652 patent and its ultimate parent '731 Application," i.e., the earliest non-provisional application in the chain of priority. *See* Pet. 1 (citing

Consequently, no term requires an express construction to assess the grounds in this Petition," beyond the definitions expressly provided in the specification. Pet. 17. In this regard, Petitioner asserts "the specification describes two mutually exclusive categories of 'modified PH20 polypeptides' (*i.e.*, 'active mutants' vs. 'inactive mutants') but the claims are limited to one (*i.e.*, 'active mutants')." *Id.* at 21. Petitioner asserts the claims are limited to "active mutants" for at least three reasons:

> First, each [claim] requires modified PH20 polypeptides with one of four replacements at position 320 that yielded an "active mutant" as a single-replacement $PH20_{1-447}$ polypeptide (*i.e.*, D320H, D320K, D329R, or D320S). All four are identified as "Active Mutants" in Table 3 and have >100% activity per Table 9.
>
> Second, claim 4 restricts the genus of "active mutants" in claim 1 (*i.e.* those with some hyaluronidase activity) to those with [at] least 100% of the activity of unmodified PH20.
>
> Third, the specification defines a "modified PH20 polypeptide" as "a PH20 polypeptide that contains at least one modification," but can also "have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide ***exhibits hyaluronidase activity***."

Id. at 23–25 (emphasis in original) (citing Ex. 1001, 85 (Table 3), 252 (Table 9),48:41–56, 47:64–48:1, 52:44–50, 76:67–77:7, 81:1–82:10, 97:49–61, 127:25–44, 173:6–9, 302:36–303:56; Ex. 1003 ¶¶ 129–132). Petitioner asserts that even if the claims include inactive mutants, "every claim still necessarily includes (and thus must describe and enable) the full subgenus of 'active mutants' in claim 1 defined by claim 4." *Id.* at 25.[6]

Ex. 1026); *see also id.* at 5, n. 5 ("'[C]ommon disclosure' refers to the shared disclosure of the '652 Patent and the '731 Application").

[6] In view of Petitioner's detailed assertions that the claims cover active mutants (*see* Pet. 17–25), we do not agree with Patent Owner that we

B. Patent Owner's Position

Patent Owner asserts that the term "modified PH20 polypeptide" is implicitly defined by Petitioner who "relies on a requirement for hyaluronidase activity, but . . . failed to provide any reasoned basis for such an assertion." Prelim. Resp. 17. Patent Owner asserts that "modified PH20 polypeptide" is defined in the Specification "as 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." *Id.* at 17–18 (citing Ex. 1001, 48:41–46); *see id.* at 19 (quoting alleged definition) (citing Ex. 1001, 48:41–46; Ex. 2055 ¶ 67). Patent Owner asserts that based on the definition "a POSA would have understood that 'modified PH20 polypeptide' is solely defined by its structure, i.e., its sequence of amino acids, and not by function." *Id.* at 21 (citing Ex. 2055 ¶ 68).

Patent Owner also points out that the Specification discloses "*modified PH20 polypeptides* that contain one or more amino acid replacements in a PH20 polypeptide and that are *inactive*, *whereby the polypeptides do not exhibit hyaluronidase activity* or exhibit low or

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"should deny trial under 37 C.F.R. § 42.204(b)(3) because [Petitioner] does not identify how the claims should be construed or provide sufficient evidence supporting its claim interpretation." *See* Prelim. Resp. 25 (title case omitted). We also do not agree that it is a "problem" for Petitioner that "neither [of its] declarant[s] addresses claim construction principles at all, let alone applies them." *Id.* at 2. Petitioner and its declarant discuss the express definition of "modified PH20 polypeptide" and other relevant portions of the Specification, and in any event, extrinsic evidence such as expert testimony is "less significant than the intrinsic record in determining the meaning of a claim term." *See, e.g.*, Pet. 17–25; Ex. 1003 ¶¶ 101–110, 129–138; *Phillips v. AWH Corp.*, 415 F.3d 1303, 1317 (Fed. Cir. 2005).

diminished hyaluronidase activity." Prelim. Resp. 22 (emphasis in original) (citing Ex. 1001, 75:56–58, 115:58–63, 116:9–12, 116:66–117:6, 187:61–65, 261:60–267:57, Tables 5 and 10; Ex. 2055 ¶¶ 75–76).

According to Patent Owner, Petitioner's "attempt to discredit the utility of 'inactive mutants' to justify importing a hyaluronidase activity limitation into the claims is improper: claims must be read 'in light of the specification,' not in spite of the specification." Prelim. Resp. 30. Patent Owner asserts that

> the specification merely states that modifications *can be made to* create active "modified PH20 polypeptides;" it does not state that all claimed "modified PH20 polypeptides" must exhibit hyaluronidase activity. The identified statements—divorced from the express definition of "modified PH20 polypeptide" and uses of the term elsewhere—do not indicate that Patent Owner "clearly express[ed] an intent to redefine" "modified PH20 polypeptide" to require enzymatic activity.

Id. at 30 (citing Ex. 1001, 115:57–124:33, 261:60–65; Ex. 2055 ¶ 87; *Bradium Techs. v. Iancu*, 923 F.3d 1032, 1044 (Fed. Cir. 2019)).

Moreover, Patent Owner contends Petitioner "wrongly argues that the claims are limited to 'active mutants' because they require each 'modified PH20 polypeptide' to have one of four replacements at position 320 that yielded an 'active mutant.'" Prelim. Resp. 31 (citing Pet. 24; Ex. 1003 ¶¶ 129–131; Ex. 2055 ¶¶ 86, 89). According to Patent Owner, the doctrine of claim differentiation applies because claims 17 and 18 require glycosylation "which the patent states is critical for hyaluronidase activity," and therefore, the additional recitations in those claims implies that the mutants in claim 1 need not be glycosylated or active. *Id.* (citing Pet. 12; Ex. 2055 ¶ 86; Ex. 1001, 70:64–71:1).

C. Analysis

On the present record, we find the evidence supports a broad definition of "modified PH20 polypeptide" that includes active molecules.

> [T]he definition in the patent documents controls the claim interpretation. . . . Any other rule would be unfair to competitors who must be able to rely on the patent documents themselves, without consideration of expert opinion that then does not even exist, in ascertaining the scope of a patentee's right to exclude.

Southwall Tech., Inc. v. Cardinal IG Co., 54 F.3d 1570, 1578 (Fed. Cir. 1995). "[T]he specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs." *Phillips v. AWH Corp*., 415 F.3d 1303, 1316 (Fed. Cir. 2005).

Here, the '652 patent defines "PH20" as a type of hyaluronidase enzyme 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, 45:59–65. The '652 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 46:9–14. The '652 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 46:18–20. The '652 patent also provides an express definition of the term "modified PH20 polypeptide," stating that this 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 48:41–54 (emphasis added).

Based on this express definition, the current record does not support the interpretation proffered by Patent Owner and Dr. Triggs-Raine that the "term 'modified PH20 polypeptide,'. . . has a purely structural meaning in the context of the specification." Prelim Resp. 21 (citing Ex. 2055 ¶ 68). Patent Owner and its declarant rely on a truncated version of the definition above that omits the text after the first period because, in their view, that text "is not part of the express definition of 'modified PH20 polypeptide'" and "merely describes an *upper limit* for the number of modifications possibly allowing a modified PH20 polypeptide to exhibit enzymatic activity." Ex. 2055 ¶¶ 67, 77–78 (emphasis in original). On this record, we disagree.

We find that this text is part of the definition of "modified PH20 polypeptide" because it continues to detail specific elements required of that term, i.e., a requirement that modifications in the PH20 polypeptide are permitted "*so long as* the resulting modified PH20 polypeptide exhibits hyaluronidase activity." Ex. 1001, 48:47–49 (emphasis added); *see* Ex. 2055 ¶ 67 (acknowledging that a "patent's definition controls," but referring,

without adequate explanation, to the second sentence of the definition paragraph as "a non-limiting example"). Indeed, while some of the language in the definitional paragraph is permissive in nature, i.e.., describing the number of amino acid replacements a modified PH20 polypeptide "can have" or "[t]ypically . . . contains" or the other modifications the polypeptide "can include," the phrase "so long as" is not. *See* Ex. 1001, 48:41–56. This distinction demonstrates that hyaluronidase activity is not an optional feature of a non-limiting example as Patent Owner posits, but a requirement of the "modified PH20 polypeptide" defined and claimed in the '652 patent. *See Alynylam Pharms., Inc. v. Moderna, Inc.*, 138 F.4th 1326, 1333 (Fed. Cir. 2025) (explaining that the "contrast" between "non-limiting terms" and more definitive statements may indicate that the latter is definitional).

Moreover, Dr. Triggs-Raine states "the modified PH20 polypeptides have multiple credible uses, including 'therapeutic uses of modified PH20 polypeptides that have the ability to degrade hyaluronan.'" Ex. 2055 ¶ 115.[7] That is, even Dr. Triggs-Raine recognizes hyaluronidase activity as the primary utility for the modified PH20 polypeptides recited in claim 1.

Thus, the evidence of record shows the '652 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, but ***only*** "so

[7] We recognize Dr. Triggs-Raine also cites "a credible use as contraceptives," but on this record, provides no evidence of a single modified PH20, as opposed to the naturally occurring PH20, that functions as a contraceptive in any species. *See* Ex. 2055 ¶ 115.

long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity." Ex. 1001, 48:47–49. That is, the definition of "modified PH20 polypeptide" in the '652 patent expressly requires the claimed "modified PH20 polypeptide" to exhibit at least some hyaluronidase activity.

Finally, Patent Owner's disclaimer of claims reciting "increased hyaluronidase activity" (claim 4) or use of the "modified PH20 polypeptide" of claim 1 to treat a hyaluronan-associated disease (claims 30 and 31) does not impact the claim differentiation argument. *See* Ex. 1001, 309:52–55, 312:8–13. The original issuance of these claims reinforces our view that claim 1 encompasses modified PH20 polypeptides with hyaluronidase activity, and there is no language in claim 1 limiting the PH20 polypeptides to inactive polypeptides with no hyaluronidase activity. *See* Ex. 1001, 309:18–43. On the current record, we therefore adopt the definition for "modified PH20 polypeptide" as recited in the '652 patent to require polypeptides with some hyaluronidase activity.[8]

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'")

[8] As to Patent Owner's assertion that the term "modified PH20 polypeptide" also encompasses enzymatically inactive polypeptides, we note the '652 patent imposes functional requirements on inactive polypeptides as well, stating that "[a]lso provided are modified PH20 polypeptides that are inactive, and that can be used, for example, as antigens in contraception vaccines." Ex. 1001, 75:56–58. We address this concept further in the written description analysis.

(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.

IX. GROUND I - WRITTEN DESCRIPTION

A. Principles of Law

In a post-grant review, as in an *inter partes* review, "the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *See Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016). This burden of persuasion never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015).

"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 "the claim language defines enormous genera: between 10^{59} and 10^{112} distinct polypeptides. . . . Testing every polypeptide within the claims' scope in search of 'active mutants' is impossible—literally." Pet. 25–26 (citing Ex. 1003 ¶¶ 125–126, 199). Petitioner asserts

> [T]he genera of modified PH20 polypeptides of claims 1–2, 6–15, and 24–25 are not only immense, but structurally and functionally diverse. They capture PH20 mutants with 2, 3, or more substitutions up to a number set by the sequence identity boundary (*i.e.*, 21 for the narrowest claims (*e.g.* claims 24 and 25) to 42 for the broadest (claim 1)). . . . Each claim also encompasses substitutions within C-terminally truncated forms of PH20 of varying lengths. Claim 1 does this explicitly, specifying 37 alternative sequences that terminate at positions 430 to 474.

Id. at 31 (citing Ex. 1003 ¶¶ 122–23).

Petitioner asserts that the '652 patent "instructs the skilled artisan 'to generate a modified PH20 polypeptide containing any one or more of the described mutation, and test each for a property or activity as described herein.'" Pet. 32–33 (citing Ex. 1001, 78:34–38; Ex. 1003 ¶ 203). Petitioner acknowledges that the '652 patent identifies six specific combinations of mutations to avoid, but asserts that the patent offers no explanation why and "[n]othing in the claim language excludes these combinations." *Id.* at 33–34 (citing Ex. 1001, 78:34–38; Ex. 1003 ¶¶ 149–150). Petitioner also acknowledges that the '652 patent identifies other changes to avoid in active mutants, i.e., "(i) any substitution at 96 different positions in the PH20 sequence, and (ii) 313 specific amino acid substitutions listed in Tables 5 and 10 that are made at other positions," but asserts that the "sequence

identity claim parameters . . . capture such mutants." *Id.* at 34–35 (citing Ex. 1001, 80:15–55; Ex. 1003 ¶¶ 151–154, 165).

Petitioner asserts that based on the prior art and the common disclosure, "a skilled artisan in 2011 would have believed that PH20 polypeptides that terminate before position 430 would be inactive," even though the claims encompass "truncations down to and beyond position 419." Pet. 38–39 (citing Ex. 1003 ¶¶ 167–170). According to Petitioner, the common disclosure "provides no examples of (or guidance concerning) PH20 mutants truncated below position 447 with one or more substitutions and that are enzymatically active," and "thus ignores the uncertainty existing in 2011 about PH20 truncation mutants that terminate between positions 419 to 433." *Id.* (citing Ex. 1003 ¶¶ 95–96, 98, 100).

Petitioner asserts that of approximately 5,917 single amino acid changes tested in a $PH20_{1-447}$ polypeptide in the common disclosure, "[m]ore than half(~57%)" were classified as "inactive mutants" and "~87% . . . had ***less*** activity than unmodified $PH20_{1-447}$." Pet. 39–40 (citing Ex. 1003 ¶¶ 106–108). Petitioner asserts this data show the unpredictability of mutation where "even introducing different amino acids at the same position in $PH20_{1-447}$ resulted in (i) increased activity, (ii) decreased activity or (iii) inactive mutants." *Id.* at 41 (citing '652 patent (Ex. 1001), Tables 3, 5, 9, 10). Petitioner asserts that:

> The results from single substitutions provide no insights into PH20 polypeptides with multiple concurrent mutations, which together can cause complex and unpredictable effects on a protein's structure and resulting function. The patent's empirical test results provide no guidance to a skilled artisan about which of the many possible PH20 mutants with different sets of 2-42 substitutions will be enzymatically active.

Id. at 42–43 (citing Ex. 1003 ¶¶ 142–143, 145–146). Petitioner asserts the common disclosure "does not identify which ***combinations*** of substitutions improve stability. It thus provides no probative insight regarding multiply-modified PH20 polypeptides with increased stability." *Id.* at 46 (emphasis in original) (citing Ex. 1003 ¶¶ 75–76).

Petitioner asserts that the statements in the common disclosure fail to "identify ***any*** actual multiply-modified PH20 polypeptides (*i.e.*, particular sets of specific amino acid substitutions), much less provide results from testing any. They simply draw boundaries around a theoretical and immense genus of modified PH20 polypeptides." Pet. 47. According to Petitioner, the common disclosure merely outlines a "prophetic research plan requiring 'iterative' make-and-test experiments that ***might discover*** multiply-modified enzymatically active PH20 polypeptides," but that "[t]his prophetic research plan is effectively meaningless—it does not indicate that any active mutant multiply-modified PH20 polypeptides will be found, much less identify ***which*** multiply-modified PH20 polypeptides are active mutants." *Id.* at 47–48 (citing Ex. 1001, 135:8–20; Ex. 1003 ¶¶ 182–186, 193–194, 200).

> Petitioner asserts the common disclosure does not identify
>
> > the structural significance of any of the ~2,500 mutations that yielded single residue "active mutant" $PH20_{1\text{-}447}$ polypeptides (or the ~3,400 inactive mutants). For example, it does not identify the effect of any replacement on any domain structure, any structural motif(s) or even the local secondary structure at the site of the substitution in the PH20 polypeptide, nor does it identify how any such (possible) structural change(s) is/are responsible for the measured change in hyaluronidase activity.

Pet. 50 (citing Ex. 1003 ¶¶ 142–143, 154).

Petitioner asserts the "single-replacement $PH20_{1\text{-}447}$ examples are not representative of the trillions and trillions of $PH20_{1\text{-}447}$ polypeptides with

between ***2 and 42 substitutions*** at any of hundreds of positions within the protein." Pet. 53 (emphasis in original) (citing Ex. 1003 ¶¶ 61, 146, 162). Petitioner asserts the "effects of numerous substitutions on the PH20 protein's various secondary structures and structural motifs are not described or discussed in the common disclosure." *Id.* (citing Ex. 1003 ¶¶ 160–161, 239).

Petitioner offers the figure below to illustrate "how ***non-representative*** the examples are: all of the examples of single-replacement $PH20_{1\text{-}447}$ mutants fit into one box of the array below:"

	Number of Changes																					
SEQ	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
3																							
7																							
32																							
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Pet. 56–57 (emphasis in original). The figure above depicts a 23 x 37 array representing the scope of claim 2, which Petitioner contends is limited to anywhere from 1 to 22 changes in any of 37 unmodified PH20 sequences in addition to the one identified replacement at position 320. *Id.* at 56. Petitioner uses the single shaded red box in the top left corner of its figure to represent that only single amino acid changes in only one sequence (SEQ ID NO: 3) were tested in the working examples of the common disclosure. *Id*. Moreover, Petitioner points out that claim 1 is even broader than claim 2, urging that it "captur[es] an even ***larger*** genus (up to 42 permitted changes) than depicted above." *Id.* at 57 (emphasis in original).

Petitioner asserts that the other challenged claims lack written description support for the same or substantially similar reasons. *See* Pet. 59–65.

C. Patent Owner's Position

Patent Owner asserts "[b]ecause [Petitioner] failed to identify any authority supporting its written-description challenge of *structural*, not functional, claims, [Petitioner]'s arguments fall short." Prelim. Resp. 34 (emphasis in original). Patent Owner asserts that "all of the cases [Petitioner] cites involve functional claims," and Petitioner "ignores cases finding written-description support of purely structural claims." *Id.* at 37 (citing cases). According to Patent Owner,

> the PTAB has found that a disclosure of structural features common to the genus is sufficient to establish written-description support for structural claims. For example, claims reciting an "isolated polynucleotide … at least 95% identical to the polynucleotide sequence of SEQ ID NO:2" were adequately supported by the specification because "*the complete structure of the polynucleotide of SEQ ID NO: 2 has been described*, and

> the genus [is] limited to [] polynucleotide[s] comprising a naturally occurring polynucleotide sequence at least 95% identical to the polynucleotide sequence of SEQ ID NO: 2." *Ex parte Bandman*, No. 2004-2319, Decision on Appeal at 4-5 (B.P.A.I. Jan. 6, 2005).

Id. at 37–38.

Patent Owner asserts "the recited structural features allow POSAs to visualize or recognize the identity of all members of the genus, because the members share 'at least 91%' of the structure of disclosed amino acid sequences (SEQ ID Nos: 3, 7 and 32-66), while limiting any amino acid sequence variation to 9%." Prelim. Resp. 39 (citing Ex. 1001, claim 1; Ex. 2055 ¶¶ 90–92). Patent Owner asserts that an ordinarily-skilled artisan "would have been able to visualize or recognize the identity of all members of the claimed genus of modified PH20 polypeptides manually or by using a computer and sequence-comparison software like CLUSTAL-Omega and BLAST, given the disclosed sequences." *Id.* at 40 (citing Ex. 1001, 58:53–61:3; Ex. 1039, 125; Ex. 2055 ¶¶ 96–98). Patent Owner asserts:

> The Petition makes no effort to explain why disclosures of single-modified PH20 polypeptides are not representative of multiply modified PH20 polypeptides when the claims do not require hyaluronidase activity. . . . It is established Federal Circuit law that "[w]ritten description asks whether that which is claimed is adequately described." Here, [Petitioner] inappropriately evaluates whether the specification describes and enables what the claim simply *covers* but does not require, and so violates recent, binding Federal Circuit law. Indeed, [Petitioner] focuses myopically on the alleged absence of "any multiply-modified PH20 polypeptides that are 'active mutants,'" but the claims do not require "active mutants."

Id. at 44–45 (citing Pet. 48–59; Ex. 2055 ¶¶ 113–114; *In re Entresto*, 125 F.4th 1090, 1097–1100 (Fed. Cir. 2025)).

Patent Owner also asserts Petitioner "is wrong regarding claim scope, because none of the six combinations[9] [the common disclosure explicitly states not to make] is encompassed by the claims. EX2055, ¶¶105–109. The disclosed combinations all require replacements at positions that do not include the claimed modification at position 320." *Id.* at 45 (citing Ex. 1001, 77:45–57, claim 1; Ex. 2055 ¶ 107).

Patent Owner asserts the "term 'modified PH20 polypeptide' in Claims 2 and 6–29 does not require hyaluronidase activity. These claims, too, are adequately supported by the specification for at least the same reasons identified for claim 1." *Id.* at 46 (citing Ex. 2055 ¶¶ 113–114).

D. Analysis

On the current record, we find the evidence, taken as a whole, better 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

[9] The six combinations referred to here are six multiply-modified PH20 polypeptides that "the common disclosure explicitly says to not make." *See* Pet. 33–34, 58–59. The six combinations are as follows:

- P13A/L464W, N47A/N131A, N47A/N219A, N131A/N219A, and N333A/N358A, which the specification states should not be made if the polypeptide contains *only* two amino acid replacements, and
- N47A/N131A/N219A, if the polypeptide contains *only* three amino acid replacements.

Prelim. Resp. 45 (citing Pet. 58; Ex. 1001, 77:54–57).

> 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* explains "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 explained above, on the current record claim 1 is reasonably interpreted to require that the recited "modified PH20 polypeptide" has hyaluronidase activity. But even if we were to agree with Patent Owner that this term also encompasses inactive mutants and immunization using PH20 polypeptide as a contraceptive antigen serves to satisfy the utility requirement for such, there is a similar concern as to whether modified PH20 polypeptides with significant differences from the native protein as encompassed by claim 1 would maintain the antigenic determinants necessary to function as contraceptives. *See* Ex. 1003 ¶¶ 113–116.

Although we agree with Patent Owner on the present record that the challenged claims do not encompass the six multiply-modified species the Specification says not to make (*see* Ex. 1001, 77:53–59) because they do not contain a modification at position 320 (*see* Prelim. Resp. 45), we are not persuaded by Dr. Triggs-Raine's statement that "the diversity of the claims is significantly limited to at least 91% sequence identity; therefore, a POSA would have understood that the claims encompass a very homogeneous group of modified PH20 polypeptides." Ex. 2055 ¶ 104.

That the modified PH20 polypeptides would be very homogenous in function is contradicted both by evidence in the '652 patent itself and by Dr. Hecht and Dr. Parker. The '652 patent discloses synthesis of a library of 6,753 single amino acid mutations in residues 1–447 of SEQ ID NO: 3. *See* Ex. 1001, 194:24–46. The '652 patent teaches that just under 10% of these mutations, i.e., over 600, "exhibit activity that is increased compared to wildtype." *Id.* at 227:24–25. Dr. Hecht, reviewing the '652 patent, states that "Table 10 contains a compilation of tested 'inactive mutants' with 3,380 entries in it." Ex. 1003 ¶ 106. Although Dr. Hecht notes some inconsistencies in the data in the '652 patent, *see id*. ¶ 107, he explains that the '652 patent data shows that "57.1% were inactive, and 29.4% others had activity <100%." *Id.* ¶ 108.

Thus, the '652 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 "[i]ntroducing multiple amino acid changes simultaneously . . . could prevent the folding of sequences into secondary structures and structural motifs and can destabilize those structures if they do form." Ex. 1003 ¶ 59. Dr. Hecht notes that claim 1 allows "21-42 changes, with each additional change (except at position 320) being to 1 of 19 other amino acids. But the up to 21-42 changes also can be at any of between 430 and 465 (or, in the case of the broadest claims, 474) different positions depending on which unmodified PH20 sequence is used." *Id.* ¶ 123. Regarding the somewhat narrower identity requirement in claim 2, Dr. Park calculates that "95% sequence identity to $PH20_{1\text{-}465}$ means that the protein can have 23 total changes," and that where one of those changes is one of five recited choices at position 320, the number of possible PH20 polypeptides with twenty-two additional changes is "extremely large by all accounts, ranging from 10^{59} to 10^{112}." *See* Ex. 1004 ¶¶ 171–172. And even for the "narrowest of the claims" (claim 24), Dr. Hecht characterizes the number of possible mutations as "astronomical in size." Ex. 1003 ¶¶ 125, 128.

Dr. Park cites Zhang (Ex. 1010), which states "analysis of Hyal1 point mutants highlights the importance of specific conserved residues in catalytic function, but also identifies active site conformation as a critical factor. Disrupted activity resulted from the R265L mutation but not from N216A or global disulfide reduction." Ex. 1010, 9441. Dr. Park notes that Zhang found "a mutation at Asn350 in the 'c-terminal EGF-like domain' abolished hyaluronidase activity but one at Asn216 did not." Ex. 1004 ¶ 96 (citing Ex. 1010, 9438–9439). Dr. Park also cites Ex. 1011 (Arming), which states:

> *In vitro* mutagenesis of the Glu113 or Glu249 to glutamine yielded PH-20 polypeptides without detectable enzymatic activity in two different assay systems. A third mutant, where Asp111 was changed to asparagine, had about 3% of the activity of the wild-type enzyme. These three acidic amino acids lie within clusters of amino acids that are conserved between mammalian and hymenopteran hyaluronidases.

Ex. 1011, 813; Ex. 1004 ¶ 101. These prior art references further demonstrate that even conservative mutations may significantly impact the PH20 polypeptide hyaluronidase function.

Dr. Hecht also addressed the use of PH20 polypeptides as antigens for contraceptives, a use contemplated by the '652 patent. *See* Ex. 1001, 187:47–67; Ex. 1003 ¶ 112. Dr. Hecht testifies that "subsequent publications reported negative results in experiments attempting to induce contraceptive by immunizing mammals (rats, mice) with PH20." Ex. 1003 ¶ 113 (citing Ex. 1019, 325; Ex. 1020, 181; Ex. 1021, 30310). Dr. Hecht cites to Rosengren (Ex. 1061), which states "several attempts were made to immunize males with PH20 as an immunocontraceptive approach in animal models. These studies involved rabbits[ ], mice[], and guinea pigs[], and only the latter experienced infertility following PH20 immunization." Ex. 1003 ¶ 114 (quoting Ex. 1061, 1154 (internal citations omitted)). This shows that even the native PH20 polypeptide does not necessarily function as a contraceptive, and supports Dr. Hecht's testimony that a "skilled artisan could not predict from the common disclosures' limited discussion of contraceptive vaccines which, if any, mutated PH20 polypeptides would confer contraceptive effect in humans." Ex. 1003 ¶ 116. These facts are analogous to those in *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc*., 759 F.3d 1285, 1300 (Fed. Cir. 2014), where the claims

encompassed structurally diverse antibodies, but the patent at issue only described structurally similar antibodies.[10]

Here, Patent Owner is asserting that claim 1 encompasses any sequence with the recited modification at position 320 and at least 91% identical to a PH20 polypeptide as an antigen that causes contraceptive activity, but the only evidence of contraceptive activity is for the native protein without any mutations. The evidence demonstrates that not even all native PH20 molecules necessarily function as contraceptives, much less mutated forms that might differ in structure and binding affinities as antigens. Rather, even for the single mutations tested, the ’652 patent employed a trial and error approach for hyaluronidase activity and did no testing to determine if any of those modified polypeptides had contraceptive function. *See* Ex. 1001, 224:55–61; *see also In re Alonso*, 545 F.3d 1015, 1020 (Fed. Cir. 2008) (“We have previously held in a similar context that ‘a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those

[10] Patent Owner’s attempt to distinguish *AbbVie* and the other cases Petitioner cites “because they are directed to claims reciting *functionally defined* genera” is unavailing. *See* Prelim. Resp. 34–37. As explained above, the presently challenged claims include a functional requirement. *See supra* § VIII. For this reason, Patent Owner’s reliance on cases it characterizes as “finding written-description support of purely structural claims” is misplaced. *Id.* at 37 (citing *GlaxoSmithKline v. Banner Pharmacaps*, 744 F.3d 725 (Fed. Cir. 2014); *Boehringer v. Kansas State*, PGR2022-00021, Papers 9, 11 (P.T.A.B. 2022) (“*Boehringer II*”); *Ex parte Friedberg et al.*, No. 2004-2314, Decision on Appeal (B.P.A.I. Nov. 17, 2004)).

specifically enumerated.'" (quoting *Noelle v. Lederman*, 355 F.3d 1343, 1350 (Fed. Cir. 2004))).

On the current record, the evidence shows it is more likely than not that the claims of the '652 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, Petitioner has demonstrated that it is more likely than not that there is insufficient written description for the challenged claims. Similarly, the current record does not appear to provide evidence of possession of the full scope of the claims of the '652 patent in the '731 application or any of the subsequent divisional or continuation applications leading to the '652 patent that claim priority to the '731 application (which appear to all have similar specifications) for the reasons given above.[11] Therefore, the challenged claims of the '652 patent do not receive the benefit of priority from the earlier filed applications, and based on this preliminary determination, the '652 patent is eligible for post-grant review because the

[11] We do not agree with Patent Owner that Petitioner only evaluates description and enablement as of 2011, rather than as of the 2012 filing date of the '731 application. *See, e.g.*, Prelim. Resp. 1, 11–12, 32. Instead, we agree with Petitioner that it "did not restrict the § 112(a) analysis to December 2011;" rather Petitioner stated that "the claims are not entitled to the 'December 28, 2012' benefit date of the '731 Application, while 'the obviousness grounds use' the December 2011 priority date being claimed." Prelim. Reply 5–6 (citing Pet. 5–6, 15–16).

effective filing date is no earlier than the '652 patent's actual filing date of December 12, 2022. *See* Ex. 1001, code (22).

X. GROUND II - ENABLEMENT

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) (bracketing in original; 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. Petitioner's Position

Petitioner asserts

> the common disclosure utterly fails to enable the immense genus of modified PH20 polypeptides claimed. Using that disclosure and knowledge in the prior art, the skilled artisan would have to perform undue experimentation to identify which of the 10^{59}+ PH20 polypeptides having multiple amino acid replacements and/or truncations within the scope of the claims are "active mutant" PH20 polypeptides.

Pet. 67 (citing Ex. 1003 ¶¶ 179–181, 200). Petitioner asserts the "claims capture massive genera of modified PH20 polypeptides, most of which would have unknowable properties absent individual production and testing." *Id.* at 69 (citing Ex. 1003 ¶¶ 159–161).

Petitioner asserts the '652 patent "provides an extremely narrow set of working examples: ~5,917 randomly generated single-replacement $PH20_{1-447}$ polypeptides, of which ~2500 were 'active mutants.' Those examples are a tiny fraction of the 10^{59} to 10^{112} modified PH20 polypeptides covered by the claims." Pet. 70 (citing Ex. 1003 ¶¶ 106–107).

Petitioner asserts the "prospective research plan [in the common disclosure] requires a skilled artisan to engage in undue experimentation to practice the full scope of the claims. First, it requires manually performing iterative rounds of ***randomized*** mutations" and "provides no meaningful guidance about producing 'active mutant' modified PH20 polypeptides." Pet. 71–72 (emphasis in original) (citing Ex. 1003 ¶¶ 147, 161, 181, 188–190, 193–194). Petitioner asserts the process described in the disclosure here "is indistinguishable from the '***iterative***, ***trial-and-error process[es]***' that have consistently been found to not enable broad genus claims to modified proteins." *Id.* at 73 (emphasis in original) (citing, *inter alia*, *Idenix Pharm. LLC v. Gilead Sci. Inc.*, 941 F.3d 1149, 1161–63 (Fed. Cir. 2019)).

Petitioner asserts "the skilled artisan could ***not*** have predicted the effects of making more than a few concurrent amino acid replacements within a PH20 polypeptide in 2011." Pet. 74 (citing Ex. 1003 ¶¶ 161, 239) (emphasis in original). Petitioner asserts the "cumulative effects of multiple changes would also have rapidly exceeded the capacity of computer-based, rational design protein engineering techniques to reliably predict the effects

of each change on the protein's structure in 2011." *Id.* at 75 (citing Ex. 1003 ¶¶ 51, 161, 200, 239; Ex. 1004 ¶¶ 161–162).

Petitioner asserts

> while a skilled artisan was highly skilled, the field of protein engineering was unpredictable and tools did not exist that permitted accurate modeling of the range of multiply-changed PH20 polypeptides being claimed. Likewise, while there was significant knowledge in the public art about hyaluronidases, there was no solved structure of the PH20 protein, experimental reports generally reported on ***loss of activity*** from mutations, and did not predictably teach how to introduce changes that ***enhanced*** stability or activity.

Id. at 76–77 (emphasis in original) (citing Ex. 1003 ¶¶ 161, 239).

C. Patent Owner's Position

Patent Owner asserts Petitioner

> again improperly imports a functional requirement (hyaluronidase activity) in an effort to align its arguments with the cited cases (*Amgen*, *Idenix*, *Wyeth*, and *Baxalta*) and in violation of recent Federal Circuit law. *See In re Entresto*, 125 F.4th at 1098 (the "scope of what is claimed [] is, in turn, determined through claim construction"). Indeed, all cited cases involved claims having functional, not structural, limitations even though the claims at issue here do not require hyaluronidase activity.

Prelim. Resp. 46–47 (citing Pet. 65–67).

Patent Owner asserts the "nature of the invention—modified PH20 polypeptides—weighs in favor of enablement, because making such polypeptides was well within the skill of a POSA in December 2012 given the guidance in the specification and the general knowledge in the art." Prelim. Resp. 48 (citing Ex. 2055 ¶¶ 116–119). Patent Owner asserts "the guidance in the specification, the prior art, and the relative skill of a POSA

each weigh[es] in favor of enablement." *Id.* at 48 (citing Ex. 2055 ¶¶ 118–120).

Patent Owner asserts the "quantity of experimentation required also weighs in favor of enablement," and that Dr. "Triggs-Raine confirms that making the claimed polypeptides in light of the specification's guidance would have involved only routine, not undue, experimentation and known, commonly used molecular biology and protein biochemistry techniques." Prelim. Resp. 49 (citing Ex. 2055 ¶¶ 128–130). Patent Owner asserts Dr. "Hecht agrees that the methodology was conventional." *Id.* at 50 (citing Ex. 1003 ¶¶ 205–213; Ex. 2055 ¶¶ 124–126).

Patent Owner asserts the "specification discloses thousands of examples of modified PH20 polypeptides, weighing in favor of enablement," and "[b]ecause the claims are not limited to 'active mutants,' [Petitioner] failed to show that these examples do not provide practical guidance for making the claimed polypeptides." Prelim. Resp. 51.

Patent Owner asserts "the breadth of the claims weighs in favor of enablement. The purely structural claims are not unreasonably broad because they recite at least 91% identity to sequences disclosed in the specification." *Id.* at 52 (citing Ex. 2006; Ex. 2055 ¶ 127).

Patent Owner asserts "the specification discloses that the claimed polypeptides are useful as 'antigens in contraception vaccines,' irrespective of whether they exhibit hyaluronidase activity." Prelim. Resp. 54 (citing Ex. 1001, 72:45–73:47, 75:56–58, 194:25–194:67; Ex. 1011, 814; Ex. 2055 ¶¶ 140–141). Patent Owner cites teachings in the '652 patent to "Primakoff 1988 (EX2010) and Tung 1997 (EX1023) as teaching that '[i]mmunization

with PH20 has been shown to be an effective contraceptive in . . . guinea pigs.'" *Id.* at 55 (citing Ex. 1001, 187:58–63; Ex. 2055 ¶¶ 137–138, 142).

Patent Owner asserts "the specification draws no distinction between inactive or active mutants, reflecting that all modified PH20 polypeptides 'provided herein' can be used as contraceptives." Prelim. Resp. 56 (citing Ex. 2055 ¶¶ 88, 140). Patent Owner further asserts that Petitioner's "cited art does not undermine the specification" because "[n]one of these cited references refute or contradict the reported success in using PH20 as a contraceptive in both male and female guinea pigs in Primakoff 1988, Primakoff 1997, or Tung 1997." *Id.* at 57–58 (citing Ex. 2055 ¶¶ 144–151).

D. Analysis

Petitioner has the initial burden to specifically identify how the specification fails to enable the claims, and we utilize the *Wands* factors to address the parties' respective arguments and evidence.

1. Breadth of Claims and Nature of the Invention

According to Patent Owner's declarant Dr. Triggs-Raine, "the diversity of the claims is significantly limited to at least 91% sequence identity; therefore, a POSA would have understood that the claims encompass a very homogenous group of modified PH20 polypeptides." Ex. 2055 ¶ 104. Dr. Triggs-Raine cites Dr. Park as stating that "bee venom hyaluronidase and human PH20 are 'highly homologous' despite only 'sharing about 30% sequence identity.' The claimed modified PH20 polypeptides require more than three times that sequence identity." *Id.* (citing Ex. 1004 ¶ 40). Dr. Triggs-Raine further states that she disagrees "with Dr. Hecht's opinion regarding the sufficiency of the number of representative species because his analysis is undergirded by his general

misunderstanding that the claims require hyaluronidase activity. As I explained above, claims 2 and 6–29 do not require any hyaluronidase activity." *Id.* ¶ 113.

Petitioner's declarant Dr. Park states, regarding the breadth of claims 1 and 2, that he "calculated the number of distinct polypeptides that exist that meet the specified criteria," i.e., one of the four recited substitutions at position 320 and either 91% or 95% "sequence identity to human PH20 proteins having varying lengths of C-terminal truncations." Ex. 1004 ¶¶ 168–172. Dr. Park's calculations show that the "number of distinct polypeptides is extremely large by all accounts, ranging from 10^{59} to 10^{112}." *Id.* ¶ 172. Petitioner's other declarant Dr. Hecht agrees, stating the "sequence identity language causes the claims to encompass an immense number of distinct PH20 polypeptides." Ex. 1003 ¶ 123. To illustrate the scale of these numbers, Dr. Hecht explains that the "aggregate weight of the smallest set containing one molecule of each of the PH20 mutants would be . . . = 3.93×10^{40} kg. The weight of the Earth is 'only' ~ 5.97×10^{24} kg." *Id.* ¶ 126.

That is, the current record shows that claims recite an extremely large number of distinct peptides and that a complete set of one molecule of each possible peptide comprising the recited replacement at position 320 and meeting the sequence identity limitations for even the narrowest challenged claims would weigh significantly more than the entire mass of planet Earth. *See* Ex. 1003 ¶ 126. While characterizing the claimed peptides as "very homogeneous," the testimony Patent Owner cites from Dr. Triggs-Raine does not dispute the accuracy of Petitioner's declarants' testimony regarding

the number of peptides encompassed by the challenged claims. *See* Ex. 2055 ¶¶ 95, 104, 127.

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

2. Skill in the Art

The parties both separately addressed the skill in the art that is discussed *supra* Section VII. On the current record, we find both parties indicate that the skill in the art is high.

3. State of the Prior Art

Dr. Triggs-Raine states "the state of the prior art regarding making modified polypeptides generally was well established as of December 2012." Ex. 2055 ¶ 117. Dr. Triggs-Raine states "making the claimed modified PH20 polypeptides would have required nothing more than routine molecular biology and protein biochemistry techniques." *Id.* ¶ 118 (citing Ex. 1001, 135:48–59). Dr. Triggs-Raine acknowledges that "non-conserved residues 'may be responsible for the *different catalytic properties* of the human hyaluronidases' and that sequence variations 'may contribute to the apparent different substrate specificity' between different hyaluronidases." *Id.* ¶ 182 (citing Ex. 1006, 6915–6916). Dr. Triggs-Raine also observes that "nonconserved residues may impact the activity and function of proteins." *Id.* ¶ 190 (citing Ex. 2016, 2; Ex. 1014, 21, 55). Dr. Triggs-Raine states "in homologous proteins (such as Hyal-1 and PH20), non-conserved loop regions are often responsible for catalytic differences between the homologous proteins." *Id.* ¶ 191 (citing Ex. 1014, 21, 55). Thus, Dr. Triggs-Raine acknowledges that mutational differences in hyaluronidase proteins generally may result in differences in activities. *See id.* ¶¶ 182, 190–191.

Dr. Hecht acknowledges that protein expression is generally routine, stating the "conventional procedures relating to production of the wild-type $PH20_{1-447}$ 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 ¶ 231 (citing Ex. 1005, 39:54–40:21). Dr. Hecht further states that "[t]he 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 ¶ 80 (citing Ex. 1033, 1028–1031).

However, Dr. Hecht also states "[d]ata in the '429 Patent and a 2007 paper by Frost (EX1013) also showed that truncations of varying length at the C-terminus of PH20 caused significant variations in hyaluronidase activity." Ex. 1003 ¶ 93 (citing Ex. 1005, 87:52–88:24; Ex. 1013, 430–432, Fig. 2). Dr. Hecht states "[t]he Zhang paper reported that a truncation just upstream of the start of the Hyal-EGF domain in HYAL1 reduced its activity to ~6%." *Id.* ¶ 95. 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.* ¶ 97.

Dr. Hecht states "[t]here were limits to using rational design techniques in the 2011-timeframe." Ex. 1003 ¶ 50 (citing Ex. 1018, 378; Ex. 1059, 1225–1226). For example, Dr. Hecht quotes the Chica reference, which states that "[t]he complexity of the structure/function relationship in enzymes has proven to be the factor limiting the general application of rational design." *Id*. ¶ 50 n.16 (quoting Ex. 1018, 378). Regarding another

approach to protein modification called "directed evolution," Dr. Hecht explains 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.* ¶ 52 (internal footnote omitted). Dr. Hecht states "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." *Id*. ¶ 55 (citing Ex. 1046, 2034; Ex. 1047, 6349, 6352). Dr. Hecht states that in a smaller, ten amino acid substitution situation, "[t]here are approximately 6 x 10^{12} different scenarios of 10 substitutions . . . (*i.e.*, 10 positions, with 19 different [alternative]amino acids, or 19^{10})." *Id.* ¶ 58.

On the current record, we find 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 understood that mutations, whether conservative or non-conservative, may impact protein function and physical shape in unpredictable ways. *See, e.g.*, Ex. 1003 ¶¶ 54–55, 61, 93–100. The evidence currently of record demonstrates that identifying which of the 10^{59} to 10^{112} members of the PH20 polypeptide genus would retain functional hyaluronidase activity or contraceptive activity was difficult and not well-established in the prior art. *See, e.g., id.* ¶¶ 50–53, 182–195.

4. Presence of Working Examples

Dr. Triggs-Raine states the '652 patent "provides a library of '6,753' PH20 mutants—which a POSA would have recognized as a significant number of exemplified species." Ex. 2055 ¶ 103 (citing Ex. 1003 ¶¶ 106,

162). Dr. Triggs-Raine states the '652 patent "explains that each modified PH20 polypeptide within this ~6,800 mutant library contains 'a single amino acid mutation compared to … residues 1–447 of SEQ ID NO:3.'" *Id.* (citing Ex. 1001, 194:29–33).

Consistent with this testimony, Dr. Hecht states that the '652 patent "provides a compilation of all the mutants that apparently were produced by the inventors in Table 8. There are 6,753 entries in this table. These are all mutants generated by substituting one amino acid from $PH20_{1-447}$." Ex. 1003 ¶ 106. Dr. Hecht goes on to explain that "Table 10 contains a compilation of tested 'inactive mutants' with 3,380 entries in it." *Id.* Based on this data, Dr. Hecht calculates that "57.1% were inactive, and 29.4% others had activity <100%," i.e., "most of the single-replacement $PH20_{1-447}$ mutants that were tested exhibited less activity than the unmodified" peptide. *Id.* ¶ 108.

Dr. Hecht further states the '642 patent "does not identify any mutated PH20 proteins that were shown to be effective in contraceptive vaccines." Ex. 1003 ¶ 116.

On the current record, we find the evidence demonstrates the presence of a limited set of working examples relative to the enormous size of the genus recited in the claims, and the evidence suggests a large percentage of these working examples would not be encompassed by the challenged claims because the modified PH20 peptide in those examples are inactive and no mutated PH20 protein was shown to be an effective contraceptive.

5. Amount of Direction or Guidance Presented

The '652 patent states "[p]roteins, such as modified PH20 polypeptides, can be purified using standard protein purification techniques known in the art." Ex. 1001, 145:36–41. Dr. Triggs-Raine states

> the specification of the ’652 patent details how to test modified PH20 polypeptides for their ability to degrade hyaluronan (*i.e.*, for their hyaluronidase activity) and cites multiple known assays for doing so. EX1001, 133:8–21, 170:59–173:2, 224:50–289:60, Examples 3–5, 292:34–301:28, Examples 8–11, 303:58–306:37 Examples 14–15. And the specification further explains that such hyaluronidase assays were known in the art as of 2012. EX1001, 52:15–17 (“Assays to assess hyaluronidase activity are known to one of skill in the art and described herein.”).

Ex. 2055 ¶ 134 n.28.

Dr. Hecht states the ’652 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 ¶¶ 103–104. As noted above, Dr. Hecht states that the data in the ’652 patent shows “most of the single-replacement $PH20_{1\text{-}447}$ mutants that were tested exhibited less activity than the unmodified $PH20_{1\text{-}447}$.” *Id.* ¶ 108.

Dr. Hecht states the ’652 patent

> does not identify any mutated PH20 proteins that were shown to be effective in contraceptive vaccines. It also does not provide guidance regarding how to identify candidate inactive PH20 mutants that may be useful as contraceptive vaccines (such as by identifying common structural or functional characteristics that would be shared by such inactive mutants). A skilled artisan could not predict from the common disclosures’ limited discussion of contraceptive vaccines which, if any, mutated PH20 polypeptides would confer contraceptive effect in humans.

Ex. 1003 ¶ 116. Moreover, Dr. Hecht states “the data for testing the 409 mutants reported in Tables 11 and 12 [of the ’652 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 $PH20_{1\text{-}447}$ form specifically.” *Id.* ¶ 76.

Dr. Hecht further states the ’652 patent

> identifies no examples of PH20 polypeptides with multiple amino acid substitutions at different positions (*i.e.*, specific amino acids being inserted into two or more different positions of the same PH20 polypeptide) that rendered active proteins. This appears to be the case because no such multiply-modified PH20 polypeptides appear to have actually been made or tested.

Ex. 1003 ¶ 181. Dr. Hecht characterizes the disclosure of the '652 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.* ¶ 182.

On the current record, we find the evidence demonstrates significant guidance on synthesis and expression of modified PH20 polypeptides. The evidence also shows, however, that the '652 patent provides minimal guidance regarding effective methods to identify which members of the immense modified PH20 polypeptide genus have hyaluronidase or contraceptive activity.

6. Quantity of Experimentation

Dr. Triggs-Raine states:

> Regarding the quantity of experimentation, a POSA would not have needed to perform undue experimentation as of December 2012 because, as explained above, a POSA would have been able to make the claimed modified PH20 polypeptides in light of the guidance provided in the common disclosure and doing so would have required nothing more than repetition of routine molecular biology and protein biochemistry techniques, which could be further facilitated by the large-scale methods exemplified in the common disclosure.

Ex. 2055 ¶ 128. Dr. Triggs-Raine states "Dr. Hecht fails to address the fact that the *nature* of any experimentation is merely routine; it is, therefore, not undue." *Id.* ¶ 130 (emphasis in original).

Dr. Hecht states

> while the PH20 protein structure models Dr. Park used provided reliable insights when modeling the change of a single residue at a position where the model was, they cannot provide reliable insights when the modeled sequence incorporates many (*e.g.*, more than ~5) substitutions not found in a naturally occurring protein. That is because (i) if the modeled sequence incorporates multiple changes, it no longer has validity as a naturally occurring sequence, and (ii) the changes significantly diminish the reliability of other positions of the model used to assess the change because they are no longer based on the structural positioning of residues within the template structure used to generate the model. Thus, a skilled artisan would have had to discover which combinations of substitutions to the PH20 protein would result in mutants that do exhibit hyaluronidase activity by making and testing all of them, an impossibly large undertaking.

Ex. 1003 ¶ 161. Dr. Hecht states that "the single-replacement $PH20_{1-447}$ polypeptides reported in the common disclosure are not representative of all the types of mutated $PH20_{1-447}$ polypeptides that have a particular substitution at position 320 and sets of between 1 and 41 *additional* substitutions at any of hundreds of positions within the PH20 protein." *Id.* ¶ 162 (emphasis in original).

Dr. Hecht states "[m]aking and identifying all of the multiply-modified PH20 polypeptides that are within the immense set of polypeptides (between 10^{59} and 10^{112} distinct mutants) defined by the claims' sequence identity parameters would require not only an undue experimentation, it likely is impossible." Ex. 1003 ¶ 179. Dr. Hecht states the directed evolution methods of the '652 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 an improved characteristic." *Id.* ¶ 196.

We find the facts here similar to those in *Idenix Pharm. LLC v. Gilead Sci. 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 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 the evidence demonstrates that a very large amount of experimentation would be necessary to enable the scope of the claims of the '652 patent.

7. Predictability of the Art

Dr. Triggs-Raine states

> a POSA as of December 28, 2012, equipped with the common disclosure, would have been able to readily visualize sequences having at least 91% identity to SEQ ID NO: 3, 7 and 32–66 because they could have considered every permutation of each of the recited sequences in an entirely predictable manner. []Likewise, a POSA . . . would have been able to align these at least 91% identity sequences with SEQ ID No. 3 and then visualize replacing the amino acid corresponding to position 320 of SEQ ID No. 3 with H, K, R, or S in an entirely predictable manner.

Ex. 2055 ¶ 97 (citing Ex. 1001, 58:53–61:3). Dr. Triggs-Raine also states "a POSA would have been able to readily and predictably . . . make the claimed modified PH20 polypeptides, as of December 2012 in light of the guidance in the common disclosure." *Id.* ¶ 121 (citing Ex. 1001, 193:33–224:49).

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) substitutions. A skilled artisan would not view the first, single amino acid substituted PH20 to as be [sic] representative of all modified PH20 proteins having that one substitution, along with 5, 10 or 15, or more additional substitutions.

Ex. 1003 ¶ 61. 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.* ¶ 99. Dr. Hecht states "[t]he effects of these myriad sets of combinations of multiple substitutions within PH20 could not have been predicted by a skilled artisan in the 2011 timeframe using the tools that were available then." *Id.* ¶ 161. Dr. Hecht notes that "[a]nother problem caused by the use in the claims of sequence identity language to define the sets of proteins is that it captures many multiply-modified PH20 polypeptides with changes that [the] common disclosures says are deleterious or eliminate hyaluronidase activity in PH20 enzymes." *Id.* ¶ 163.

Dr. Hecht states the "skilled artisan also could not predict whether any combinations of up to 9 or up to 2 additional (or more) substitutions could be made anywhere in the $PH20_{1-419}$ sequence or comparably truncated PH20 polypeptide that would restore hyaluronidase activity to an inactive D320K or D320S containing $PH20_{1-419}$ mutant." *Id.* ¶ 171. Dr. Hecht continues:

> In other words, the common disclosure not only does not help the skilled artisan identify which of the trillions of possible PH20 polypeptides of varying length with 2 to 42 substitutions have hyaluronidase activity; to practice the full scope of the claims it requires the skilled artisan to ignore what little guidance is in the

> specification about single-substitutions and truncations that render PH20 polypeptides inactive.

Id. ¶ 172. Dr. Hecht states that the artisan following the '652 patent's "iterative mutagenesis and screening research plan cannot know in advance of conducting multiple rounds of experiments, whether modified PH20 polypeptides will be produced that have sets of 5, 10, 15, or more substitutions and retain sufficient activity that will be selected for the next round of the process." *Id.* ¶ 193. On the record before us, we credit Dr. Hecht's testimony as showing that, even with the information in the common disclosure, one of ordinary skill in the art would not have been able to predict which modified PH20 polypeptides, particularly those with multiple modifications beyond the recited replacements at position 320, would have hyaluronidase or contraceptive activity. *Id.* ¶¶ 116, 143–145, 161–195.

On the current record, we find the evidence shows it is highly unpredictable which modified PH20 polypeptides within the scope of the claims of the '652 patent would have hyaluronidase activity or any functional utility such as use as a contraceptive.

E. Conclusion

As we balance the *Wands* factors, we find that the totality of the evidence shown in the current record as discussed above better 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 we determine that it is more likely than not that the claims fail to comply with the enablement requirement of 35 U.S.C. § 112(a).

XI. GROUND III - OBVIOUSNESS

A. Principles of Law

The Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007) reaffirmed the framework for determining obviousness set forth in *Graham v. John Deere Co*., 383 U.S. 1 (1966). In *KSR*, the Court summarized the four factual inquiries set forth in *Graham* (383 U.S. at 17–18) that are applied in determining whether a claim is unpatentable as obvious under 35 U.S.C. § 103 as follows: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the art;[12] and (4) considering objective evidence indicating obviousness or non-obviousness. *KSR*, 550 U.S. at 406.

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." Ex. 1005, 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,

[12] *See supra* Section VII.

> in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity.

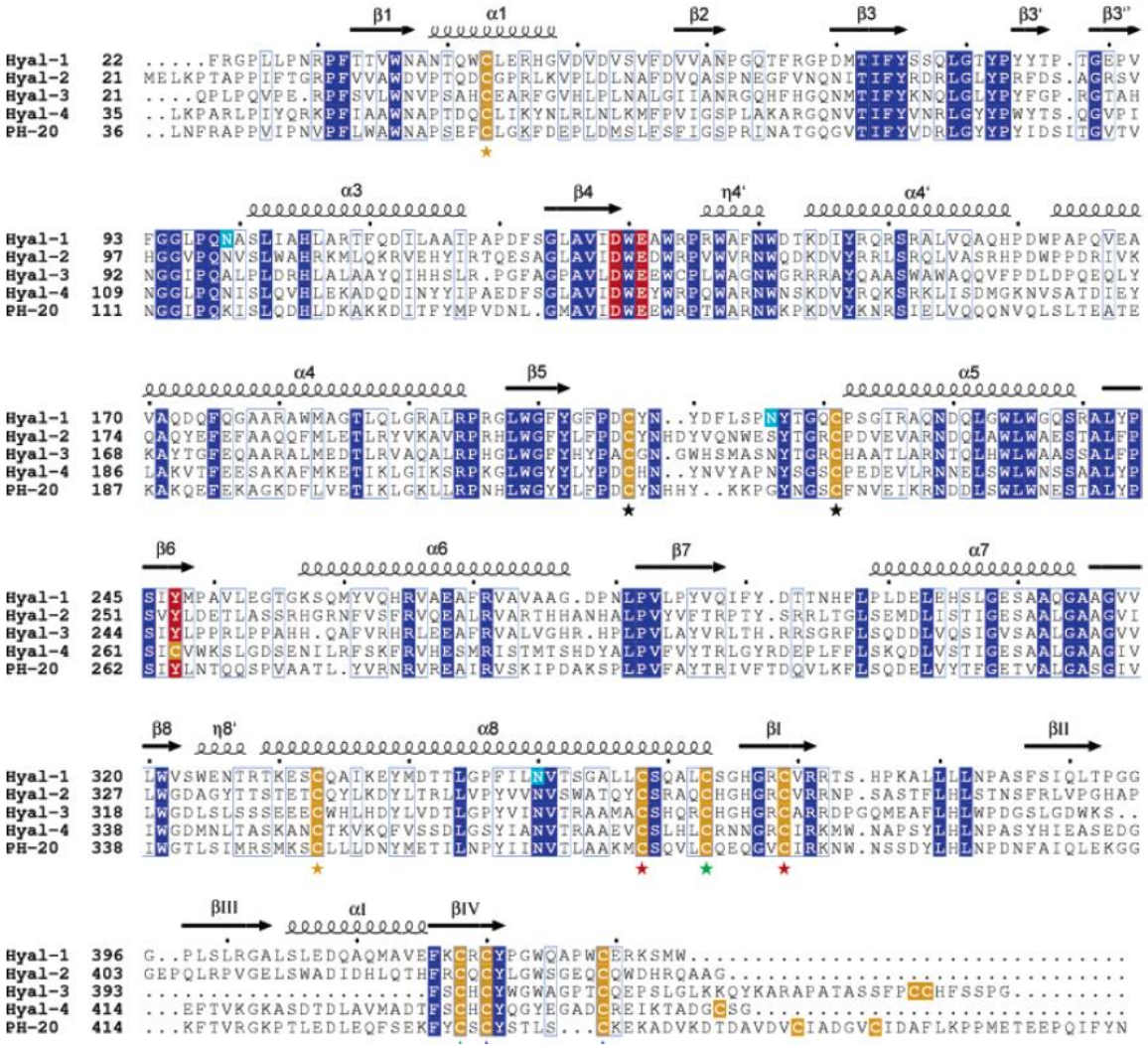
Id. at 16:14–20. The ’429 patent claims a specific truncated version of the hyaluronidase glycoprotein composed of positions 36–482 of SEQ ID NO: 1. *See id*. at 153:39.

2. Chao (Ex. 1006)

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

Chao states “[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 “[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 reports “the crystal structure of the enzyme showing that it contains an EGF-like domain not seen previously, and examine the impact of alternative splicing on the enzyme structure and function.” *Id.*

Chao states “[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:



Id. at 6916. Figure 3 above shows:

> Structure-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.

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 (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. 88–89 (citing Ex. 1003 ¶ 216; Ex. 1004 ¶ 32). Petitioner asserts Chao "identified a characteristic pattern for the Hyal-EGF domain in PH20 at positions 337–409." *Id.* at 92–93 (citing Ex. 1006, 6911; Ex. 1004 ¶¶ 97–98; Ex. 1003 ¶¶ 84, 87).

Petitioner asserts that a "skilled artisan would first identify the essential residues in PH20 by comparing proteins homologous to PH20 that were known in 2011. The artisan would have done that using conventional sequence alignment tools in conjunction with the information in the'429 Patent and in Chao, as well as information publicly known in 2011." Pet. 93 (citing Ex. 1003 ¶¶ 20–21, 222–225; Ex. 1004 ¶¶ 22–30, Appendix D-3; Ex. 1017, 224–226). Petitioner asserts that Dr. Park performed such an analysis and that "Position 320 is within a non-essential region of $PH20_{1–447}$, which is shown by Dr. Park's analysis and [also] by Chao's Figure 3; both report the same bounding essential residues (*i.e.*, C316 and L327)." *Id.* at 94 (citing Ex. 1003 ¶ 217; Ex. 1004 ¶¶ 31–32, Appendix D-2; Ex. 1006, 6916).

Petitioner asserts that according to Dr. Park's analysis, "[t]he wild-type residue at position 320 in PH20 is aspartic acid (D), which occurs in ~10% of the proteins (including PH20). The most prevalent amino acid found at position 320 in this set of homologous sequences is lysine (K)

(57.95%), which is present in 51 different hyaluronidase proteins. Serine is also present in 2 known homologous hyaluronidase proteins." Pet. 97 (citing Ex.1004 ¶¶ 30–32, 41–43, 106, 113, 116 Appendix D-1; Ex. 1003 ¶¶ 225, 227–228).

Petitioner asserts that a "skilled person would have found lysine and serine to be obvious choices for a single amino acid substitution for aspartic acid at position 320 in $PH20_{1-447}$." Pet. 99 (citing Ex. 1003 ¶¶ 231–232). Petitioner asserts "[f]irst, lysine is the most prevalent amino acid at positions corresponding to 320 in PH20." *Id.* at 98 (Ex. 1003 ¶¶ 228, 231; Ex.1004 ¶¶ 43, 106, 116). Petitioner asserts second, "lysine was known to be favored in sequences that form α-helix secondary structures due to its high helix propensity . . . and position 320 is within the α8 helix sequence in PH20." *Id.* (citing Ex. 1003 ¶¶ 202, 230; Ex. 1004 ¶¶ 32, 69–70, 108; Ex. 1006, 6916, Fig. 3; Ex. 1050, 422–24, Table 2).

Petitioner asserts that Patent Owner "relied on [the '429 patent's] 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." Pet. 100. Petitioner also asserts "[p]atentee should not be permitted to now contend that a skilled artisan would not have reasonably expected that the D320K and D320S substitutions in $PH20_{1-447}$ would yield an enzyme with substantially the same activity as unmodified $PH20_{1-447}$." *Id.* at 100–101.

2. Patent Owner's Position

Patent Owner asserts Petitioner "cannot deny that a modified PH20 polypeptide with an amino acid modification at position 320 is not mentioned in the '429 Patent or Chao, much less the specific H, K, R, and S

replacements claimed for position 320. The elements of the claims are absent from the asserted prior art." Prelim. Resp. 60–61. Patent Owner asserts that neither Petitioner nor "its declarants provides a claim chart identifying where each claim limitation is found in the art, because they cannot do so." *Id.* at 61 (citing Ex. 2055 ¶¶ 164–165).

Patent Owner asserts Petitioner "has not asserted nor shown that common sense might supply this limitation. . . . Nor has [Petitioner] provided a reasoned explanation supported by evidence that POSAs would have had a reason to make the claimed modification at position 320 in the first place." Prelim. Resp. 61–62 (citing Ex. 2055 ¶ 165). Patent Owner asserts Petitioner "also fails to demonstrate that common knowledge supplied this missing limitation," and Petitioner "fails to provide a reasoned explanation supported by evidence that POSAs would have had a reason to combine the '429 Patent and Chao to arrive at the claimed invention with a reasonable expectation of success." *Id.* at 63.

Patent Owner asserts the "Petition provides no *reason* why a POSA would have been motivated to make an amino acid substitution(s) in non-essential regions of PH20, let alone identify position 320 as one such position, particularly given that the '429 Patent does *not* identify any non-essential residues." Prelim. Resp. 65 (emphasis in original). Patent Owner asserts that Petitioner and its declarants "do not explain why a POSA would have been motivated to expend resources to make an amino acid substitution in non-essential regions of PH20 when [Petitioner's] cited art suggests that doing so would be pointless ('without altering the biological activity')." *Id.* (citing Ex. 2055 ¶ 171). Patent Owner asserts that in "falsely equating non-conserved residues as 'non-essential,' [Petitioner] fails to establish that

POSAs would have considered position 320 as a region to modify in view of the '429 Patent and Chao." *Id.* at 68 (citing Ex. 2055 ¶¶ 188–193).

Patent Owner asserts that Petitioner's argument based on rational protein design principles "is simply a restatement that such mutations *can be* made, and [Petitioner] never provides a *reason why* a POSA would have been motivated to combine the two references (or any of the dozen or so references [Petitioner] also cites) to make the claimed amino acid substitution in PH20." Prelim. Resp. 69–70.

Patent Owner also asserts that neither the '429 Patent and Chao provide any reason to select position 320 as an amino acid to modify. Prelim. Resp. 3–74 (citing Ex. 2055 ¶¶ 161–203). Patent Owner notes that Petitioner "argues that POSAs would have had to perform nearly thirty different steps—beyond the disclosures in the '429 Patent and Chao—to make the D320K or D320S modifications, but [Petitioner] does not provide a sufficient reason why a POSA would have performed *any* of these steps based on the combination of the '429 Patent and Chao." *Id.* at 74 (citing Pet. 95–99; Ex. 1003 ¶¶ 83, 205, 227–233; Ex. 1004 ¶¶ 20–167; Appendix C, Appendix D-1; Ex. 2055 ¶¶ 212–214).

According to Patent Owner,

> [u]nder 37 CFR §42.65(b)(2), [Petitioner] must explain how the test was performed and the data was generated. Here, Park does not explain how he prepared "Perl scripts" and how the data was generated using his bespoke scripts. Park merely states that he "wrote" and "ran" several "perl scripts," but failed to disclose what Perl code he used in his scripts, how he determined that these scripts would work as intended, or how he ran the scripts.

Prelim. Resp. 75–76 (citing Ex. 1004 ¶¶ 145–146; Ex. 2055 ¶¶ 215–216). Patent Owner asserts Petitioner "does not establish that POSAs would have

drawn conclusions about which amino acid substitutions would be tolerated at positions within PH20 based on an alignment of sequences that include other hyaluronidases, particularly given that it was known that hyaluronidases have different substrate specificities and exhibit varying levels of activity." *Id.* at 76 (citing Ex. 2055 ¶¶ 177–178, 187).

Patent Owner asserts that Petitioner "fails to establish that the '429 Patent combined with Chao provides the requisite reasonable expectation of success that a D320K or D320S substitution in PH20 would not only be tolerated, but would result in a protein that exhibits at least comparable hyaluronidase activity to unmodified $PH20_{1-447}$." Prelim. Resp. 82. Patent Owner asserts "[o]nly hindsight—provided by counsel—led Park and Hecht to position 320." *Id.* at 85.

3. Analysis

On the current record, we agree with Patent Owner that Petitioner has not provided any persuasive reason to particularly target position 320 of a PH20 polypeptide for modification as required by claim 1 of the '652 patent. Neither the '429 patent nor Chao specifically identifies or discusses position 320 of the PH20 polypeptide. *See, e.g.*, Pet. 93–95; Prelim. Resp. 60–61.

We are not persuaded by Petitioner's argument that multiple sequence alignments identify amino acids that are tolerated at particular positions (*see* Pet. 95–96), because tolerance alone 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. Appx. 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 ¶ 31. According to Petitioner, the amino acids at these 379 positions "would be considered 'non-essential' residues" and therefore it would have been obvious to make modifications at any of these positions. *See id.*; *see also* Pet. 88 (characterizing "non-essential regions of PH20" as "particular locations" that would be obvious to modify).

But nothing in the prior art or Dr. Park's analysis directs the ordinary artisan to position 320 itself. For example, Dr. Park notes that Chao did not identify position 320 of PH20 as part of the catalytic active site, unlike positions 146, 148, and 219, nor was position 320 one of the residues identified as being in the cleft where ligand binds. *See id.* ¶ 91. Dr. Park also indicates that position 320 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.* ¶¶ 98–101 (citing Ex. 1006, 6912; Ex. 1008, 825; Ex. 1011, 811–813).

Moreover, while Dr. Hecht asserts that the '429 patent suggests making "single amino acid substitutions in non-essential regions of polypeptides," Petitioner does not sufficiently demonstrate why this would have led a POSA to modify position 320 of PH20. *See, e.g.*, Ex. 1003 ¶¶ 216–218. Indeed, Dr. Hecht states position 320 is located in the "α-helix structure in PH20" and "[i]ntroducing random amino acids could disrupt th[e] pattern [of polar and non-polar residues typically required in α-helices], which could have a range of effects in this region of the helical structure." *Id.* ¶ 202. Petitioner did not point us to anything in Dr. Hecht's Declaration that explains why position 320 was of interest in any way, as compared to

any of the other 379 positions within the PH20 polypeptide Dr. Park identifies as "non-essential." *See* Ex. 1004 ¶ 31, Appendix D-2.

We are also not persuaded by Petitioner's arguments regarding Chao. *See* Pet. 90–92. Dr. Park identified seven different amino acids that favor alpha helix formation. *See* Ex. 1004 ¶ 70. 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 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)). On this record, Petitioner has not satisfied this burden of showing specific reasons to modify position 320 of the PH20 polypeptide.

Accordingly, on the current record, Petitioner has not shown that it is more likely than not to establish that the combination of the '429 patent and Chao with the knowledge and teaching described by Dr. Hecht and Dr. Park demonstrates that the claims of the '652 patent would have been obvious.

XII. CONCLUSION

Petitioner has, at this stage of the proceedings, established that it will more likely than not prevail in showing that at least one of the challenged claims is unpatentable. This determination is, however, based on a preliminary record and is not final on any issues of patentability. We will

make a final determination on the patentability of the challenged claims, as necessary and applying the preponderance of the evidence standard, based on a fully developed record through trial.

XIII. 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, 2 and 6–29 of the ’652 patent is hereby *granted* on the grounds set forth in the Petition, commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 324(d) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial; and

FURTHER ORDERED that the trial will be conducted in accordance with a separately issued Scheduling Order.

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