

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MERCK SHARP & DOHME LLC,  
Petitioner,

v.

HALOZYME, INC.,  
Patent Owner.

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PGR2025-00046  
Patent 12,091,692 B2

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Before JEFFREY N. FREDMAN, SUSAN L. C. MITCHELL, and  
MICHAEL A. VALEK, *Administrative Patent Judges*.

FREDMAN, *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. 12,091,692 B2 (Ex. 1001, “the ’692 patent”). Halozyme, Inc. (“Patent Owner”) elected to waive the Patent Owner Preliminary Response. Paper 15, 1.<sup>1</sup>

Concurrent with filing its waiver of its Preliminary Response, Patent Owner filed a statutory disclaimer of claims 3, 4, 6, and 34–40 of the ’692 patent, leaving claims 1, 2, 5, and 7–33 of the ’692 patent at issue in the Petition. *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 on behalf of the Director (37 C.F.R. § 42.4(a)) and in consideration of the Petition and the cited evidence of record, we determine that the information presented shows that it is more likely than not that Petitioner would prevail in establishing unpatentability of claims 1, 2, 5, and 7–33 of the ’692 patent, and therefore, we grant post-grant review for the reasons articulated below.

We note, however, that this decision to institute trial is not a final decision as to patentability of claims for which post-grant review is

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<sup>1</sup> The parties also filed briefs directed to discretionary denial issues. *See* Papers 12, 16. The Director ruled on discretionary denial issues. *See* Paper 17. We do not address discretionary denial issues here.

instituted. Our final decision will be based on the full record developed during trial.

## 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 ten 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. 12,049,652 (PGR2025-00033); U.S. Patent No. 12,104,185 (PGR2025-00039); U.S. Patent No. 12,037,618 (PGR2025-00042); U.S. Patent No. 12,077,791 (PGR2025-00050); U.S. Patent No. 12,264,345 (PGR2025-00052); U.S. Patent No. 12,195,773 (PGR2025-00053). *See* Paper 11, 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 several patents related to the '692 patent. Pet. 7; Paper 11, 2.

Patent Owner states that the '692 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; U.S. Patent No. 12,195,773; and U.S. Patent No. 12,264,345.  
Paper 11, 2.

#### IV. THE '692 PATENT

##### A. *Background*

The '692 patent issued September 17, 2024, from U.S. Application 17/327,568, filed May 21, 2021. Ex. 1001, codes (21), (22), (45). The '692 patent is a continuation of U.S. Application 16/912,590, filed on June 25, 2020, now U.S. Patent 11,066,656 B2, 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 '692 patent is drawn to “[m]odified PH20 hyaluronidase polypeptides, including modified polypeptides that exhibit increased stability and/or increased activity.” Ex. 1001, 2:37–39. The '692 patent teaches “[h]yaluronan (hyaluronic acid; HA) is a polypeptide that is found in the extracellular matrix of many cells, especially in soft connective tissues.” *Id.* at 2:44–46. The '692 patent teaches “[c]ertain diseases are associated with expression and/or production of hyaluronan. Hyaluronan-degrading enzymes, such as hyaluronidases, are enzymes that degrade hyaluronan. By catalyzing HA degradation, hyaluronan-degrading enzymes (e.g., hyaluronidases) can be used to treat diseases or disorders associated with accumulation of HA or other glycosaminoglycans.” *Id.* at 2:51–57. The '692 patent teaches that “[v]arious hyaluronidases have been used

therapeutically . . . . Many of these are ovine or bovine forms, which can be immunogenic for treatment of humans.” *Id.* at 2:62–3:1.

The ’692 patent states that modifications for PH20 polypeptides include amino acid replacement, deletion, and/or insertions. Ex. 1001, 3:10–12. With regard to modified PH20 hyaluronidase polypeptides, the ’692 patent further teaches:

[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 3:16–36.

The ’692 patent teaches “modified PH20 polypeptides provided herein exhibit altered activities or properties compared to a wildtype, native or reference PH20 polypeptide.” *Id.* at 73:59–61. The ’692 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 73:61–74:5.

*B. Post-Grant Review Eligibility*

As a threshold issue, we must determine whether the '692 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 April 29, 2025, is within nine months of the '692 Patent's September 17, 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 recited for the '692 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 '692 Patent." Pet. 6.

Because the analysis of priority and PGR-eligibility in this Institution Decision relies on substantially the same analysis relevant to Petitioner's

challenge based on alleged lack of written description (Ground 1), we address post grant review eligibility and written description together below. *See infra* Section IX. As discussed below, we determine that the '692 patent is eligible for post grant review. *See id.*

## V. ILLUSTRATIVE CLAIM

Claim 1 is illustrative of the challenged claims in the '692 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 NO: 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 a modification at a position corresponding to position 313 with reference to amino acid positions of SEQ ID NO:3;

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 the amino acid sequence selected from the group consisting of SEQ ID NO: 3, 7 and 32–66.

Ex. 1001, 317:19–40.

## 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.<br>§ | Claim(s) Challenged <sup>2</sup> |
|--------|----------------------------------------------|----------------|----------------------------------|
| 1      | Written Description                          | § 112          | 1, 2, 5, 7–33                    |
| 2      | Enablement                                   | § 112          | 1, 2, 5, 7–33                    |
| 3      | '429 patent <sup>3</sup> , Chao <sup>4</sup> | § 103          | 1, 2, 5, 7–26, 29–33             |

See Pet. 7–8. 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. 2001.

## 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

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<sup>2</sup> Petitioner originally challenged claims 1–40 for lack of written description and enablement, and challenged claims 1, 2, 4, 5, 7–26, and 29–40 for obviousness. See Pet. 7–8. We have adjusted the claims challenged to only those that remain in effect following Patent Owner’s disclaimer.

<sup>3</sup> US 7,767,429 B2, issued Aug. 3, 2010 (the “’429 patent”; Ex. 1005).

<sup>4</sup> Chao et al., *Structure of Human Hyaluronidase-1, a Hyaluronan Hydrolyzing Enzyme Involved in Tumor Growth and Angiogenesis*, 46 *Biochemistry* 6911–20 (2007) (Ex. 1006).



analyze protein structure (*i.e.*, sequence searching and alignments, protein modeling software, etc.).

Pet. 16 (citing Ex. 1003 ¶ 13).

Petitioner's proposal is sufficiently comprehensive to encompass the level of skill reflected in prior art relevant to the '692 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 be an expert in hyaluronidases. *See* Pet. 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.*

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<sup>5</sup> or are used with their common and ordinary meaning. Consequently, no term requires an express construction to assess the grounds in this Petition,” in addition to those expressly defined in the specification. Pet. 17. Petitioner asserts “the common disclosure describes two mutually exclusive categories of ‘modified PH20 polypeptides’ (*i.e.*, ‘active mutants’ vs. ‘inactive mutants’).” *Id.* at 22. Petitioner asserts the claims are limited to “active mutants” for three reasons:

First, dependent claims 5, 7, 10, 13–14, and 23–25 require modified PH20 polypeptides that include a position 313 mutation (*e.g.*, M313K) that yielded PH201–447 polypeptides with >40% activity. Each is read correctly as being limited to “active mutants.” . . .

Second, dependent claims 3, 6, and 27–28 require modified PH20 polypeptides with “increased resistance or stability” or “increased hyaluronidase activity” relative to an unmodified PH20. All require modified PH20s with hyaluronidase activity (*i.e.*, “[a]s used herein, ‘increased stability’ . . . means the modified PH20 . . . exhibits greater hyaluronidase activity . . .”, “[a]s used herein, ‘increased activity’ means that, when tested under the same conditions, the modified PH20 hyaluronidase exhibits greater hyaluronidase activity...”).

Third, dependent claims 28 and 30–40 define pharmaceutical compositions or methods that require use of PH20 with hyaluronidase activity[.]

*Id.* at 24–25 (citing Ex. 1001, 85 (Table 3), 256 (Table 9), 31:65-66, 50:25–54, 50:64–51:12, 99:12–24, 132:52–133:4, 178:36–39, 311:18–312:44; Ex. 1003, ¶¶ 135–38). Petitioner states that the

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<sup>5</sup> Petitioner uses the term “common disclosure” to refer to the Specifications of both the ’692 patent and the ultimate parent application, the ’731 Application, filed on December 28, 2012. *See* Pet. 1–2 (citing Ex. 1026).

common disclosure’s description of multiply-modified PH20 polypeptides and producing them also indicate they are “active mutants.” For example, it defines a “modified PH20 polypeptide” as “a PH20 polypeptide that contains at least one amino acid modification,” but explains it can “have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide *exhibits hyaluronidase activity*.”

Pet. 26-27 (emphasis in original) (citing Ex. 1001, 46:63–47:11; 46:19–23, 74:19–22, 75:14–21, 79:15–80:17; Ex. 1003 ¶ 139).

Petitioner asserts that even if the claims include inactive mutants, “every claim still encompasses (and must describe and enable) the subgenus of ‘active mutants’ (*e.g.*, claim 1 contains the genus of ‘active mutants’ defined in claim 6).” *Id.* at 27; *cf. id.* at 85 (The common disclosure “identifies *no* epitopes or structures on PH20 that induce antibody production that confers contraceptive effects.”).<sup>6</sup>

### *B. Analysis*

We find that on the present record, 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.

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<sup>6</sup> Petitioner provides detailed assertions that the claims cover active mutants. *See* Pet. 20–26. 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. 20–26; *Phillips v. AWH Corp.*, 415 F.3d 1303, 1317 (Fed. Cir. 2005).

*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 ’692 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, 44:13–18. The ’692 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 44:30–35. The ’692 patent states that “PH20 polypeptides also include those that contain chemical or posttranslational modifications and those that do not contain chemical or posttranslational modifications.” *Id.* at 44:39–42. The ’692 patent provides an express definition of the term “modified PH20 polypeptide” which

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 46:63–47:11 (emphasis added).

Based on this express definition, the current record does not support the interpretation of Dr. Triggs-Raine that the “term ‘modified PH20 polypeptide,’ therefore, has a purely structural meaning in the context of the specification.” Ex. 2001 ¶ 68. Indeed, when reproducing the definition from this column of the ’692 patent, Dr. Triggs-Raine does not include any text after the first period, stating that “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. 2001 ¶¶ 67, 77–78.

On this record, however, we find that the entire text quoted above is part of the definition of “modified PH20 polypeptide” because it continues to detail specific elements required including a requirement that replacements in the PH20 polypeptide are permitted “so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity.” Ex. 1001, 47:2–4; *see* Ex. 2001 ¶ 67 (stating a “patent’s definition controls”). Dr. Triggs-Raine recognizes the “therapeutic use of hyaluronidases” and notes that “different hyaluronidases were known to have different functions and substrates.” Ex. 2001 ¶¶ 29, 113.<sup>7</sup> That is, Dr. Triggs-Raine recognizes hyaluronidase as the primary utility for the modified PH20 polypeptides recited in claim 1.

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<sup>7</sup> We recognize Dr. Triggs-Raine also cites “the role of PH20 in contraception,” but on this record, provides no evidence that a single modified PH20, as opposed to the naturally occurring PH20, functions as a contraceptive in any species. *See* Ex. 2001 ¶ 40.

Thus, the evidence of record shows the '692 patent recognizes a broad understanding of a “modified PH20 polypeptide” as encompassing PH20 sequences from a variety of different mammalian species, with or without precursor or signal sequences, with or without post-translational modifications, and with up to 150 amino acid replacements.

The express definition of “modified PH20 polypeptide” in the '692 patent permits up to 150 amino acid replacements but **only** “so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity.” Ex. 1001, 46:19–23. That is, the provided definition of “modified PH20 polypeptide” in the '692 patent expressly requires some hyaluronidase activity. And Patent Owner’s disclaimer of claims 3, 4, 6, and 34–40 does not impact the claim differentiation argument. The original issuance of these claims indicates that claim 1 encompasses modified PH20 polypeptides with hyaluronidase activity, and there is no limitation in claim 1 that expressly includes inactive PH20 polypeptides with no hyaluronidase activity. See Ex. 1001, 317:19–40. On the current record, we therefore adopt the definition for “modified PH20 polypeptide” as recited in the '692 patent to encompass polypeptides with some hyaluronidase activity.<sup>8</sup>

We determine that we need not expressly construe any other claim terms for the purpose of deciding whether to institute post-grant review. See

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<sup>8</sup> As to Dr. Triggs-Rainee’s statement that that the term “modified PH20 polypeptide” encompasses enzymatically inactive polypeptides (Ex. 2001 ¶ 75), we note the '692 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, 74:3–5. We address this concept further in the written description analysis.

*Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (“[W]e need only construe terms ‘that are in controversy, and only to the extent necessary to resolve the controversy’”) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng ’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

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

## 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 “claims encompass all PH20 polypeptides that are enzymatically active and that meet the sequence identity parameters in the claims. But the specification does not identify which of the 10<sup>60</sup>+ species in the claims’ scope are those polypeptides, much less demonstrate possession of all of them.” Pet. 35. Petitioner asserts the claims

define genera of modified PH20 polypeptides that are not only immense in number but are structurally and functionally diverse. They include mutants with between 2–21 substitutions for the narrowest claims (*e.g.* claims 24 and 25) to 2–42 for the broadest (claim 1). The optional sets of substitutions can be anywhere in the sequence (*i.e.*, clustered in a narrow region, spaced apart in groups, or spread randomly throughout the sequence), to any of 19 other amino acids, and arranged in any manner. The claims thus capture a mutant with 5 substituted hydrophobic residues clustered in a small region, and one with 42 substitutions that mix polar, charged, aliphatic, and aromatic amino acids in any manner.

*Id.* at 35–36 (citing Ex. 1003 ¶¶ 128–129; Ex. 1001, 59:7–14, 46:1–5, 46:14–16, 40:25–31).

Petitioner asserts the ’692 patent “instructs the skilled artisan ‘to generate a modified PH20 polypeptide containing any one or more of the described mutation[s], and test each for a property or activity as described herein.’” *Id.* at 37 (citing Ex. 1001, 76:47–52; Ex. 1003 ¶ 204). Petitioner acknowledges that the ’692 patent identifies inactive amino acid substitutions and “identifies these changes as: (i) any substitution at 96 different positions in the PH20 sequence, and (ii) 313 specific amino acid



substitutions listed in Tables 5 and 10.” *Id.* at 37–38 (citing Ex. 1001, 78:29–79:2). But, Petitioner notes, the “claim language however captures ‘active mutants’ that include one or more of the substitutions in Tables 5 and 10.” *Id.* at 38.

Petitioner asserts that based on the prior art and the common disclosure, it is reported “that wild-type PH20 polypeptides terminating at or below position 442 have **significantly reduced or no** hyaluronidase activity, with those terminating below position 432 lacking hyaluronidase activity and those between positions 432 and 448 showing widely varying activity” and asserts that the ’692 patent “does not describe ‘active mutant’ PH20 polypeptides truncated before position 447, particularly multiply-modified PH20 mutants terminating significantly before that position.” *Id.* at 38–39 (citing Ex. 1003 ¶¶ 94, 97, 100; Ex. 1001, 72:23–29; Ex. 1005, 87:52–88:24; Ex. 1013).

Petitioner asserts that of approximately 5,917 tested single amino acid changes, “~87% of the 5,917 single-replacement PH20<sub>1-447</sub> polypeptides that were made and tested as having **less** activity than unmodified PH20<sub>1-447</sub>.” *Id.* at 43 (citing Ex. 1003 ¶¶ 110, 114–115). Petitioner asserts the data shows the unpredictability of mutation where “different substitutions at the same position in PH20<sub>1-447</sub> yielded both active and inactive mutants, along with unreported effects for >800 mutants.” *Id.* at 45 (citing Ex. 1001, Tables 8, 9, 10). Petitioner asserts that:

The empirical test results for single substitution mutants do not identify to a skilled artisan which of the 10<sup>60</sup>+ PH20 mutants with a 313 substitution and 1-41 additional substitutions are enzymatically active (or for that matter, are inactive or cannot be made and are useless). Instead, all it shows is that **most** single-

substitutions [have] impaired or eliminated hyaluronidase activity.

*Id.* at 46 (citing Ex. 1003 ¶¶ 147, 149, 204). Petitioner asserts the '692 patent “does not describe or provide meaningful guidance concerning which of the claimed  $10^{60}+$  multiply-modified PH20 polypeptides may have increased stability.” *Id.* at 49 (citing Ex. 1003 ¶¶ 69, 76).

Petitioner asserts that the '692 patent “does not describe any multiply-modified PH20 polypeptides that are ‘active mutants.’ Instead, it simply presents **the idea** of making such multiply-modified PH20 polypeptides.” *Id.* at 49 (citing Ex. 1003 ¶¶ 151–152). Petitioner asserts that the '692 patent outlines a “prophetic research plan requiring ‘iterative’ make-and-test experiments that **might discover** such PH20 polypeptides” but that the “research plan does not identify **which** multiply-modified PH20 polypeptides can be made or **are** active mutants.” *Id.* at 50 (citing Ex. 1003 ¶¶ 183, 194–95, 198); *see also* Ex. 1001, 42:24–26, 133:5–50, 133:59–135:34, 135:61–140:34.

Petitioner asserts the '692 patent does not identify

the structural features or significance of any of the ~2,500 mutations that yielded single residue “active mutant” PH20<sub>1-447</sub> polypeptides (or the ~3,400 inactive mutants or ~830 uncharacterized 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. 52–53 (citing Ex. 1003 ¶¶ 146–147, 156).

Petitioner asserts the “single-replacement PH20<sub>1-447</sub> examples are not representative of the  $10^{60}+$  PH20<sub>1-447</sub> polypeptides having **2 to 42**

***additional substitutions*** to any of 19 other amino acids at any of hundreds of positions within the protein.” *Id.* at 55 (emphasis in original) (citing Ex. 1003 ¶¶ 61, 150, 164). Petitioner asserts the “common disclosure, however, does not identify effects of any single substitution on the various domains, secondary structures and structural motifs within any PH20 polypeptides within the scope of the claims.” *Id.* at 56 (citing Ex. 1003 ¶¶ 162, 163, 240).

Petitioner asserts that the figure below illustrates “how ***non-representative*** the single-replacement PH20<sub>1-447</sub> mutants are:”

|     | 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 |
| 3   |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 32  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 33  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 34  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 35  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 36  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 37  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 38  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 39  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 40  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 41  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 42  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 43  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 44  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 45  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 46  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 47  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 48  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 49  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 50  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 51  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 52  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 53  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 54  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 55  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 56  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 57  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 58  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 59  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 60  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 61  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 62  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 63  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 64  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 65  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 66  |                   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |

Pet. 58 (emphasis in original). The figure depicts a 22 x 36 array with a single shaded red box representing all of the tested single nucleotide mutations in SEQ ID NO: 3. *Id.*

Petitioner asserts that the other claims in the '520 patent lack written description support for the same or substantially similar reasons. *See id.* at 59–68.

C. *Analysis*

On the current record, we find the evidence supports Petitioner's position.

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

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

*Id.* at 1349. *Ariad* 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 we noted, on the current record claim 1 is reasonably interpreted to encompass PH20 polypeptides with some hyaluronidase activity. But even if we were to agree with Patent Owner that immunization using PH20

polypeptide as a contraceptive antigen serves to satisfy the utility requirement for the instant claims, there is a similar concern as to whether 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.

That the modified PH20 polypeptides would be homogenous in function is contradicted both by evidence in the '692 patent itself and by Dr. Hecht and Dr. Parker. The '692 patent discloses synthesis of 6,753 single amino acid mutations in residues 1–447 of SEQ ID NO: 3. *See* Ex. 1001, 200:1–24. The '692 patent teaches that just under 10% of these mutations, i.e. over 600, “exhibit activity that is increased compared to wildtype.” *Id.* at 232:46–47. Appendix A of Dr. Hecht’s Declaration shows 3,380 of these mutations were inactive, or 57.13%. *See* Ex. 1003, Appendix A-1, 175.

Thus, the '692 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 313)

being to any of 19 alternative 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.* ¶ 129. Dr. Park calculates that “95% sequence identity [i.e., the higher percentage identity recited by the narrowest of the challenged claims] to PH20<sub>1-465</sub> means that the protein can have 23 total changes,” and that where one of those changes is one of five choices at position 313 as required by claim 1, the number of possible PH20 polypeptides with twenty-two additional changes is “extremely large by all accounts, ranging from 10<sup>60</sup> to 10<sup>113</sup>.” *See* Ex. 1004 ¶¶ 177–178. Dr. Hecht characterizes the number of possible mutations as “astronomical in size.” Ex. 1003 ¶ 134.

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 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 '692 patent. See Ex. 1001, 71:7–9; Ex. 1003 ¶ 118. Dr. Hecht stated “subsequent publications reported negative results in experiments attempting to induce contraceptive by immunizing mammals (rats, mice) with PH20.” Ex. 1003 ¶ 119 (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 (45,46), mice, (47), and guinea pigs (48), and only the latter experienced infertility following PH20 immunization.” Ex. 1003 ¶ 111 (quoting Ex. 1061, 1154 (internal citations omitted)).

Dr. Hecht states

published reports showed that antibodies that do not impair fertility can form in humans naturally or in response to administration of recombinantly produced PH201-447. This suggests that there are structures on the wild-type human PH20 that can be recognized by antibodies that do not cause contraception in humans. But there is nothing in the common disclosure that distinguishes those structures on PH20 from structures that might induce antibodies that do confer a contraceptive effect, or whether the latter structures are preserved in any particular modified PH20 polypeptide. The common disclosure does not provide any guidance that would allow a skilled artisan to determine whether any active or inactive mutants are useful as contraceptive vaccines.

Ex. 1003 ¶ 122. This shows that even the native PH20 polypeptide does not necessarily function as a contraceptive. 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 contained structurally diverse antibodies, but the patent at issue only described structurally similar antibodies.

Therefore, the only evidence of any contraceptive activity is for the native protein without any mutations. The evidence demonstrates that not 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 '692 patent employed a trial-and-error approach for hyaluronidase activity and did no testing to determine if any of the mutations had contraceptive function. *See* Ex. 1001, 200:22–24; *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 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 '692 patent fail to satisfy the written description requirement because they “recite a description of the problem to be solved while claiming all solutions to it and . . . cover any compound later actually invented and determined to fall within the claim’s functional boundaries—leaving it to the pharmaceutical industry to complete an unfinished invention.” *Ariad*, 598 F.3d at 1353.

Accordingly, on the current record, we find that Petitioner has demonstrated that it is more likely than not that the '692 patent does not comply with the written description requirement. Similarly, the current record does not appear to provide evidence of possession of the full scope of the claims of the '692 patent in the '731 application or any of the subsequent divisional or continuation applications leading to the '692 patent that claim priority to the '731 application (which appear to all have similar specifications) for the reasons given above. Therefore, the '692 patent might not receive the benefit of priority to the earlier filed applications, and based on this preliminary determination, is eligible for post-grant review because the effective filing date is no earlier than the '692 patent's filing date of December 19, 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  $10^{60}+$  PH20 polypeptides having multiple amino acid replacements and/or truncations within the scope of the claims that are useful because they are “active mutants,” those “inactive mutants” that the disclosure contends are useful as a contraceptive antigen, and those which have no utility.

Pet. 67–68 (citing Ex. 1003 ¶¶ 180–182, 201). Petitioner asserts the “the claims capture a massive number of multiply-modified PH20 polypeptides that have **unknowable** properties absent the skilled artisan producing and testing  $10^{60}$  and  $10^{113}$  distinct mutants pursuant to the common disclosure’s prophetic “make and test” methodology.” *Id.* at 70 (citing Ex. 1003 ¶ 161–163, 173).

Petitioner asserts the ’692 patent “provides an extremely narrow set of working examples: ~5,916 randomly generated single-replacement PH20<sub>1-447</sub> polypeptides, of which ~2500 were ‘active mutants.’ . . . These examples are a tiny fraction of the  $10^{60}$  to  $10^{113}$  modified PH20 polypeptides covered by the claims.” *Id.* at 71 (citing Ex. 1003 ¶ 111–112).

Petitioner asserts the “research plan requires a skilled artisan to engage in undue experimentation” because “it describes a prophetic, ‘iterative’ ‘make and test’ process for **discovering** active mutant PH20 polypeptides” involving “manually performing iterative rounds of

**randomized** mutations (up to 41 rounds per starting molecule under the broadest claims) to **discover** which of the  $10^{60}+$  possible modified PH20 polypeptides the claims encompass might possess hyaluronidase activity *Id.* at 72 (emphasis in original) (citing Ex. 1003 ¶¶ 141, 147, 189–191).

Petitioner asserts the “**“iterative, trial-and-error process[es]”** the common disclosure specifies here are thus indistinguishable from those consistently found to not enable broad genus claims to modified proteins or other useful compounds.” *Id.* at 74 (emphasis in original) (citing *Idenix Pharm. LLC v. Gilead Sci. Inc.*, 941 F.3d 1149, 1161–63 (Fed. Cir. 2019)).

Petitioner asserts “skilled artisans around this time period could **not** have predicted the effects of making more than a few concurrent amino acid replacements within a PH20 polypeptide.” *Id.* at 75 (citing Ex. 1003 ¶ 163, 240). Petitioner asserts the “cumulative effects of multiple changes would also have rapidly exceeded the capacity of computer-based, rational design techniques to reliably predict the effects of each change on the protein’s structure.” *Id.* at 76 (citing Ex. 1003 ¶ 163).

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 public knowledge about hyaluronidases, there was no solved structure of the PH20 protein. Also, the public literature generally reported on **loss of activity** from mutations in hyaluronidases, and did not predictably teach how to introduce changes that preserved or **enhanced** stability or activity of such proteins.

*Id.* at 77–78 (emphasis in original) (citing Ex. 1003 ¶¶ 163, 240; Ex. 1011, 812–814; Ex. 1010, 9437–9439).

*C. 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 evidence.

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

Petitioner's declarant Dr. Park states, regarding the breadth of claim 1, that he "calculated the number of distinct polypeptides that exist that meet the specified criteria." Ex. 1004 ¶ 178. Dr. Park's table is reproduced below:

| <i>PH20<br/>length</i> | <i>Sequence<br/>Identity %</i> | <i>#<br/>Changes</i> | <i>Pos. 313<br/>Choices</i> | <i>Add'l<br/>Changes</i> | <i># of Distinct<br/>Polypeptides</i> |
|------------------------|--------------------------------|----------------------|-----------------------------|--------------------------|---------------------------------------|
| 474                    | 91                             | 42                   | 19                          | 41                       | $1.20 \times 10^{113}$                |
| 474                    | 95                             | 23                   | 19                          | 22                       | $9.85 \times 10^{66}$                 |
| 474                    | 91                             | 42                   | 8                           | 41                       | $5.05 \times 10^{112}$                |
| 474                    | 91                             | 42                   | 1                           | 41                       | $6.32 \times 10^{111}$                |
| 465                    | 91                             | 41                   | 19                          | 40                       | $2.68 \times 10^{110}$                |
| 465                    | 95                             | 23                   | 19                          | 22                       | $6.39 \times 10^{66}$                 |
| 465                    | 91                             | 41                   | 1                           | 40                       | $1.41 \times 10^{109}$                |
| 433                    | 91                             | 41                   | 19                          | 40                       | $1.35 \times 10^{109}$                |
| 430                    | 91                             | 41                   | 19                          | 40                       | $1.01 \times 10^{109}$                |
| 433                    | 91                             | 41                   | 1                           | 40                       | $7.10 \times 10^{107}$                |
| 430                    | 91                             | 41                   | 1                           | 40                       | $5.30 \times 10^{107}$                |
| 465                    | 91                             | 41                   | 8                           | 40                       | $1.13 \times 10^{110}$                |
| 447                    | 91                             | 40                   | 19                          | 39                       | $2.65 \times 10^{107}$                |
| 447                    | 91                             | 40                   | 1                           | 39                       | $1.40 \times 10^{106}$                |
| 430                    | 95                             | 21                   | 8                           | 20                       | $3.52 \times 10^{60}$                 |
| 433                    | 95                             | 21                   | 8                           | 20                       | $4.06 \times 10^{60}$                 |

*Id.* Dr. Park's table shows that the "number of distinct polypeptides is extremely large by all accounts, ranging from  $10^{60}$  to  $10^{113}$ ." *Id.* Petitioner's declarant Dr. Hecht agrees, stating the "sequence identity language causes the claims to encompass an immense number of distinct PH20

polypeptides.” Ex. 1003 ¶ 129. To illustrate how large a number like  $10^{113}$  is, Dr. Hecht states that an “aggregate weight of one set of these mutants from the ’692 Patent claims, where one assumes one molecule of each mutant is in the set. . . is  $3.15 \times 10^{38}$  kg. The weight of the Earth is ‘only’  $\sim 5.97 \times 10^{24}$  kg.” *Id.* ¶ 132.

That is, a complete set of one single molecule of protein that comprises all possible mutations in PH20 as recited in claim 1 would weigh about significantly more than the entire mass of planet Earth. *See id.*

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*

Petitioner addressed the skill in the art that is discussed *supra* Section VII. On the current record, we find that the skill in the art is high.

## 3. *State of the Prior Art*

Dr. Hecht acknowledges protein expression is routine, stating the “conventional procedures relating to production of the wild-type PH20<sub>1-447</sub> protein that are described in the ’429 Patent could be applied to produce forms of PH20<sub>1-447</sub> that incorporate a single amino acid substitution . . . with little effort.” Ex. 1003 ¶ 214 (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.” *Id.* ¶ 93 (citing Ex. 1005, 87:52–88:24; Ex. 1013, 430–432, Fig. 2). Dr. Hecht states the “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<sub>1-446</sub> vs. PH20<sub>1-447</sub> vs. PH20<sub>1-448</sub>) exhibit variability in their activity.” *Id.* ¶ 97.

Dr. Hecht states “[t]here were limits to using rational design techniques in the 2011-timeframe.” *Id.* ¶ 50 (citing Ex. 1018, 378; Ex. 1059, 1225–1226). “The complexity of the structure/function relationship in enzymes has proven to be the factor limiting the general application of rational design.” *Id.* at n.17 (citing Ex. 1018, 378). Dr. Hecht states regarding another approach to protein modification, termed directed evolution, that the “challenge with directed evolution is scale. One has to identify the successful mutant out of an immense number of possibilities, which presents different kinds of challenges.” *Id.* ¶ 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 even in a smaller, ten amino acid substitution example, “[t]here are approximately  $6 \times 10^{12}$  different scenarios of 10 substitutions.” *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 the prior art was aware that mutations, whether conservative or non-conservative, may impact protein function and physical shape. The evidence of record demonstrates that identifying which of the  $10^{60}$  and  $10^{113}$  members of the PH20 polypeptide genus would either retain functional hyaluronidase activity or contraceptive activity was not established as known in the prior art.

#### 4. *Presence of Working Examples*

Dr. Hecht agrees that the '692 patent "lists 6,753 PH20<sub>1-447</sub> mutants that were produced from a library 'created by mutagenesis of a PH20 template.'" Ex. 1003 ¶ 106 (citing Ex. 1001, 200:22–24, 200:6–9). Dr. Hecht states "the number of 'inactive mutants' listed in Table 5 does not match the number of tested inactive mutants listed in Table 10 (*i.e.*, 3,368 vs. 3,380)." *Id.* ¶ 111. Dr. Hecht calculates that based on the data in Table 10 of the '692 patent that 57.1% were inactive, and 26.7% others had activity <100%." *Id.* ¶ 114.

Dr. Hecht states the '692 patent "does not identify any **mutated** PH20 polypeptides that were effective when used in a contraceptive vaccine." *Id.* ¶ 122.

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



5. *Amount of Direction or Guidance Presented*

The '692 patent states “[p]roteins, such as modified PH20 polypeptides, can be purified using standard protein purification techniques known in the art.” Ex. 1001, 150:63–65.

Dr. Hecht states the '692 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. Dr. Hecht states that the data in the '692 patent shows “most of the single-replacement PH20<sub>1-447</sub> mutants that were tested exhibited less activity than the unmodified PH20<sub>1-447</sub> (*i.e.*, 57.1% were inactive, and 29.4% others had activity <100%).” *Id.* ¶ 114.

Dr. Hecht states the '692 patent

does not provide any guidance that would allow a skilled artisan to determine whether any active or inactive mutants are useful as contraceptive vaccines (such as by identifying common structural or functional characteristics shared by those inactive mutants), without making and testing all  $\sim 10^{60}$  (or more) modified PH20 polypeptides within the parameters of each claim.

*Id.* ¶ 122. Dr. Hecht states “the data for testing the 409 mutants reported in Tables 11 and 12 [of the '692 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<sub>1-447</sub> form specifically.” *Id.* ¶ 76. Dr. Hecht states the '692 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.

*Id.* ¶ 182. Dr. Hecht characterizes the disclosure of the '692 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.* ¶ 183.

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 '692 patent provides minimal guidance regarding effective methods to identify which members of the immense modified PH20 polypeptide genus function to retain either hyaluronidase activity or contraceptive activity.

#### 6. *Quantity of Experimentation*

Dr. Hecht states

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 ¶ 163 (emphasis added). Dr. Hecht states that “the single-replacement PH20<sub>1-447</sub> polypeptides reported in the common disclosure are not representative of all the types of mutated PH20<sub>1-447</sub> polypeptides that

have a particular substitution at position 313 and sets of between 1 and 41 *additional* substitutions at any of hundreds of positions within the PH20 protein.” *Id.* ¶ 164 (emphasis in original).

Dr. Hecht states “[m]aking and identifying all of the multiple-modified PH20 polypeptides that are within the immense set of polypeptides (between  $10^{60}$  and  $10^{113}$  distinct mutants) defined by the claims’ sequence identity parameters is not only undue experimentation, it likely is impossible.” *Id.* ¶ 180. Dr. Hecht states the directed evolution methods of the ’692 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.* ¶ 197.

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 ’692 patent.

7. *Predictability of the Art*

Dr. Hecht states that the

effects caused by one substitution in a protein like PH20 thus 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 . . . [as] representative of all modified PH20 proteins having that one substitution, along with 5, 10 or 15 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 the “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.* ¶ 163. 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 common disclosure says are deleterious or eliminate hyaluronidase activity in PH20 enzymes.” *Id.* ¶ 165.

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<sub>1-419</sub> sequence or comparably truncated PH20 polypeptide that would restore hyaluronidase activity to an inactive M313K, containing PH20<sub>1-419</sub> mutant.” *Id.* ¶ 172. Dr. Hecht continues:

In other words, the common disclosure also does not help the skilled artisan identify which of the 10<sup>60</sup>+ possible PH20 polypeptides of varying length with 2 to 42 substitutions have hyaluronidase activity; to make and use all such enzymatically

active PH20 polypeptides within the full scope of the claims requires the skilled artisan to ignore what little guidance is in the specification about single-substitutions and truncations that render PH20 polypeptides inactive.

*Id.* ¶ 173. Dr. Hecht states that the artisan following the '692 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.* ¶ 194. On the record before us, we credit Dr. Hecht's testimony as showing it is highly unpredictable which polypeptides would have hyaluronidase or contraceptive activity. *Id.* ¶¶ 76, 122, 172–184.

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 '692 patent would have any functional utility such as hyaluronidase activity or contraceptive activity.

*D. Conclusion*

As we balance the *Wands* factors, we find that the totality of the evidence shown in the current record as discussed above supports Petitioner's position. Accordingly, Petitioner has demonstrated that it is more likely than not that undue experimentation would have been required to enable the broad scope of the claims, and 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;<sup>9</sup> 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.” *Id.* at 6:15–20. The ’429 patent states:

Suitable conservative substitutions of amino acids are known to those of skill in this art and can be made generally without altering the biological activity, for example enzymatic activity, of the resulting molecule. Those of skill in this art recognize that,

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<sup>9</sup> 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:

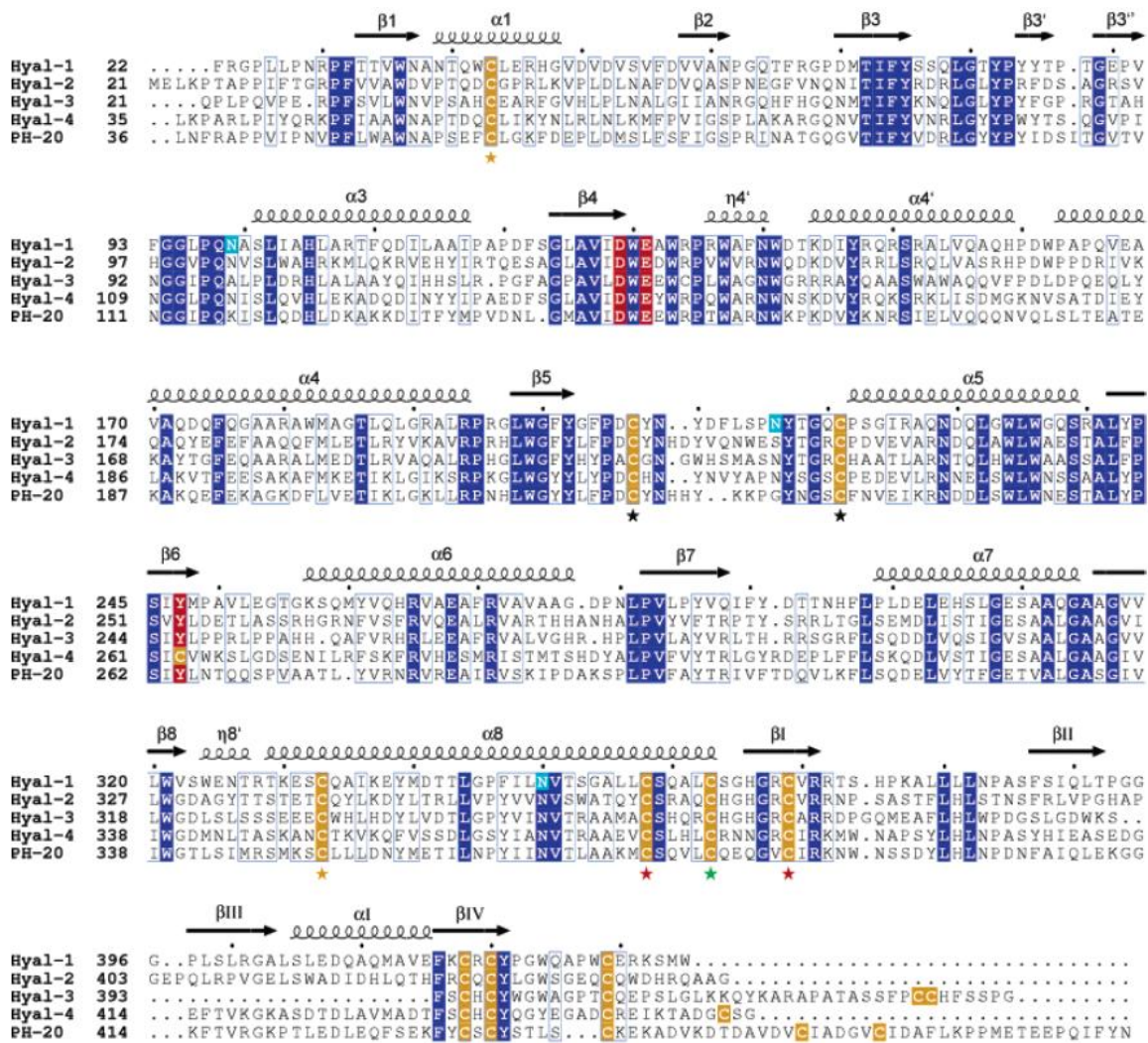


Figure 3 shows:

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.* at 6916.



C. *Asserted Obviousness over the '429 Patent and Chao*

1. *Petitioner's Position*

Petitioner asserts that the '429 patent “teaches making a *particular* type of modification (a single amino acid substitution) at a *particular* location (non-essential regions of PH20) in a *particular* PH20 sequence (PH20<sub>1-447</sub>) to yield equivalents of PH20<sub>1-447</sub> (*i.e.*, those that do not substantially alter the activity or function of PH20<sub>1-447</sub>).” Pet. 93 (citing Ex. 1003 ¶¶ 217; Ex. 1004 ¶ 32). Petitioner asserts “Chao showed that human and non-human hyaluronidases share a highly conserved active site and identified residues that interact with HA, *inter alia*, by superimposing HYAL1 and bee venom hyaluronidase structures.” *Id.* at 94 (citing Ex. 1006, 6917; Ex. 1004 ¶¶ 89–91; Ex. 1003 ¶¶ 81–82).

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, in particular by using a multi-sequence alignment of those proteins.” *Id.* at 97 (citing Ex. 1003 ¶¶ 223–225; Ex. 1004 ¶¶ 22, 25–30, Appendix D-3; Ex. 1017, 224–226). Petitioner asserts that Dr. Park performed such an analysis and that “Position 313 is within a non-essential region of PH20<sub>1-447</sub>, Dr. Park’s analysis and Chao’s Figure 3 both report the same bounding essential residues (*i.e.*, W304 and C316).” *Id.* at 98 (citing Ex. 1003 ¶ 228; Ex. 1004 ¶¶ 31–32, Appendix D-2; Ex. 1006, 6916).

Petitioner asserts that in Dr. Park’s alignment, the “wild-type residue at position 313 in PH20 is methionine (M), which occurs at positions corresponding to position 313 in ~14% of homologous proteins. Lysine (K) is the most prevalent amino acid found at those positions (~40%) (*i.e.*,

leucine occurs in 35 different hyaluronidase proteins).” *Id.* at 100–101 (citing Ex.1004 ¶¶ 105, 106, 113, Appendix D-1; Ex. 1003 ¶ 229).

Petitioner asserts that a

skilled artisan would have viewed lysine (K) as an obvious choice for a single substitution at position 313 in PH20<sub>1-447</sub>. First, its high prevalence of occurrence and presence in 2 of the 5 human hyaluronidases signal that it was well-tolerated at this position in many different hyaluronidase enzymes. Second, lysine was known to have a high helix propensity, meaning it is favored in sequences that form  $\alpha$ -helix secondary structures.

*Id.* at 101 (citing Ex. 1050, 422–24, Table 2; Ex 1003 ¶ 230; Ex. 1004 ¶¶ 69, 70, 117).

Petitioner asserts that Patent Owner “relied on its statements that a skilled artisan would have expected **any** single amino acid substitution in **any** non-essential position of PH20<sub>1-447</sub> to not substantially affect the activity of the enzyme.” *Id.* at 103. Petitioner also asserts “[p]atentee should not be permitted to now contend that a skilled artisan would not have reasonably expected that the M313K substitution in PH20<sub>1-447</sub> would yield an enzyme with substantially the same activity as unmodified PH20<sub>1-447</sub>.” *Id.*

## 2. Analysis

On the current record, Petitioner has not provided any persuasive reason to particularly target position 313 of a PH20 polypeptide for modification as required by claim 1 of the ’692 patent. Neither the ’429 patent nor Chao specifically identifies or discusses position 313 of the PH20 polypeptide. *See, e.g.*, Pet. 98; Prelim. Resp. 61.

We are not persuaded by Petitioner’s argument that multiple sequence alignments identify amino acids that are tolerated at particular positions (*see* Pet. 93–97), because tolerance is not a positive reason to make a

substitution. “It is not enough, even after *KSR*, to support a determination of obviousness that a reference includes a broad generic disclosure and a common utility to that in the claims and other prior art references—there must be some reason to select a species from the genus.” *Knauf Insulation, Inc. v. Rockwool Int’l A/S*, 788 Fed. 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. Dr. Park distributes the twenty standard amino acids into four categories depending on their roles in forming secondary structure such as alpha helices or beta sheets, with each category having a minimum of six members. *See id.* ¶ 70. Nothing in the prior art or Dr. Park’s analysis directs the ordinary artisan to position 313 itself, and Dr. Park notes that Chao did not identify position 313 of PH20 as part of the catalytic active site, unlike positions 146, 148, and 219, nor was position 313 one of the residues identified as being in the cleft where ligand binds. *See id.* ¶ 91. Dr. Park indicates that position 313 was not identified by Chao as part of the Hyal-EGF domain, was not identified by Stern in the active site, and was not identified by Arming as impacting PH20 activity. *See id.* ¶¶ 98–101 (citing Ex. 1006, 6912; Ex. 1008, 825; Ex. 1011, 811–813).

Indeed, Dr. Hecht states that “[i]ntroducing random amino acids could disrupt that [alpha helical] pattern, which could have a range of effects in this region of the helical structure.” Ex. 1003 ¶ 203. And while Dr. Hecht asserts that the ’429 patent suggests conservative mutations generally, Petitioner does not point us to any specific teaching by Dr. Hecht to modify position 313 of PH20. *See, e.g., id.* ¶¶ 202–204. Petitioner does not point us to anything in Dr. Hecht’s Declaration that explains why position 313 was of

interest in any way, versus position 312 or 314 or any other position within the PH20 polypeptide.

We also are not persuaded by Petitioner's argument that Chao "identified a characteristic pattern for the Hyal-EGF domain in PH20 at positions 337–409." Pet. 93 (citing Ex. 1006, 6911; Ex. 1004 ¶¶ 97–98; Ex. 1003 ¶¶ 84–85). This statement is not a reason to substitute lysine, but rather a statement. 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,  $\alpha 1$ ,  $\alpha 3$ ,  $\eta 4'$ ,  $\alpha 4'$ ,  $\alpha 4$ ,  $\alpha 5$ ,  $\alpha 6$ ,  $\alpha 7$ , and  $\alpha 8$ , 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 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 313 of the PH20 polypeptide.

Accordingly, on the current record, we find that 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 '692 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, 5, and 7–33 of the '692 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.

PGR2025-00046  
Patent 12,091,692 B2

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