

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,
Petitioner,

v.

HALOZYME, INC.,
Patent Owner.

PGR2025-00052
Patent 12,264,345 B1

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

HARDMAN, *Administrative Patent Judge*.

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
35 U.S.C. § 328(a)

I. INTRODUCTION

This is a Final Written Decision in a post-grant review challenging the patentability of claims 1–17 of U.S. Patent No. 12,264,345 B1 (Ex. 1001, “the ’345 patent”). We have jurisdiction under 35 U.S.C. § 6.

Petitioner has the burden of proving unpatentability of the challenged claims by a preponderance of the evidence. 35 U.S.C. § 326(e). Having reviewed the parties’ arguments and cited evidence, for the reasons discussed below, we find that Petitioner has demonstrated by a preponderance of the evidence that claims 1–17 are unpatentable.

A. Procedural History

Petitioner Merck Sharp & Dohme LLC filed a Petition requesting post-grant review of all claims of the ’345 patent. *See* Paper 1 (“Pet.”). Patent Owner Halozyme, Inc. did not file a Preliminary Response or a brief directed to discretionary denial issues. Under the then-existing Board procedures, the Chief Clerk referred the case to a Board panel to consider the merits and non-discretionary considerations and determine whether to institute a post-grant review. *See* Paper 11, 1–2.

We determined, based on the arguments and evidence of record, that the ’345 patent was eligible for post-grant review and that at least one of the challenged claims was more likely than not unpatentable. *See* Paper 12 (“Inst. Dec.”). Thus, on October 16, 2025, pursuant to 35 U.S.C. § 324, the Board instituted trial of all challenged claims (claims 1–17). *Id.*

Following institution, Patent Owner filed a Patent Owner’s Response to the Petition (Paper 28, “PO Resp.”), Petitioner filed a Reply to Patent Owner’s Response (Paper 64, “Reply”), and Patent Owner filed a Sur-reply (Paper 84, “Sur-reply”).

Patent Owner filed a Motion for Additional Discovery (Paper 26), Petitioner opposed the motion (Paper 29), and the Board denied the motion (Paper 32).

Patent Owner filed a Motion to Terminate (Paper 35), Petitioner filed an opposition (Paper 41), Patent Owner filed a reply (Paper 45), and the parties each filed an authorized supplemental brief regarding the Motion to Terminate (Papers 58, 61). The Board denied Patent Owner's Motion to Terminate. Paper 35. Patent Owner requested Director Review of the Board's order denying its Motion to Terminate (Paper 83), but that request was not considered because the request "is outside the scope of Director Review" (Ex. 3101).

The parties filed, and the Board resolved, various motions to seal. Several motions to seal remain pending and will be resolved in due course.

We held an oral hearing July 23, 2026, a transcript of which is of record. Paper 88.

B. Real Parties-In-Interest

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

C. Related Matters

The '345 patent is subject to a civil action in *Halozyme, Inc. v. Merck Sharp & Dohme LLC f/k/a/ Merck Sharp & Dohme Corp.*, 2:25-cv-03179 (D.N.J.), along with the following related U.S. patents: 10,865,400; 11,041,149; 11,066,656; 11,952,600; 12,018,298; 12,037,618; 12,049,652; 12,054,758; 12,091,692; 12,104,185; 12,110,520; 12,152,262; 12,077,791; and 12,195,773. Paper 86, 1.

The '345 patent is also related to several patents subject to post-grant review proceedings including those in the Table below:

U.S. Patent No.	PGR No.	PGR Petition Filed	At Issue In Civil Action
11,952,600	PGR2025-00003	Nov. 12, 2024	Yes
12,018,298	PGR2025-00004	Nov. 26, 2024	Yes
12,152,262	PGR2025-00006	Dec. 10, 2024	Yes
12,123,035	PGR2025-00009	Dec. 27, 2024	No
12,110,520	PGR2025-00017	Jan. 17, 2025	Yes
12,060,590	PGR2025-00024	Feb. 21, 2025	No
12,054,758	PGR2025-00030	Feb. 4, 2025	Yes
12,049,652	PGR2025-00033	Mar. 7, 2025	Yes
12,104,185	PGR2025-00039	Mar. 28, 2025	Yes
12,037,618	PGR2025-00042	Apr. 15, 2025	Yes
12,091,692	PGR2025-00046	Apr. 29, 2025	Yes
12,077,791	PGR2025-00050	May 7, 2025	Yes
12,195,773	PGR2025-00053	Jun. 6, 2025	Yes
12,371,685	PGR2025-00087	Nov. 10, 2025	Yes
10,865,400	IPR2026-00312	Mar. 23, 2026	Yes
11,041,149	IPR2026-00313	Mar. 23, 2026	Yes
11,066,656	IPR2026-00314	Mar. 23, 2026	Yes

See Paper 86, 2. Petitioner also “filed petitions for *inter partes* review of related U.S. Patent Nos. 10,865,400 (IPR2026-00312), 11,041,149 (IPR2026-00313), and 11,066,656 (IPR2026-00314), which are at issue in the above-referenced civil action.” *Id.* at 1.

Patent Owner states that the '345 patent is related to the following pending U.S. Patent Applications and patents:

Application No.	Filed
18/922,889	Oct. 22, 2024
19/071,005	Mar. 5, 2025
19/071,055	Mar. 5, 2025
19/075,092	Mar. 5, 2025
19/071,264	Mar. 5, 2025

Application No.	Filed
19/546,132	Feb. 20, 2026
19/550,132	Feb. 25, 2026
19/550,136	Feb. 25, 2026
19/551,393	Feb. 26, 2026
19/551,420	Feb. 25, 2026
19/720,762	Jun. 25, 2026
19/720,766	Jun. 25, 2026
19/722,345	Jun. 26, 2026
19/722,335	Jun. 26, 2026

Paper 64, 2.

D. The '345 Patent

The '345 patent issued on April 1, 2025, from U.S. Application 18/778,554, filed on July 19, 2024. Ex. 1001, codes (45), (21), (22). The '345 patent is a continuation of a lengthy set of applications claiming continuity to U.S. Application 13/694,731 (the "'731 Application"), filed December 28, 2012, which claims the priority benefit of provisional applications U.S. 61/796,208, filed November 1, 2012, and U.S. 61/631,313, filed December 30, 2011. *Id.* at code (60).

The '345 patent is drawn to "[m]odified PH20 hyaluronidase polypeptides, including modified polypeptides that exhibit increased stability and/or increased activity." Ex. 1001, 2:43–45. The '345 patent teaches "[h]yaluronan (hyaluronic acid; HA) is a polypeptide that is found in the extracellular matrix of many cells, especially in soft connective tissues." *Id.* at 2:50–52. The '345 patent teaches "[c]ertain diseases are associated with expression and/or production of hyaluronan. Hyaluronan-degrading enzymes, such as hyaluronidases, are enzymes that degrade hyaluronan. By catalyzing HA degradation, hyaluronan-degrading enzymes (e.g., hyaluronidases) can be used to treat diseases or disorders associated

with accumulation of HA or other glycosaminoglycans.” *Id.* at 2:57–63. The ’345 patent teaches that “[v]arious hyaluronidases have been used therapeutically Many of these are ovine or bovine forms, which can be immunogenic for treatment of humans.” *Id.* at 3:1–7.

Regarding modified PH20 hyaluronidase polypeptides, the ’345 patent teaches:

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

Id. at 3:33–42. The ’345 patent teaches that the “modified PH20 polypeptides provided herein exhibit altered activities or properties compared to a wildtype, native or reference PH20 polypeptide.” *Id.* at 73:66–74:1.

E. Illustrative Claims

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

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

Ex. 1001, 301:37–44.

F. Asserted Grounds of Unpatentability

Petitioner contends that the challenged claims are unpatentable based on the four grounds listed below.

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

Petitioner relies on the Declarations of Michael Hecht, Ph.D., Sheldon Park, Ph.D., James Naismith, Ph.D., and Garnett Kelsoe, Ph.D. *See* Exs. 1003, 1004, 1133, 1134, respectively. Patent Owner relies on the Declarations of Melanie Simpson, Ph.D., Gregory Petsko, Ph.D., Gary Cherr Ph.D., and James Moon, Ph.D. *See* Exs. 2068, 2070, 2072, 2074, respectively.

II. ANALYSIS

A. 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

¹ US 7,767,429 B2, issued Aug. 3, 2010 (the “’429 patent”) (Ex. 1005).

² 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).

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

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

Patent Owner responds “[s]olely for the purposes of the analysis herein, Patentee applies Petitioner’s POSA definition (Pet., 16-17; EX1003, ¶13; ID, 7-16). Petitioner’s declarant [Dr.] Hecht agreed that POSAs under Petitioner’s definition ‘would have been able to speak with someone with hyaluronidase experience as part of a multi-disciplinary team.’” PO Resp. 31 (citing Ex. 2076, 63:8–64:2).

We find that Petitioner’s undisputed proposal is sufficiently comprehensive to encompass the prior art relevant to the ’345 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, the parties agree 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. We also agree with Patent Owner that a POSA would be able to apply key scientific concepts (*e.g.*, biochemistry, recombinant biology, sequence analysis and protein modeling) to enzymes such as hyaluronidases and speak with a multidisciplinary team about these enzymes. *See, e.g., id.* at 31, 62, 67–68. We find that all of the experts of

record in this proceeding have sufficient technical training and experience to meet these requirements and are qualified to testify from the perspective of a POSA.

We consider the POSA level as of the 2011–2012 timeframe, which includes the December 28, 2012, priority date Patent Owner asserts for the written description and enablement challenges. *See, e.g.*, PO Resp. 11–12 n.6 (Patent Owner indicating that it “applies the December 28, 2012, filing date of the ’731 application for purposes of responding to Petitioner’s written description, enablement, and indefiniteness challenges,” and “the December 30, 2011, priority date for purposes of responding to Petitioner’s obviousness challenge”). Patent Owner alleges that for its written description, indefiniteness, and enablement challenges, “Petitioner and its experts erroneously rely upon a December 30, 2011, date (Pet., 31-97; *id.*, 42, 51, 88, 92; EX1003, ¶11), rather than the proper December 28, 2012, date.” PO Resp. 44–45 n.10. However, Petitioner does not restrict the § 112 analyses to December 2011; rather, Petitioner states that the claims are not entitled to claim priority to either the provisional application filed on December 30, 2011, or the ’731 Application filed on December 28, 2012. Pet. 16. Petitioner then states, “Conversely, the obviousness ground[] rel[ies] on prior art published before and knowledge/perspectives of a skilled artisan before December 2011.” *Id.* In any event, the record does not reflect any material difference in the state of the art between the December 30, 2011, and December 28, 2012 priority dates that would change our findings herein.

B. 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.*

In our Institution Decision, we addressed the construction of the terms “hyaluronidase domain” and “modified PH20 polypeptides.” *See* Inst. Dec. 8–10. Below we first address “hyaluronidase domain,” then turn our analysis to “modified PH20 polypeptides.”

1. “hyaluronidase domain”

In our Institution Decision, we construed the claim term “hyaluronidase domain” as meaning a “region of about 340 amino acids in length that corresponds to amino acid residues 38–374 of the precursor human PH20 sequence set forth in SEQ ID NO:6.”³ Dec. 10 (quoting Ex. 1001, 68:19–24). Following institution, neither party objects to this construction or otherwise addresses the construction of this claim term.⁴ Accordingly, we maintain this construction.

³ According to Petitioner’s declarant Dr. Hecht, “[p]ositions 38-374 of SEQ ID NO:6 correspond to positions 3-339 in SEQ ID NO:3 and in SEQ ID NO:7.” Ex. 1003 n.135; *see also* PO Resp. 19 (discussing differences between SEQ ID NO:3, 6, and 7).

⁴ Indeed, although Patent Owner does not expressly address the construction of the term “hyaluronidase domain,” it nevertheless acknowledges that the hyaluronidase domain corresponds to amino acids 3–339 of SEQ ID NO: 7. *See* PO Resp. 3 (stating, “the inventors claimed a narrow subgenus of

2. “*modified PH20 polypeptides*”

In our Institution Decision we construed the term “modified PH20 polypeptide” as encompassing polypeptides with some hyaluronidase activity. Inst. Dec. 9–10. In reaching this conclusion, we primarily relied on the intrinsic evidence in a definitional passage in the ’345 Specification, which states:

As used herein, “modified PH20 polypeptides” or “variant PH20 polypeptide” 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.

Ex. 1001, 47:3–18.

Based on the evidence of record at that time, we determined that the ’345 patent recognizes a broad understanding of a “modified PH20 polypeptide” as encompassing PH20 sequences from a variety of different mammalian species, with or without precursor or signal sequences, with or without post-translational modifications, and with up to 150 amino acid replacements. . . . On the current record, we therefore adopt the definition for “modified PH20 polypeptide” as recited in the ’345 patent to encompass polypeptides with some hyaluronidase activity.

Inst. Dec. 9–10. Following institution, the parties continue to dispute this term.

variants comprising a *hyaluronidase domain corresponding to amino acids 3-339 of SEQ ID NO: 7* with a modification at a specific position: M313”), 82 (referring to “hyaluronidase domain (amino acids 3-339 of SEQ ID NO:7)”).

We now address the parties' contentions regarding the term "modified PH20 polypeptides" on the complete record.

a) Petitioner's Position

Petitioner asserts "[t]he common disclosure⁵ describes two mutually exclusive categories of 'modified PH20 polypeptides,'" i.e., "active mutants" and "inactive mutants." Pet. 26. Petitioner contends that "[e]very claim's scope either includes or is limited to an unidentified number of enzymatically active, multiply-modified PH20 polypeptides meeting the sequence identity parameters of the claims," for three reasons:

First, claims 6 and 7 claim "modified PH20 polypeptides" with at least one substitution that *retained* hyaluronidase activity in PH20₁₋₄₄₇

Second, claims 4 and 5 specify modified PH20 polypeptides that include a mutated form of a "contiguous sequence" from human PH20 (SEQ ID NO:7). The common disclosure describes modified PH20 polypeptides that comprise a "contiguous sequence" of human PH20 as being *enzymatically active*. . . .

Third, dependent claims 12-14 define pharmaceutical compositions comprising "a therapeutically active agent," which the common disclosure indicates are compositions that "can contain a *further* therapeutically active agent," and are formulated so that "the PH20 and any other active agent, remain active," meaning the PH20 has hyaluronidase activity.

Id. at 28–31.

⁵ Petitioner uses the term "common disclosure" to refer to the specifications of the '345 patent and the '731 application. *See* Pet. 6 n.6. Petitioner states, and Patent Owner does not dispute, that these two specifications "are substantively identical." *Id.*

b) Patent Owner's Response

Patent Owner asserts that it “does not dispute that the claims encompass PH20s with hyaluronidase activity” but “does contend that the claims are defined by structure only, and encompass *both* enzymatically active and enzymatically inactive PH20s.” PO Resp. 32. Patent Owner states “[t]here is no language in the claim requiring the polypeptide to perform a specific function. . . . The parties do not dispute this.” *Id.* (citing Ex. 2076, 172:21–173:9).

Regarding the definitional passage in the Specification, Patent Owner asserts that “the definition of ‘modified PH2) polypeptide’ is limited to the first sentence.” PO Resp. 34. According to Patent Owner,

[t]he definition provided in the first sentence is also consistent with the usage of the term “modified PH20 polypeptide” throughout the specification, which describes the invention by reference to amino acid sequences, regardless of function or whether the modified PH20s are “active” or “inactive.”

If Petitioner were correct and the second sentence also is part of the definition, then the term “modified PH20 polypeptide” as used in the specification and claims would be limited to enzymatically active PH20 polypeptides, which Petitioner argues must have at least 40% activity. But that interpretation contradicts how the term is used in the specification. The specification repeatedly uses the term “modified PH20 polypeptide” to refer to inactive polypeptides.

Id. at 35; *see also id.* at 37 (citing Ex. 1001, 74:1–3, 74:10–12; 77:50–52, 117:35–39, 117:54–118:40, 118:51–58, 193:29–33, 255:27–56; Ex. 2068 ¶¶ 266–268). Patent Owner asserts:

Petitioner's expert, [Dr.] Hecht, admitted that he did not even ‘consider this [disclosure]’ referring to inactive modified PH20 polypeptides in forming his opinion ‘because [it] seemed

contradictory to his ‘interpretation’ that the claims require activity. . . . But a proper claim construction analysis involves examining how the term is used throughout the entire specification, without disregarding sections of the specification that may conflict with a preconceived interpretation.

Id. at 37–38 (citing Ex. 2076, 189:1–192:16).

Patent Owner concludes that “the patent makes clear that ‘modified PH20 polypeptide’ encompasses both active and inactive polypeptides” and that “inactive PH20s do have a credible utility” as antigens in contraception vaccines. *Id.* at 38–39, 40 (citing Ex. 2068 ¶ 392; Ex. 2074; Ex. 2072).

c) Petitioner’s Reply

Petitioner responds that:

The claim construction dispute is narrow: are the claims limited to “properly folded” modified PH20 polypeptides (*i.e.*, a “**structurally and functionally distinct genus**” of PH20s), or do they **also** include 10⁴³+ other PH20 sequences in the claim parameter’s “sequence space” (*i.e.*, a genus outweighing Earth)?

Reply 1 (citing PO Resp. 31–32; Ex. 2068 ¶ 33; Ex. 2070 ¶¶ 51, 58, 128 n.12; Ex. 1130, 62:13–23; 68:6–69:5; Ex. 1133 ¶¶ 77–80, 44–46, 55–58, 92–101; Reply § III.C.1(b); Ex. 1003 ¶¶ 141–42). Petitioner asserts that a POSA would read “the claims **as a whole** as directed to properly folded PH20s, which either encompass or require activity.” *Id.* at 3 (citing Pet. 28–31; Ex. 1026, 90:33–34; Ex. 1003 ¶¶ 146–152; Ex. 1133 ¶¶ 105–110; *TIP Sys., LLC v. Phillips & Brooks/Gladwin, Inc.*, 529 F.3d 1364, 1375 (Fed. Cir. 2008)).

Petitioner cites the testimony of Patent Owner’s expert Dr. Simpson, where she testified that “‘PH20’ **provides context** to ‘modified PH20 polypeptide.’” *Id.* at 2 (citing Ex. 1130, 57:9–58:4; *Bicon, Inc. v. Straumann*

Co., 441 F.3d 945, 952 (Fed. Cir. 2006)). Petitioner also cites the testimony of Patent Owner’s expert Dr. Petsko, stating: “***POSAs think of PH20 as a folded protein***,” and expert Dr. Simpson, stating that the Specification’s definition of PH20 refers to properly folded and enzymatically active proteins. *Id.* at 2–3 (citing Ex. 2070 ¶ 345; Ex. 1026, 50:31–32; Ex. 1130, 60:14–61:12, 61:19–23; Ex. 2070 ¶ 128 n.12; Ex. 1133 ¶¶ 92–104; Ex. 1133 ¶¶ 87–89; Ex. 1131, 32:8–37:20, 146:14–148:8; Ex. 2068 ¶¶ 283, 376; Ex. 2070 ¶¶ 50, 434).

d) Patent Owner’s Sur-Reply

Patent Owner asserts that the “claimed modified PH20 polypeptides are defined by their structure—an M313 mutation and no more than 20 total modifications within the hyaluronidase domain—not by their function,” and that “Petitioner’s expert, Dr. Kelsoe, admitted as much” in the following testimony: “‘Q So you don’t read claim 1 to require any hyaluronidase activity, right? **A. To the best of my understanding, no.**’” Sur-reply 1 (quoting Ex. 2302, 41:6–12; 48:1–4). Patent Owner asserts that “Petitioner’s expert, Dr. Hecht, admitted at deposition that the term ‘modified PH20 polypeptide’ is used in the specification to refer to both active and inactive PH20s.” *Id.* at 1–2 (citing Ex. 2076, 189:1–194:12, 172:21–173:17, 213:1–215:19, 221:8–223:22).

According to Patent Owner, Petitioner’s argument that proper folding is required for a “modified PH20 polypeptide” conflicts with the Specification:

Petitioner’s new “properly folded” construction is premised on the term “PH20” in the phrase “modified PH20 polypeptide.” Reply, 1-3; EX2301, 200:9-16. Petitioner’s construction is incorrect because the term “modified PH20

polypeptide” is itself a defined term. Petitioner improperly imports the definition of constituent term “PH20” into the separately defined “modified PH20 polypeptide.”

Id. at 2.

e) Evidence and Analysis

“The construction of claims is simply a way of elaborating the normally terse claim language in order to understand and explain, but not to change, the scope of the claims.” *Embrex, Inc. v. Serv. Eng’g Corp.*, 216 F.3d 1343, 1347 (Fed. Cir. 2000).

We first turn to the intrinsic evidence because the specification “is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1314 (Fed. Cir. 2005) (en banc). “[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.” *Id.* at 1316.

[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).

(1) Intrinsic evidence

Our analysis begins with the claims and Specification of the ’345 patent. In relevant part, claim 1 recites a “modified PH20 polypeptide.” The ’345 patent states: “PH20 refers to a type of

hyaluronidase that occurs in sperm and is neutral-active.”⁶ Ex. 1001, 44:20–21; *cf. id.* at 67:2–6. The ’345 patent further explains that “[r]eference to PH20 includes precursor PH20 polypeptides and mature PH20 polypeptides (such as those in which a signal sequence has been removed), truncated forms thereof that have activity, and includes allelic variants and species variants, variants encoded by splice variants, and other variants.” *Id.* at 44:37–42. The ’345 patent states that “PH20 polypeptides also include those that contain chemical or posttranslational modifications and those that do not contain chemical or posttranslational modifications.” *Id.* at 44:46–49.

The ’345 patent has a detailed “Definitions” section (*id.* at 43:19–66:67) which states the following regarding the term “modified PH20 polypeptide”:

As used herein, “modified PH20 polypeptide” or “variant PH20 polypeptide” 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

⁶ The Specification defines “neutral active” as “the ability of a PH20 polypeptide to enzymatically catalyze the cleavage of hyaluronic acid at neutral pH, such as at a pH between or about between pH 6.0 to pH 7.8.” Ex. 1001, 49:4–7.

any one or more other modifications, in addition to at least one amino acid replacement as described herein.

Id. at 47:3–18 (emphasis added).

The “Definitions” section further addresses other terms that relate to “modified PH20 polypeptide.” In particular, the “Definitions” section states:

As used herein, activity refers to a functional activity or activities of a polypeptide or portion thereof associated with a full-length (complete) protein. Functional activities include, but are not limited to, biological activity, catalytic or enzymatic activity, antigenicity (ability to bind or compete with a polypeptide for binding to an anti-polypeptide antibody), immunogenicity, ability to form multimers, and the ability to specifically bind to a receptor or ligand for the polypeptide.

Id. at 48:41–49. The term “hyaluronidase activity” is more narrowly defined such that it specifically “refers to the ability to enzymatically catalyze the cleavage of hyaluronic acid.” *Id.* at 48:50–51.

Other portions of the “Definitions” section also refer to the activity of the protein. For example, in its definition of a “denaturing condition,” the ’345 patent states that “a condition is denaturing if the activity of the protein is reduced by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or more in the presence of the condition than in its absence.” *Id.* at 49:48–51. The “Definitions” section also states that

“increased stability” with reference to a modified PH20 hyaluronidase means that, in the presence of the same denaturing or denaturation condition(s) (e.g., presence of a denaturing excipient such as a preservative), the modified PH20 hyaluronidase exhibits **greater hyaluronidase activity** compared to an unmodified PH20 hyaluronidase not containing the amino acid replacement(s).

Id. at 51:6–12 (emphasis added).

The “Definitions” section defines both “phenophile” and a “thermophile” as proteins that “exhibit[] at least or about at least 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 250%, 300%, 400%, 500%, 600%, 700%, 800%, 900%, 1000% or more of the activity of the unmodified or reference PH20 hyaluronidase” in the presence of a phenolic preservative or under elevated temperatures, respectively. *Id.* at 53:24–55. The “Definitions” section also states that “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 of the resulting molecule.” *Id.* at 56:12–16. The “Definitions” section explains, regarding “substantially pure,” that “further purification would not detectably alter the physical and chemical properties, such as enzymatic and biological activities, of the substance.” *Id.* at 60:17–25.

The “Definitions” section also states that “a conjugate refers to a modified PH20 polypeptide linked directly or indirectly to one or more other polypeptides or chemical moieties . . . whereby at least one modified PH20 polypeptide is linked, directly or indirectly to another polypeptide or chemical moiety *so long as the conjugate retains hyaluronidase activity.*” *Id.* at 61:60–67 (emphasis added). The “Definitions” section further states:

As used herein, a co-formulation refers to a composition containing two or more active or pharmaceutical or therapeutic agents and one or more excipients. For example, a co-formulation of a fast-acting insulin and a hyaluronan degrading enzyme contains a fast-acting insulin, a hyaluronan degrading enzyme, and one or more excipients.

Id. at 62:37–42.

After the “Definitions” section, in a different section discussing the PH20 polypeptide, the ’345 patent states: “Due to the role of PH20 in

fertilization, PH20 can be used as an antigen for immunocontraception.” *Id.* at 71:16–18. The ’345 patent also states that “provided are modified PH20 polypeptides that are inactive, and that can be used, for example, as antigens in contraception vaccines.” *Id.* at 74:11–13.

In sum, considering the intrinsic evidence as a whole, the Specification of the ’345 patent supports an understanding that some activity is required for a polypeptide to be a “modified PH20 polypeptide,” and it is the enzymatic activity of hyaluronidase specifically that is the most frequently identified activity recited in the Definitions section of the ’345 patent. Indeed, the definitions of “PH20” and “modified PH20 polypeptide” both require hyaluronidase activity. *See* Ex. 1001, 44:20–21, 49:4–7 (“PH20 refers to a type of hyaluronidase that . . . is neutral-active” and “neutral active refers to the ability . . . to enzymatically catalyze the cleavage of hyaluronic acid at neutral pH”); 47:8–11 (“A modified PH20 polypeptide can have up to 150 amino acid replacements so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity.”). Similar language is used later in the definition of a “conjugate” to explain that even when the modified PH20 polypeptide is linked to another polypeptide or chemical moiety it “retains hyaluronidase activity.” *Id.* at 61:60–67. In contrast, the discussion regarding the potential use of “modified PH20 polypeptides that are inactive” as antigens in contraception vaccines appears only in non-definitional sections of the ’345 patent. *Id.* at 71:16–18, 74:11–13. Accordingly, we find that this disclosure does not modify the definition’s explicit requirement that the claimed “modified PH20 polypeptide” exhibit hyaluronidase activity. *Id.* at 47:3–11.

(2) *Extrinsic evidence*

Both Petitioner and Patent Owner cite prior art references replete with disclosures demonstrating that PH20 is a polypeptide with hyaluronidase activity. We cite a selection of this evidence below.

“PH20 refers to a type of hyaluronidase that occurs in sperm and is neutral-active.” Ex. 1007, 10:31–32; *cf.* Ex. 1011, 810 (“PH-20 hyaluronidase from human sperm”); Ex. 1013, 429–430 (“expression of the PH20 enzyme . . . demonstrated the hyaluronidase activity associated with the cell membrane”); Ex. 1021, 30310 (“glycosylphosphatidylinositol-anchored sperm hyaluronidase PH-20”); Ex. 1024, 84 (“Recombinant human PH20 (rHuPH20) is a soluble recombinant form of human PH20 that can be used to depolymerize hyaluronan.”); Ex. 2086, 171 (“While plasma membrane PH-20 shows hyaluronidase activity only at neutral pH, inner acrosomal membrane PH-20 was found to be active both at neutral and acidic pH.”); Ex. 2100, 542 (“macaque sperm surface protein PH-20 is a hyaluronidase”); Ex. 2107, 151 (“PH-20 is a sperm plasma-membrane protein that has been shown to have hyaluronidase activity in several mammalian species including nonhuman primates.”); Ex. 2108, 80 (“PH-20 has a hyaluronidase activity that is required for sperm penetration through the cumulus cell layer that surrounds the oocyte.”).

The parties cite a subset of references showing that PH20, as well as being a hyaluronidase, has also been considered for use as an antigen in contraceptive vaccines. “[F]ormulations of recombinant mouse PH20 (mPH20, SPAM-1) were therefore produced as part of an effort to develop immunocontraceptive vaccines for use as biological control agents for

mice.” Ex. 1019, 331; *cf.* Ex. 1022, 1146 (“immunization of male guinea pigs with PH-20 reproducibly leads to infertility”); Ex. 1023, 1133 (same).

Turning to the expert testimony, Petitioner’s experts Dr. Hecht and Dr. Naismith testify that a POSA reading the Specification would understand the challenged claims to encompass enzymatically active mutants, i.e., modified PH20 polypeptides with hyaluronidase activity. *See, e.g.*, Ex. 1003 ¶¶ 149, 152 (interpreting claims 1, 6, and 7 as defining modified PH20 polypeptides that exhibit hyaluronidase activity); Ex. 1133 ¶ 100 (agreeing with Dr. Hecht).⁷ When asked on cross-examination, “How are you drawing the line between what’s a definition and what’s not a definition [in the Specification]?”, Petitioner’s expert Dr. Hecht answered:

Because the first sentence that you just read is, “as used herein,” okay, a modified PH20 polypeptide, okay. And then it continues saying a modified PH20 – that it’s – it’s now giving us more detail and saying it can have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity.

⁷ Another of Petitioner’s experts, Dr. Kelsoe, was asked in his deposition “if claim 1 [of a related patent] requires the modified PH20 polypeptides to contain any hyaluronidase activity?” and he replied, “It does not. It simply claims 95 percent identity.” Ex. 2302, 41:6–12. However, unlike Petitioner’s other experts, Dr. Kelsoe was not asked to consider a POSA’s understanding of the definitions provided in the Specification. *See* Ex. 1134 ¶¶ 15–16 (stating that he was instructed to apply an understanding of “modified PH20 polypeptides” that did not require activity and that based on the “understanding of the term provided by counsel” he assumed it includes both properly folded and misfolded, inactive polypeptides).

Ex. 2076, 181:9–18. When a further question asked, “the specification, in fact, uses the term[] modified PH20 polypeptides to refer to inactives?”, Dr. Hecht recognized a distinction in the ’345 patent and stated:

I think it seems to contradict itself because it seems elsewhere to define it, as I read earlier. And then in the paragraph you read, it seems to violate that definition.

It says “as used herein” on my declaration, page 70, which appears, to me, to be a definition of how it is used herein and so – which says, “so long as the resulting polypeptides exhibit hyaluronidase activity.” That seemed a pretty strong statement to me in terms of how it is used herein whereas the paragraph you read seems to contradict that.

Id. at 191:18–192:11.

Patent Owner’s expert Dr. Simpson disagrees with Dr. Hecht.⁸ Dr. Simpson states, “[i]n my opinion, a POSA would have understood the claims do not require hyaluronidase enzymatic activity, let alone $\geq 40\%$ hyaluronidase enzymatic activity.” Ex. 2068 ¶ 256. Dr. Simpson relies on the fact that claim 1 does not expressly reference hyaluronidase activity and on statements in the ’345 patent discussing “inactive mutants” (which do not appear the “Definitions” section of the Specification) to support her position that “a POSA would understand that modified PH20 polypeptides with a M313A, M313H, M313K, M313L, M313P, M313R, or M313Y substitution

⁸ We note that Patent Owner’s experts Dr. Moon and Dr. Petsko did not independently analyze claim construction. Dr. Moon stated, “I understand that PH20 is a sperm-associated protein having hyaluronidase activity and is involved in fertilization in mammals.” Ex. 2074 ¶ 38. Dr. Petsko stated, “I have not been asked to opine regarding claim construction and do not do so in this declaration.” Ex. 2070 ¶ 246.

are not always active.” *Id.* ¶¶ 261, 264, 266–268, 272. However, in deposition, Dr. Simpson acknowledged that in the Specification “PH20 is defined as a type of hyaluronidase that occurs in sperm and is neutral-active.” Ex. 1130, 62:2–3.

Petitioner’s expert Dr. Naismith states, “Dr. Simpson is reading the phrase ‘modified PH20 polypeptide’ to have the identical meaning as the phrase ‘modified polypeptide.’ This reading effectively strikes the word ‘PH20’ out of the claims.” Ex. 1133 ¶ 103. Dr. Naismith states, “PH20 is expressly defined in the common disclosure to have a form a POSA would understand is folded.” *Id.* ¶ 104. Dr. Naismith states that “the defined meaning of PH20 would have led a POSA to conclude that ‘modified PH20 polypeptides’ are those that (i) contain at least one amino acid modification and (ii) are properly folded proteins, as that is the form that the PH20 protein exists in on the surface of sperm cells.” *Id.* Dr. Naismith stated in deposition that “when I use just PH20 that conveys to me, as it does in the common disclosure, that is a folded active form of the protein.” Ex. 2301, 64:20–22.

f) Analysis

The instant claims differ from many of the claim sets previously considered by the Federal Circuit because they do not expressly recite a function for the polypeptide. *See, e.g., In re Kubin*, 561 F.3d 1351, 1353 (Fed. Cir. 2009) (“wherein the polypeptide binds CD48”); *Bayer Healthcare LLC v. Baxalta Inc.*, 989 F.3d 964, 971 (Fed. Cir. 2021) (“a functional factor VIII polypeptide”); *Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1072 (Fed. Cir. 2005) (“[a]n isolated polypeptide having DNA polymerase activity”).

However, as discussed above, the definition of the term “PH20” in the ’345 patent states that “PH20 refers to a type of hyaluronidase that occurs in sperm and is neutral-active”—meaning that it is understood to have activity at neutral pH. Ex. 1001, 44:20–21. Further, the second sentence of the definition of “modified PH20 polypeptide” in the ’345 patent allows mutations in the PH20 polypeptide “*so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity.*” *Id.* at 47:3–11 (emphasis added). Thus, we agree with Petitioner that the term, interpreted in light of the Specification, requires at least some hyaluronidase activity.

We disagree with Patent Owner’s argument that Petitioner’s reliance on the “PH20” definition “improperly imports the definition of constituent term ‘PH20’ into the separately defined ‘modified PH20 polypeptide.’” Sur-reply 2. Here, the “modified PH20 polypeptide” definition follows and builds upon the “PH20” definition. Moreover, the fact that both definitions specifically refer to the protein’s hyaluronidase activity supports Petitioner’s position that the claimed “modified PH20 polypeptide” must exhibit such activity.

Patent Owner’s argument that the claims should not be read to exclude the use of enzymatically-inactive peptides as contraceptives (the only other possible utility recited in the ’345 patent) is unavailing. PO Resp. 39–40; *cf.* Ex. 1001, 117:35–39. First, “[t]he fact that a patent asserts that an invention achieves several objectives does not require that each of the claims be construed as limited to structures that are capable of achieving all of the objectives.” *Phillips*, 415 F.3d at 1327 (citing *Liebel–Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 908 (Fed. Cir. 2004)). Second, unlike the definitions of “PH20” and “modified PH20 polypeptide”

in the “Definitions” section of the Specification, the passages describing possible contraceptive use do not contain any characteristics suggesting they are definitional in nature. *See Alnylam v. Moderna*, 138 F.4th 1326, 1333 (Fed. Cir. 2025) (enumerating “characteristics” of definitions such as the fact that the text appears in the “Definitions” section, sets the term off in quotation marks, and uses phrases like “refer to” that indicate that specification language is definitional in nature). Accordingly, the statement that “[a]lso provided are modified PH20 polypeptides that are inactive, and that can be used, for example, as antigens in contraception vaccines” does not redefine the term, nor otherwise void the definitional language in the Specification stating that a “modified PH20 polypeptide can have up to 150 amino acid replacements, *so long as* the resulting modified PH20 polypeptide *exhibits hyaluronidase activity*.” Ex. 1001, 74:10–12, 47:3–11 (emphasis added).

The extrinsic evidence also supports that “PH20” is understood by POSAs to refer to the protein’s hyaluronidase activity, and not just its structure. Indeed, virtually every publication cited by both parties reference the enzyme’s hyaluronidase activity. And while Patent Owner’s expert Dr. Simpson suggests that the term “PH20” does not impose any particular function on the polypeptide, Dr. Simpson also acknowledged that in the Specification “PH20 is defined as a type of hyaluronidase that occurs in sperm and is neutral-active.” Ex. 1130, 62:2–3.

We agree with Dr. Naismith that excluding any function from the term “PH20” “effectively strikes the word ‘PH20’ out of the claims.” Ex. 1133 ¶ 103. That is, by electing to include the defined term “PH20” in the claims of the ’345 patent, Patent Owner chose to inform POSAs that the claimed

polypeptides would have the properties that the '345 patent expressly defines as being part of a “PH20” polypeptide, which include hyaluronidase activity. Just as the phrase “steel baffles” in *Phillips* required that “the baffles must be made of steel,” the term “PH20 polypeptide” requires a compound that is both a polypeptide and that has the activity conferred by the term “PH20.” *See Phillips*, 415 F.3d at 1324.

For these reasons, we reject Patent Owner’s position that the claims recite a modified PH20 polypeptide in purely structural terms, and construe “modified PH20 polypeptide” to require a polypeptide that has hyaluronidase activity.

g) Conclusion

For the reasons discussed above, we construe the claim term “hyaluronidase domain” as meaning a “region of about 340 amino acids in length that corresponds to amino acid residues 38–374 of the precursor human PH20 sequence set forth in SEQ ID NO:6” and the term “modified PH20 polypeptide” to require a polypeptide that has hyaluronidase activity.

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

C. Ground I - Written Description

1. 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) (quoting *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc)). “[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 (alteration in original).

We analyze the asserted grounds of unpatentability in accordance with these principles to determine whether Petitioner has met its burden to establish by a preponderance of the evidence that the claims fail to comply with the written description requirement.

2. *Petitioner’s Position*

Petitioner asserts that “the ’345 Patent claims ***at least*** . . . 10⁴³+ different modified PH20 polypeptides comprising a mutated hyaluronidase domain,” “[b]ut the common disclosure describes ***no single*** modified PH20 polypeptide (actual or prophetic) that combines (i) a position 313 substitution ***plus*** (ii) one or more insertions, deletions, or substitutions restricted to the ‘hyaluronidase domain’ (much less demonstrates possession of ***all*** of them).” Pet. 40. Petitioner asserts that “[t]he claim language permits any combination of modifications (up to 15 or 20 total), including one substitution at 313 and any modification at 336 other positions within

the ‘hyaluronidase domain,’” while also “permit[ting] **additional** variability outside the mutated ‘hyaluronidase domain,’” including use of truncated and non-human PH20 sequences. *Id.* at 41–42, 46 (citing Ex. 1003 ¶¶ 171–172), 50–52 (citing, e.g., Ex. 1001, 44:37–46, 49:4–8; Ex. 1003 ¶¶ 131, 133; Ex 1004 ¶¶ 177, 182, 184, Appendix J-1). Petitioner asserts that “the common disclosure provides **no insights** into the three-dimensional structure(s) of **any** multiply-modified PH20 protein. Instead, it only identifies single amino acid changes and reports their empirically observed effects on hyaluronidase activity—with many being from the **prior art.**” *Id.* at 43 (citing Ex. 1001, 67:1–70:67).

Petitioner asserts that “there are **no examples** (prophetic or actual) of modified PH20 polypeptides with multiple modifications **restricted within** positions 3-339 of SEQ ID NO:7, much less one with a position 313 replacement.” *Id.* at 45 (citing Ex 1003 ¶¶ 154, 167, 180–81 112). Instead, “[t]he common disclosure makes only passing reference to a conserved ‘hyaluronidase domain’ in its discussion of the prior art, and attaches no particular significance to it for making ‘modified PH20 polypeptides.’” *Id.* (citing Ex. 1001, 3:60–4:17, 68:14–57, 79:16-80:3, Table 8; Ex. 1003 ¶¶ 155–58).

Petitioner further asserts that “the common disclosure **does not identify which** of the $10^{43}+$ different PH20 polypeptides being claimed have **either** of these two alleged utilities” (i.e., hyaluronidase or contraceptive utility), and instead “only provides a ‘research plan’ that instructs skilled artisans ‘to generate a modified PH20 polypeptide containing any one or more of the described mutation, and test each.’” *Id.* at 52–53 (Ex. 1001, 76:57–61; Ex. 1003 ¶¶ 207–09, 211). Petitioner further asserts that the

claims “capture modified PH20 polypeptides with modifications that the common disclosure instructs should not be made” because the positions are less tolerant to change or are required for hyaluronidase activity. *Id.* at 53–54 (citing Ex. 1001, 69:3–13, 78:36–79:11; Ex. 1003 ¶¶ 150, 187–89, 199–200, Appendix A-10).

Petitioner also asserts that “despite acknowledging that extensive C-terminal truncations can render a PH20 polypeptide inactive, the common disclosure describes *no enzymatically active*, modified PH20 polypeptides terminating before position 447” and “thus does not demonstrate possession of any such enzymatically active, truncated, multiply-modified PH20 polypeptides meeting the claim parameters.” *Id.* at 55, 57.

Petitioner additionally asserts that although the “common disclosure reports that a library of ~6,753 single-replacement human PH20₁₋₄₄₇ sequences were made,” “~87% had *less* activity than unmodified PH20₁₋₄₄₇.” *Id.* at 58–59 (citing Ex. 1001, 200:9–14, 133:11–23, 200:29–31; Ex. 1003 ¶¶ 108, 115). Petitioner asserts that the data in the patent is “not analyzed” but rather “is simply presented” with no attempt “to assess the impact of any single substitution on the protein’s structure, much less extrapolate these results to PH20 polypeptides with multiple substitutions.” *Id.* at 59–60 (citing Ex. 1003 ¶¶ 179–180, 184). According to Petitioner, “[t]he unexplained data by itself reveals no trends or correlations even for single-replacement human PH20₁₋₄₄₇ polypeptides.” *Id.* at 61.

Petitioner further asserts that the ’345 patent “describes *no* enzymatically active multiply-modified PH20 polypeptides—it only presents *the idea* of making them . . . [and] simply draws mathematical boundaries around immense numbers of possible PH20 polypeptides or list[s] optional

substitutions for mutants.” *Id.* at 63–64. Petitioner asserts that the ’345 patent “proposes a prophetic research plan requiring ‘iterative’ make-and-test experiments that ***might discover*** enzymatically active, multiply-modified PH20 polypeptides.” *Id.* (citing Ex. 1001, 140:44–56, 41:8–15, 133:11–45, 133:62–67, 134:3–135:43, 138:45–58, 136:4–140:43; Ex. 1003 ¶ 207).

Petitioner further asserts that the common disclosure does not identify a structure-function relationship for useful multiply-modified PH20 polypeptides, including because it

does not identify any structural features shared by the ~2,500 singly-substituted “active mutant” PH20₁₋₄₄₇ polypeptides (or by the ~3,400 putative “inactive mutants”). It also does not identify the effect of any individual replacement on any (i) domain structure, (ii) structural motif(s), or (iii) even the local secondary structure at the site of the substitution. Nor does it identify how any such (possible) structural change(s) is/are responsible for measured changes in hyaluronidase activity. Instead, it simply lists single replacements to random amino acids that yielded “active mutants” or putative “inactive mutants.” And it says nothing about ~830 single mutants that were not classified.

Id. at 67 (citing Ex. 1003 ¶¶ 179–180, 184; Ex. 1001, 232:38–67, Tables 9, 10).

Petitioner further asserts that the common disclosure lacks a representative number of multiply-modified PH20 polypeptides, contending that “[t]he ~2,500 ‘active mutant’ ***singly***-substituted PH20₁₋₄₄₇ polypeptides in the common disclosure are not representative of the unknown number of enzymatically active ***multiply***-modified PH20 polypeptides being claimed.” *Id.* at 69 (citing Ex. 1003 ¶¶ 62, 184, 197). According to Petitioner,

The examples are restricted to *one type of change* (a single amino acid replacement) in *one type of PH20 polypeptide* (SEQ ID NO: 3). By contrast, the claims encompass multiply modified mutants with myriad structures within the “hyaluronidase domain” in addition to one replacement at position 313. Consequently, a skilled artisan would not have viewed the examples of single amino acid replacements in PH20₁₋₄₄₇ in the common disclosure as being *representative* of the diversity of the genera of multiply-modified PH20 polypeptides being claimed.

Id. at 72 (citing Ex. 1003 ¶¶ 62, 107, 126, 139, 184, 195, 107).

Petitioner asserts that the remaining challenged claims in the ’345 patent lack written description support for the same or similar reasons. *See id.* at 41, 72–73.

3. *Patent Owner’s Response*

Patent Owner asserts that “Petitioner uses the math of permutations like a parlor trick, focusing on pure numbers, to distract from the fundamental fact that the scope of the claims is confined to the M313 variants and subvariants with up to 19 modifications in the hyaluronidase domain.” PO Resp. 4. Patent Owner asserts:

Record evidence in this case demonstrates that the patent’s specification describes both a representative number of species *and* common structural features of the narrow set of claimed modified PH20 variants such that POSAs could “‘visualize or recognize’ the members of the genus,” under either the Board’s preliminary construction or Patentee’s proposed construction. Thus, the specification would have conveyed to POSAs that the inventors indeed had possession of the full scope of subvariant polypeptides as of December 28, 2012.

Id. at 44.

Patent Owner asserts that “[t]he specification describes and characterizes the common structural features of M313 variants, including the variants recited in claim 6 (M313A, M313G, M313H, M313K, M313P, M313R, M313T, and M313Y), and their subvariants containing no more than 20 total modifications in the hyaluronidase domain.” *Id.* at 45. Patent Owner asserts that POSAs “would have understood the claimed PH20s exhibit the same mechanism of action and share the same characteristic PH20 alpha-beta barrel tertiary structure, including a common active site and the same key catalytic residues, absent changes of the type the patent identifies as inactivating.” *Id.* at 45–46. Patent Owner asserts that

[Dr.] Petsko generated homology models of multiply modified PH20s identified in the patent with the M313K mutation, including chimpanzee PH20, gibbon PH20, orangutan PH20. EX2070, ¶¶57, 420-439. The modified chimpanzee PH20 contains six modifications when compared to SEQ ID NO: 3. Similarly, the modified orangutan and gibbon PH20s differ at 14 and 17 positions compared to SEQ ID NO: 3, respectively and the modified gibbon PH20 has 21 changes as compared to SEQ ID NO: 44 (which, as [Dr.] Simpson and [Dr.] Petsko explain, the ’457 publication^[9] teaches is active).

Id. at 45–46. Patent Owner contends that “these multiply-mutated M313K subvariants all share a common tertiary alpha-beta barrel structure.” *Id.* at 46.

Patent Owner points out that the Specification identifies specific amino acids necessary for enzymatic activity, amino acids involved in

⁹ The “’457 publication” is U.S. Patent Application Publication No. 2010/0143457 A1 to Wei et al., published June 10, 2010 (Ex. 2165). It is referenced in the ’345 patent. *See, e.g.*, Ex. 1001, 68:23–32, 69:21–29, 78:64–79:5, 72:32–38, 134:42–45.

disulfide bridges, and sites involved in substrate binding. *Id.* at 48–49 (citing Ex. 1001, 69:4–10, 68:38–50, 68:58–65; Ex. 2068 ¶ 303). Patent Owner asserts that “because the specification discloses the structural features necessary for activity, POSAs would have understood them as common to active M313 variants and subvariants (further would have been able to reasonably and reliably distinguish inactive PH20s by changes of the kind identified in the patent as destroying them).” *Id.* at 49.

Patent Owner asserts:

Through the comprehensive mutagenesis data (Tables 9-10), the patent shows, for each of the 447 positions in SEQ ID NO: 3, the tolerance of each position to substitution as it relates to enzymatic activity. This allows POSAs to distinguish between positions that are (1) critical to activity, (2) generally intolerant in that they permit only very limited substitution, (3) generally tolerant in that they permit a broad range of substitutions.

Id. at 50–1 (citing Ex. 2070 ¶¶ 44–56, 263–388; Ex. 2068 ¶¶ 305–306).

Patent Owner asserts that “[t]hese data collectively would have provided more than sufficient blaze marks for POSAs to visualize or recognize all the members of the claimed genus, reliably distinguishing actives from inactives.” *Id.* at 52–53 (citing Ex. 2068 ¶ 311). Patent Owner asserts that unlike the situations in *Ariad* and *AbbVie Deutschland GmbH v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300 (Fed. Cir. 2014),

[a] “later actually invented” protein does not fall into the claims merely by showing hyaluronidase activity; it would have to fall within the narrow structural scope of the claims—the M313 mutation and up to 20 total modifications in the hyaluronidase domain—to be covered. And, as the inventors identified by sequence and structure-function mapping the full scope of the narrow set of claimed M313 variants and subvariants, they in fact possessed the full scope of the genus.

Id. at 53–54.

Patent Owner asserts that “[Dr.] Petsko’s and [Dr.] Simpson[’s] analyses show that in fact the claimed subvariants are structurally homogenous. And the large number of inactivating mutations are not evidence of unpredictability.” *Id.* at 57 (citing Ex. 2068 ¶¶ 379–380). Patent Owner asserts that “the patent solves this problem; the inventors performed the work to identify those positions amenable to substitution. POSAs with the patent in hand can identify active singly and multiply modified subvariants.” *Id.* (citing Ex. 2070 ¶¶ 343–365; Ex. 2068 ¶¶ 316–323).

Patent Owner asserts, as to C-terminal truncations, that the ’345 patent provides data

showing the effect that serial single amino acid C-terminal truncations had on activity—truncations that run ***from position 465 in the mature sequence all the way down to 430***. In other words, the ’457 publication [referenced in the Specification of the ’345 patent] provides activity data [for all of the] modified PH20 polypeptides terminating well before position 447.

As Drs. Simpson and Petsko further explain, POSAs would have reasonably known based on [the] ’457 publication’s results what the activity would be for PH20s that terminate at each position recited in claims 4–5 (*i.e.*, positions 430–465).

Id. at 58–59 (citing Ex. 2068 ¶¶ 324–335; Ex. 2070 ¶¶ 218–230).

Patent Owner asserts, as to multiply-modified polypeptides, that “POSAs would have expected the resulting multiply modified PH20 polypeptide to be active because the ’457 publication teaches that the multiply modified proteins (without the modification at position 313) were

active.” *Id.* at 61 (citing Ex. 2068 ¶¶ 338–339; Ex. 2070 ¶¶ 214–215).

Patent Owner asserts that

the genus of the claims here contains structurally homogeneous modified PH20s. The claims are thus not directed to a structurally diverse genus, as in *AbbVie*, but to M313 variants and their sub-variants with no more than 19 additional modifications in the hyaluronidase domain. Moreover, the working examples comprehensively characterize the structure-function of PH20 (SEQ ID NO: 3) through the mutagenesis data.

Id. at 61–62.

4. *Petitioner’s Reply*

Petitioner responds that its

description of the claims’ ‘sequence space’^[10] is not a ‘parlor trick’—Halozyme’s experts **confirmed** it ($\sim 10^{43}$ to $\sim 10^{56}$ sequences). Also undisputed is that the claims permit (i) modifications at any non-recited position (including up to 19 modifications anywhere in the ‘hyaluronidase domain’), (ii) additions/deletions, and (iii) substitutions to any of 19 other amino acids.

Reply 3–4 (citing Ex. 1003 ¶¶ 126, 135, 139–141, 190–192; Ex. 1004 ¶¶ 175–176; Ex. 1130, 90:1–16, 90:25–91:5, 91:18–92:1; Ex. 1131, 58:18–59:19, 61:6–8, 65:18–66:3; Ex. 2070 ¶¶ 235–236; Ex. 1026, 53:1–7, 68:18–34; Ex. 1130, 90:25–91:5; Ex. 1131, 54:24–55:6).

¹⁰ Petitioner and its experts use the term “sequence space” to refer to the size of the potential genus “defined by the sequence identity claim parameters,” *i.e.*, “one required replacement at position 313 and up to 14 or 19 additional changes to positions within hyaluronidase domain corresponding to positions 3 to 339 of SEQ ID: 7.” Ex. 1133 ¶ 48 (citing Ex. 1003 ¶¶ 126–144). We use this term the same way herein.

Petitioner asserts that “[o]nly properly folded PH20s could have a common set of structural features, but the disclosure fails to identify what they are and which of the $10^{43}+$ sequences will fold to have them.” *Id.* at 10. Petitioner asserts that “[a]s a **claim element**, the ‘hyaluronidase domain’ modification simply defines the boundaries of the ‘sequence space’—the possible amino acid sequences within which the claimed PH20 polypeptides must be found.” *Id.* at 11–12 (citing *Ariad*, 598 F.3d at 1349).

Petitioner asserts that Patent Owner

anchors its “common structural feature” arguments on the “ α/β barrel” motif in human PH20. But the disclosure nowhere mentions a “PH20 α/β barrel,” discusses this motif, or portrays it as a common structural feature of any set of modified PH20s. It also does not identify any amino acid sequences for the PH20 α/β barrel motif or its elements. Nor does it reference the “distorted” (α/β) barrel motif in human PH20, explain that it does not contain PH20’s active site, or explain how it differs from the canonical α/β structure.

Id. at 13–14 (citing Ex. 1133 ¶¶ 151–158, 165–170; Ex. 1008, 824–825, 829, 833; Ex. 1006, 6911–6913; Ex. 1033, 1027). Petitioner asserts that a “POSA could not have used knowledge of the **canonical** ‘ α/β barrel’ motif to visualize the **structurally distinct** PH20’s α/β motif because the two **are materially different**.” *Id.* at 15 (citing Ex. 1133 ¶¶ 136–139, 144, 150–152; Ex. 2070 ¶ 52). Petitioner asserts that the “disclosure contains no description of the Hyal-EGF domain or its sequence, despite its essential role in the structure and function of enzymatically active PH20s.” *Id.* at 16 (citing Ex. 1003 ¶¶ 89, 222; Ex. 1133 ¶¶ 185, 187, 190–193, 198).

Petitioner asserts that Patent Owner is wrong that “examples of singly-substituted PH20s ‘provide structure/function correlations POSAs can use to identify the active M313’” for two reasons:

First, effects on PH20 folding and activity from single-substitutions cannot predict effects of *combinations* of changes. . . . Even positions Dr. Petsko labeled “100% tolerated” varied extensively in activity, demonstrating the unpredictability of single substitutions.

Second, listing options and leaving a POSA [to] figur[e] out which combinations yield active PH20s does not describe species of multiply-modified PH20s.

Id. at 19–20 (citing PO Resp. 50; Ex. 1133 ¶¶ 264–269).

Petitioner asserts that Patent Owner “points to 7 alleged ‘examples’ of ‘M313 variants.’ None are described in the disclosure. Three are based on native *primate* sequences with known activity, while four were tested. None of the 7 illustrate the unpredictability of making 5+ changes to a native sequence.” *Id.* at 20–21 (citing PO Resp. 54–55, Ex. 2070 ¶¶ 434–437; Ex. 1133 ¶¶ 114–119; Ex. 1133 ¶¶ 114–119; Ex. 1003 ¶¶ 55–62).

5. *Patent Owner’s Sur-Reply*

Patent Owner responds that

the parties’ primary dispute is whether the patent data could be used to predict the effects of multiple changes in the PH20 sequence such that the POSA could visualize and recognize the claimed genus and practice the full scope of the claims without undue experimentation.

The evidence shows a POSA could do so.

Sur-reply 5. Patent Owner asserts that “an accurate homology model of PH20’s structure, showing the distorted PH20 alpha-beta barrel fold and location of each amino acid in the structure, was available to a POSA” and “[w]ith this information, Dr. Simpson, a PH20 expert, and Dr. Petsko explained how POSAs could, *using the patent’s disclosure*, visualize and recognize the genus.” *Id.* at 5–6 (citing Pet. 11–16, 89, 113–118; Ex. 1004

¶¶ 37, 105–174; Ex. 2077, 176:2–5; Ex. 1130, 97:14–99:10; Ex. 2070 ¶¶ 112–230, 343–439; Ex. 2068 ¶¶ 95–157).

Patent Owner asserts that the “disclosure provides a granular structure/function correlation that teaches, on a position-by-position basis, the effect on activity of substituting different amino acids into every position within the primary structure.” *Id.* at 7. Patent Owner asserts that

Drs. Petsko and Simpson testified that a POSA’s ability to practice the claims was not limited to independent changes at highly tolerated positions. Instead, POSAs could evaluate additional substitutions or “make informed decisions about making several changes close together in the protein using the data in the ’345 patent regarding which substitutions were tested and the results for each, combined with an assessment of the local environment of the residues in question.”

Id. at 10 (citing Ex. 2070 ¶ 324; Ex. 1130, 97:14–98:10, 101:21–102:21, 190:12–195:25). Patent Owner asserts that “[i]t is undisputed that POSAs understand the characteristics of amino acids, such as their charge/size/polarity and propensity to be present in secondary structures, and could evaluate their replacement using routine techniques, including visualizing interactions at the atomic level.” *Id.* at 11 (citing Ex. 2070 ¶¶ 61–67, 343–439). Patent Owner asserts that “with the patent data in hand, the POSA can avoid the billions of PH20s that will be inactivated by changes identified in the patent.” *Id.* at 12.

Patent Owner asserts that “Petitioner, unlike in other § 112 cases, has a complete failure of proof in this regard: it does not point to a single example of a modified PH20 that contradicts what a POSA would predict using the data in the patent.” *Id.* at 14. According to Patent Owner, Petitioner “identifies no prior art or post-filing evidence showing that combining

mutations, including through epistasis or otherwise, renders visualizing, making, and using multiply-mutated PH20s unpredictable in light of the mutagenesis data.” *Id.* at 16. Patent Owner asserts that numerosity is not a basis for invalidity under Section 112 and that a “POSA could ‘reliably predict’ actives and practice the claims without ‘undue’ experimentation.” *Id.* at 17–19.

Patent Owner asserts that the

specification discloses the common structural features based on th[e] primary structure and the related mutagenesis data:

- No more than 20 total modifications in the hyaluronidase domain;
- The M313A, M313G, M313H, M313K, M313P, M313R, M313T, and M313Y mutations;
- And for actives:
 - o A PH20 alpha-beta barrel fold, with known catalytic and binding sites.
 - o Lack of the inactivating changes identified in the disclosure.

Id. at 20–21. Patent Owner asserts that “[t]here is no dispute that there are several highly active representative species disclosed in the specification. Moreover, Petitioner’s new expert [Dr. Naismith] admitted that all actives within the genus fold to the same PH20 alpha-beta barrel fold with catalytic and binding residues properly positioned, just as in the representative species.” *Id.* at 23 (citing Ex. 2301, 213:10–18, 85:19–99:18, 101:11–20, 159:13–25).

6. *Evidence and Analysis*

a) Description in the '345 patent

Our review begins with the claims and Specification of the '345 patent.¹¹ Claim 1 recites a “modified PH20 polypeptide” comprising a substitution at position 313 and up to 20 total modifications in the hyaluronidase domain. *See* Ex. 1001. As set forth above, we interpret the claim to require hyaluronidase activity. *See supra* Section II.B.2.

The Specification generally discloses polypeptides with single point mutations at a variety of positions. *See, e.g.,* Ex. 1001, 12:35–17:2. The Specification identifies several short regions within the PH20 sequence that encode catalytic sites for the PH20 hyaluronidase enzyme in the Peptide 1 and Peptide 3 regions. *Id.* at 71:25–33. Significantly, the Specification details single modifications at a large percent of positions of the mature, soluble PH20 polypeptide with analysis showing whether the modification impacted hyaluronidase activity. *See id.* at 200:25–229:32, 232:28–255:24. The '345 patent also references an earlier patent application publication (the '457 publication), which discloses three double mutations and a single example of a triple mutation in the PH20 hyaluronidase enzyme, which all show hyaluronidase activity. *See* Ex. 2068 ¶¶ 338–340; Ex. 2165, Table 16.

The Specification, however, does not provide any other information regarding PH20 polypeptides with more than one mutation nor does it provide any information regarding the three-dimensional structure of any

¹¹ Because there is no dispute that the specifications of the '345 patent and the '731 application are substantively identical (*see supra* n.5), for expediency we refer herein to disclosures in the Specification of the '345 patent, with the understanding that the same disclosures appear in the “common disclosure.”

PH20 polypeptide or any hyaluronidase enzyme. *See generally* Ex. 1001; Ex. 1003 ¶¶ 112–113, 151 (“there are no ‘double’ or ‘triple’ (or more) mutants that combined sets of single mutations classified as causing both ‘active’ mutants[] and ‘inactive’ mutants or were within particular regions of the PH20 sequence”), 264 (“[T]he PH20 model built with SWISS-MODEL could not reliably assess[] multiple amino acid changes, and would have very low reliability when assessing modified sequences containing 10-20 concurrent changes.”).

b) Expert testimony

The claims define modified PH20 polypeptides comprising a substitution at M313 and that may include up to 19 additional modifications within the hyaluronidase domain (*i.e.*, a total of 20 modifications including the M313 substitution). *See* Ex. 1003 ¶ 126; Ex. 1133 ¶ 46. We accept Petitioner’s undisputed assertion that these modifications result in at least 1.85×10^{56} potential polypeptide sequences within the genus of claim 1 and a minimum of 2.01×10^{43} potential sequences encompassed by the narrowest of the claims. Ex. 1003 ¶¶ 141, 144; Ex. 1004 ¶¶ 175–176; Ex. 1133 ¶ 112; *see also* Ex. 1130, 90:14–16.

(1) *Hyaluronidase activity*

The experts disagree on the impact of the claimed $10^{43}+$ different polypeptide sequences on hyaluronidase activity and enzyme structure.

(a) *Petitioner’s Evidence*

Dr. Hecht states that “the effects on the structure of a PH20 polypeptide that result from making combinations of substitutions or other modifications within the amino acid sequence of the PH20 polypeptide

could not have been accurately predicted by a skilled artisan in the 2011 timeframe using the tools that were available then.” Ex. 1003 ¶ 196.

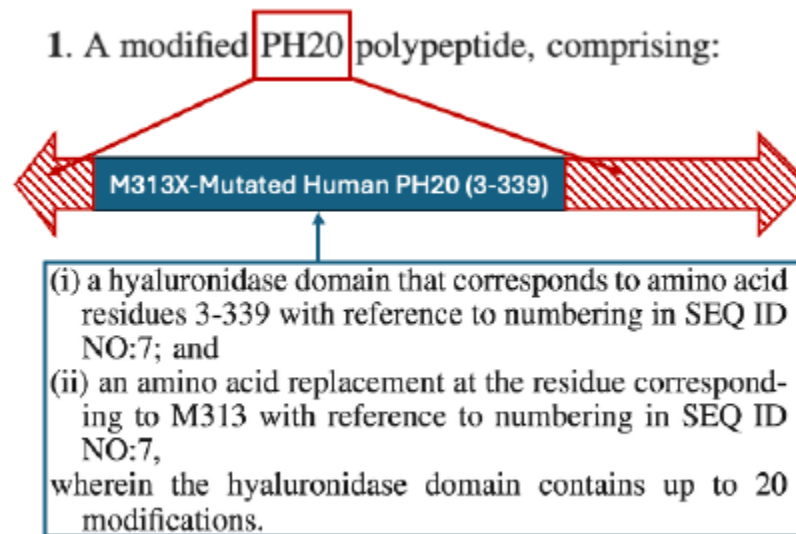
Dr. Naismith concurs with Dr. Hecht, stating that “[t]here is no teaching in the patent or modelling software that would allow sets of . . . combined substitutions that differ by more than around five changes from a known stably folded active PH20 to be predictably active.” Ex. 1133 ¶ 117.

Dr. Naismith also states that other than the “seven examples of PH20 polypeptides with more than one change” identified by Drs. Petsko and Simpson, neither of them “identify or discuss any multiply modified PH20 polypeptide within the claim parameter sequence space in their declarations, particularly ones having 5, 10, 15 or 20 changes.” *Id.* ¶¶ 114, 119.

Dr. Hecht notes that the challenged claims are directed to modified PH20 polypeptides, but the claims “only define a portion of them explicitly,” i.e., the portion comprising positions 3 to 339 of the mature human PH20 protein (SEQ ID NO:7), wherein “this 3-339 human PH20 sequence: (i) must contain one substitution at M313, and (ii) may include up to 19 additional modifications within the 3-339 segment (*i.e.*, a total of 20 modifications including the M313X substitution).” Ex. 1003 ¶ 126.

Dr. Hecht asserts that the remainder of what the claimed modified PH20 polypeptides can be “must at least derive from a ‘PH20’” but is “not defined using parameters for changes to a defined reference sequence.” *Id.* ¶ 127.

Dr. Hecht depicts the parameters in claim 1 with the graphic reproduced below:



Id. ¶ 126. The above graphic purports to contrast the scope of the preamble phrase “PH20” with the parameters recited in claim 1, which relate to only positions 3 to 339 of the mature human PH20 protein (SEQ ID NO:7). Dr. Hecht states that “[j]ust this defined portion [of claim 1] (blue [in the above graphic] captures 1.85×10^{56} distinct amino acid sequences.” *Id.* (citing Ex. 1004 ¶ 176). He further asserts that “[t]he claims do not indicate how much or how little of the starting PH20 sequences must be retained in the ‘modified PH20 polypeptide’ or where the 3-339 human PH20 segment (blue) can or must be positioned relative to the starting PH20 sequences (red) [in the above graphic].” *Id.* ¶ 133.

Dr. Park “used the SWISS-MODEL program to generate a model of the PH20 structure” that “would be very similar if not identical to the model that SWISS-MODEL would have generated in 2011.” Ex. 1004 ¶¶ 156, 161. Dr. Park states “[i]n 2011, a second or third substitution could possibly be considered, but modeling multiple substitutions is more challenging and predictions can quickly become unreliable. This is especially true if the

mutated residues are close to each other, either in sequence or in space, so that they interact with each other.” *Id.* ¶ 168.

Dr. Park cites Zhang (Ex. 1010), which states, “analysis of Hyal1¹² 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 ¶ 97; 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.

¹² Hyal1 (also referred to in the record as “HYAL1” or “Hyal-1”) is one of the five homologous hyaluronidases, which also include PH20, encoded in the human genome. Ex. 1006, 6911. In the 2011–2012 timeframe, Hyal1 was the only human hyaluronidase for which the crystal structure had been solved. Ex. 2068 ¶¶ 119, 134. The parties’ experts agree it would have been the best template for structural modeling and analysis of PH20 that would have been available to a POSA at that time. *See id.*; Ex. 1004 ¶¶ 158, 162 (Dr. Park stating that he used HYAL1 for his structural analysis and he “expected that a PH20 structure modeled on the HYAL1 template would be a reliable PH20 model given the high degree of sequence identity.”); Ex. 1003 ¶ 260 (agreeing).

Ex. 1011, 813; Ex. 1004 ¶ 102. According to Petitioner, Zhang and Arming demonstrate that even conservative mutations may significantly impact the PH20 polypeptide hyaluronidase function. *See* Reply 12–13.

Dr. Naismith states that “[i]f the set of polypeptides being claimed includes any polypeptide with an amino acid sequence that meets only the . . . three claim requirements, it is both enormous and highly heterogeneous.” Ex. 1133 ¶ 40. Dr. Naismith states:

Dr. Petsko’s textbook references Dr. Dobson’s work and provides an illustration of the impact of even a single mutation to the structure and stability of a globular protein (*e.g.*, PH20). In this example, the single mutation does not prevent secretion of the globular protein but disrupts its stability to the degree that the original folded protein partially or completely unfolds in the extracellular environment.

Id. ¶ 76 (citing Ex. 2164, 160; Ex. 1140, 329). Dr. Naismith states: “as Dr. Petsko’s textbook explains, ‘the partially unfolded form is prone to aggregation, which results in the formation of fibrils [] and other aggregates that accumulate in the extracellular space.’” *Id.* (quoting Ex. 2164, 160) (alteration in original). Dr. Naismith states that “[l]arge numbers of those amino acid sequences will exist in an unfolded state that exhibit myriad three-dimensional structures, while other sequences will adopt misfolded or partially folded (*e.g.*, molten globules) structures.” *Id.* ¶ 79 (citing Ex. 1014, 91–92).

Dr. Naismith states:

I do not agree that the 94% requirement^[13] is a “structural feature” of a modified PH20 polypeptide. It is a claim

¹³ Although the challenged claims do not expressly recite a “94% sequence identity” requirement, the parties agree that such identity is required by the

requirement that is determined mathematically. . . . It does not define any particular physical characteristic of a modified PH20 molecule. It functions solely to limit the size of the sequence space of the modified PH20 polypeptides.

Id. ¶ 83. Dr. Naismith states that a “POSA would consider ‘structural features’ of a protein to be the physical characteristics of the protein molecule.” *Id.* ¶ 85.

Dr. Naismith states that “Drs. Petsko and Simpson identified seven examples of PH20 polypeptides with more than one change These limited examples do not meaningfully probe the combinatorial sequence space covered by the claims. They are also not representative of the breadth of modified PH20 polypeptides within the scope of the claims.” *Id.*

¶¶ 114–115. Dr. Naismith states: “I do not believe a POSA in the 2011–2012 timeframe could have visualized from the common disclosure the set

claims’ recitation of a hyaluronidase domain corresponding to “residues 3–339” with “up to 20 modifications.” Ex. 1001, 301:37–44. As Dr. Petsko explains, the claims encompass a set of “modified PH20 polypeptides that have no more than 20 total modifications in the hyaluronidase domain (residues 3–339 of SEQ ID NO: 7),” and “[t]hus, they share at least 317 of the 337 amino acids (94%) of the hyaluronidase domain.” Ex. 2070 ¶ 49; *see also id.* ¶ 128 (“the claims cover certain PH20 variants—modified PH20s with 94% identical hyaluronidase domains and the specified change at position 313”); Ex. 1133 n.30 (acknowledging “the 94% identical hyaluronidase domain parameter of the ’345 Patent”); *id.* at n.35 (“I refer to the 94% identical hyaluronidase domain requirement (*i.e.*, up to 20 modifications within the hyaluronidase domain corresponding to residues 3–339 in SEQ ID NO:7) and the position 313 replacement requirement of the ’345 Patent.”); Ex. 1134 ¶ 15 (“I have been informed by counsel that the modified PH20 polypeptide can also have up to 20 modifications within the hyaluronidase domain, and that this means the modified PH20 polypeptides have at least 94% sequence identity to SEQ ID NO: 7.”).

of modified PH20 polypeptides with more than about 5 changes within the claim parameter sequence space that will fold and be enzymatically active.” *Id.* ¶ 123.

Dr. Naismith states that “[c]omputational tools available in the 2011-2012 timeframe also were not capable of identifying and predicting the myriad types of subtle disruptions to a protein structure that collectively determine if a particular mutated sequence will properly fold and remain stably folded.” *Id.* ¶ 128 (citing Ex. 1003 ¶¶ 50–51; Ex. 1004 ¶ 169).

In deposition, Dr. Hecht stated: “my sense was that the [] patent lists a minuscule and highly biased sample of what would be within [the claims], in the sense that it only lists single amino acid substitutions while at the same time it’s attempting to claim things that have 20 or more substitutions.” Ex. 2076, 203:6–12. When asked, “the skilled person would expect that if they made five changes in HYAL1, they change [residues] 131, 247, 129, 202 and 245, they would reasonably expect that they would dramatically reduce the activity in the protein, right?”, Dr. Hecht stated: “Yes . . . if one made all these mutations simultaneously in the same sequence, one would anticipate a huge reduction in activity.” *Id.* at 227:6–21.

In deposition, Dr. Park acknowledged that a “homology model can help you to evaluate the impact of a substitution.” Ex. 2077, 54:4–5. Dr. Park stated that a POSA would have performed “multiple sequence alignment to identify non-essential regions, and reasonably expect that the amino acids found at those positions may be introduced without substantially altering biological activity.” *Id.* at 71:11–16.

When discussing a sequence with two mutations at the time of invention, Dr. Park noted that

[t]he problem is when you're looking at one substitution, there are only so many interactions that a single amino acid can make, and those are relatively straightforward to discern for an expert. . . .

Once you start introducing the mutations, more than one mutation . . . if those substitutions happen to be very close to each other, what happens is now suddenly you have to deal with many more possible changes in the interactions

So now that results in both positive and negative interactions, all of which need to be tracked and estimated. Unfortunately, a person viewing the structure would not be able to differentiate many of these subtle changes, especially if there are multiple mutations nearby.

Id. at 198:12–199:19. Dr. Park later stated that “[a]s you introduce more and more mutations, the number of possible favorable and unfavorable interactions increases exponentially, and can quickly overwhelm a person’s ability to evaluate them.” *Id.* at 202:9–13.

When asked whether for multiple mutations “you could submit that sequence for PH20 into SWISS-MODEL, and you download a PDB [protein data bank] file with the resulting homology model, right?”, Dr. Park answered: “sure, you can download it. But what do you do with it? The problem is you can’t do anything, and there’s no methodology that will allow you to compare two structures containing substitutions that are near each other if it’s a large number.” *Id.* at 204:9–205:14. Dr. Park further noted that “modeling is not just generating the PDB file, but also looking at it and making sense of it. And you will -- one will run into a combinatorial, combinatorially intractable situation very quickly if mutations occur close to each other.” *Id.* at 205:20–206:3. Dr. Park noted that this “is a struggle that

the whole community has to deal with, and was not a solved problem back in 2011.” *Id.* at 212:16–18.

In deposition, Dr. Naismith addressed the issue of how sequence differences between Hyal1 and PH20 would impact protein folding, stating that “what is really interesting with that is despite the fact that they have the same fold, they actually have some differences in function, which shows you it is quite difficult to detect.” Ex. 2301, 86:14–17. When asked “Did you look at the experimentally determined PH20 structure?”, Dr. Naismith answered: “I don’t believe there is experimentally. There certainly wasn’t one at 2011/2012.” *Id.* at 87:19–23. When asked “Is there any limit to the structure, the three-dimensional structure that an unfolded protein could take?”, Dr. Naismith stated: “I can’t give you a number but it is exponentially large if you consider 15 mutations, for example. For unfolded proteins I would expect them to be very large.” *Id.* at 92:19–93:6.

When asked about multiple mutations, Dr. Naismith stated, “So this is something all of the experts talk about, which is as you make an increasing number of single site mutations, so you go from 1 to 2 to 3 to 4 to 5, that you can’t assume that the mutations do not interact with one another in unpredictable ways.” *Id.* at 106:17–22.

The Scientific Background for the 2024 Nobel Prize in Chemistry (“Scientific Background”) states, regarding protein structure prediction, that the reliability of contact prediction [i.e., pairs of amino acids in contact with each other in 3D] remained low for many years, until CASP12^[14] in 2016, when the accuracy suddenly

¹⁴ CASP (Critical Assessment of protein Structure Prediction) was a series of biannual challenges designed to assess the state of the art in protein structure prediction. Ex. 1027, 6.

increased dramatically. It turned out that the methods used to analyse correlated mutations had been oversimplified and could not distinguish between directly and indirectly correlated residues.

Ex. 1027, 7. The Scientific Background further states that in 2020, “while the contact and distance prediction performance remained at around 70% in CASP14, the GDT [global distance test] score for the best predictions on difficult targets had now reached about 90%, and this was due to the new AlphaFold2 (AF2) program.” *Id.* at 9. Dr. Naismith explains that the Scientific Background presents “an accurate historical perspective on the capabilities of computational tools to accurately predict a protein’s tertiary structure from its amino acid sequence” and shows that those “tools did not reach predictive accuracy levels comparable to experimental determination of structure until around 2019.” Ex. 1133 ¶ 133.

(b) Patent Owner’s Evidence

Dr. Petsko states that the “patent data show, for each of the 447 positions in SEQ ID NO: 3, the tolerance of each position to substitution. . . . The POSA would expect that single or multiple changes in positions that tolerate mutations will generally maintain activity.” Ex. 2070 ¶¶ 54–55.

Dr. Petsko states:

PH20, Hyal-1 and bee venom hyaluronidase share several common features, including a common mechanism of action, common active site, and common critical residues involved in structure and function. Hyal-1 and PH20 also share a common alpha-beta barrel fold, with bee venom hyaluronidase adopting a similar fold. . . . The similarities shared by these three different proteins provide key insight into how POSAs in the 2012 time frame would think about concepts like common structural features, structure/function correlation and

representative examples disclosed across the scope of a claimed set of protein variants.

Id. ¶¶ 126–127. Dr. Petsko states: “a POSA would have expected that an active, folded modified PH20 that has a hyaluronidase domain that is 94% identical to . . . wild type (‘WT’) would adopt the same alpha-beta barrel fold as WT PH20.” *Id.* ¶ 101. Dr. Petsko states that a “POSA could select 23 residues to change and reasonably expect to obtain an active PH20 as those changes were based on the data in the patent. For example, there are 40 positions that tolerated all tested substitutions, 87 that tolerated 90% or more and 158 that tolerated 60% or more.” *Id.* ¶ 359.

Dr. Simpson states that

one can illuminate common structural features of hyaluronidases (and other enzymes) through mutagenesis studies, by modifying the primary structure and determining the impact of the change on activity.

In particular, as a conceptual matter, POSAs can experimentally assess potential common structural features of the three-dimensional protein by introducing mutations to its primary structure and seeing what abolishes activity, and then evaluating the results in the context of an experimental structure (*e.g.*, a crystal structure) or a homology model.

Ex. 2068 ¶¶ 155–156. Dr. Simpson states that the “patent data provide a POSA with an extremely powerful tool to engage in further modification of the protein in a reasonably predictable manner.” *Id.* ¶ 157.

In deposition, when Dr. Petsko was asked regarding the genus of claim 1 whether it would have been “possible to experimentally determine which ones are properly folded and enzymatically active in 2011 or 2012?”, he answered: “Not from experimenting on the entire ensemble.” Ex. 1131, 64:12–17.

As to the tertiary structure of PH20, when Dr. Petsko was asked, “When you reviewed the common disclosure, did you see a description of the PH20 polypeptides that used alpha-beta barrel fold to describe it?”, he answered: “Not in the text of the specification, but the structure of the bee venom hyaluronidase was referenced in the patent application.” *Id.* at 94:14–20. When asked whether a POSA in 2012 “would be able to predict the change to a protein’s net free energy of stabilization¹⁵ associated with a set of 10 or 15 or 20 mutations?”, Dr. Petsko answered: “No. They would not be able to predict the number. They would be able to get a sense of whether those were likely to be destabilizing or not.” *Id.* at 102:1–9. Despite that statement, when asked whether “you would be able to predict whether that mutated 15 or 20 residue-mutated PH20 will exhibit the activity that you are hoping to get?”, Dr. Petsko answered: “My opinion is that you could do so.” *Id.* at 111:9–16. Dr. Petsko also stated that “[t]he information content of that particular set of substitutions [in the ’345 patent] is enormous. And when combined with the structural information from modeling the PH20 structure, it allows you to visualize and make predictions

¹⁵ “[T]he ‘net free energy of stabilization’ is the difference in free energy between folded and unfolded states of a protein.” Ex. 1133 ¶ 74 (citing Ex. 1003 ¶ 64); *see also* Ex. 1014, 90; Ex. 2164, 0047 (“the net free energy of stabilization of most folded proteins—the difference in free energy between the folded and unfolded states—is actually rather small” meaning that the proteins are only “marginally stable”). “Mutations introduced into an amino acid sequence can (and usually will) alter the net free energy of stabilization of the protein” and if they “decrease the net free energy of stabilization . . . the folded protein will be more prone to partial or complete unfolding” and thus loss of stability “which is necessary for it to exhibit biological activity (*e.g.*, to bind the HA substrate and hydrolyze it).” Ex. 1133 ¶ 75.

about much more of the dataset than just what you see here.” *Id.* at 113:2–18.

In deposition, Dr. Simpson stated that a POSA “would have all the information they needed with respect to [a modified PH20 polypeptide’s] activity to create a sequence that was 95% identical, that would either adopt the fold and be enzymatically active, or adopt the fold and not be enzymatically active, or not adopt the fold.”¹⁶ Ex. 1130, 99:5–10.

(c) *Review*

As to hyaluronidase activity, we credit Petitioner’s evidence showing that a POSA in 2011–2012 would not have been capable of predictably determining the full scope of PH20 polypeptides having modifications in addition to the recited modification at position 313 that would have retained hyaluronidase activity over the competing evidence offered by Patent Owner. As Dr. Park explained, SWISS-MODEL (and other then-available computational modeling techniques) would not have reliably provided such information. Ex. 1004 ¶¶ 168–169; *see also* Ex. 2077, 202:9–207:4 (explaining the limits of such techniques because “[a]s you introduce more and more mutations, the number of possible favorable and unfavorable interactions increases exponentially, and can quickly overwhelm a person’s ability to evaluate them”). That testimony is confirmed by Scientific

¹⁶ Dr. Simpson and Dr. Petsko’s depositions “were directed towards the related U.S. Patent 11,952,600, which has a sequence identity parameter of 95% identity.” Ex. 1133 n.30, n.35, n.67. Nevertheless, Petitioner applies this testimony to the present challenged claims, which the parties agree have a “94% identical hyaluronidase domain parameter of the ’345 Patent.” *See id.*; *see also supra* n.12.

Background, which noted that prior to significant scientific innovations occurring after 2012, “the methods used to analyse correlated mutations had been oversimplified and could not distinguish between directly and indirectly correlated residues.” Ex. 1027, 7. That is, in the 2011–2012 timeframe, a POSA employing the then-available analytical techniques in view of the written description in the ’345 patent could not have determined which of the many multiply-modified PH20 polypeptides within the scope of claim 1 would retain hyaluronidase activity and which would not, and the Specification does not reasonably convey to those skilled in the art that the inventors had possession of that subject matter. Ex. 1003 ¶¶ 49–54, 205; Ex. 1004 ¶¶ 63, 168–169; Ex. 1131, 102:1–9, 109:1–14; Ex. 1133 ¶¶ 59, 76, 120, 123–133.

Patent Owner’s evidence does not undermine Petitioner’s showing. While Dr. Petsko testified that the single substitution data in the Specification shows several positions that tolerated most of the tested substitutions, there were also many that did not. *See* Ex. 2070 ¶ 359. More importantly, the data do not show results for polypeptides having multiple modifications, which greatly complicates the interactions involved, undermining predictability. *See, e.g.*, Ex. 1133 ¶ 128; Ex. 2077, 198:12–199:19, 202:9–13, 204:7–206:3, 212:16–18; Ex. 2301, 106:17–22. This unpredictability is further evidenced by Dr. Naismith’s testimony, which refers to Dr. Petsko’s textbook as illustrating an example in which a “single mutation does not prevent secretion of the globular protein but disrupts its stability to the degree that the original folded protein partially or completely unfolds in the extracellular environment.” Ex. 1133 ¶ 76 (citing Ex. 2164, 160; Ex. 1140, 329). This shows that even a single mutation can

dramatically impact the protein's structure and stability and in turn its activity. *Id.* Indeed, Petitioner cites references demonstrating this specifically for PH20 polypeptides. Ex. 1010, 9441; Ex. 1011, 813.

While Drs. Petsko and Simpson suggest that a POSA would have been able to use the data in the Specification to make reasonable predictions about the effect of multiple modifications on hyaluronidase activity, we view this testimony to at most describe a research plan (i.e., a “tool to engage in further modification”¹⁷) for finding active polypeptides rather than demonstrating the inventors were in possession of the full scope of claimed polypeptides. This is particularly so given the limits of the then-available analytical tools noted above and the fact that the structural connections and three-dimensional modeling Patent Owner's experts attempt to make (*see, e.g.*, Ex. 2070 ¶¶ 129–213, 297–342; Ex. 2068 ¶¶ 123–125, 245, 294–313, 318) do not appear in the written description itself. To the extent the experts disagree on this point, we credit the testimony of Petitioner's experts over that of Patent Owner's. *See* Ex. 1133 ¶¶ 111–230 (identifying problems with the approaches proposed by Patent Owner's experts).

For the above reasons, we find that a preponderance of the evidence of record better supports a finding that in the 2011–2012 timeframe, it would have been unpredictable to identify which multiple mutants retained

¹⁷ Ex. 2068 ¶ 157.

hyaluronidase activity, even with the single substitution data provided in the Specification.

(2) *Contraceptive effect*

As explained above, we construe the term “modified PH20 polypeptides” to require peptides that exhibit hyaluronidase activity. *See supra* Section II.B.2. But even if we were to accept Patent Owner’s position that the term is broader and includes inactive versions of such peptides that can be used as antigens to provide a contraceptive effect, the preponderance of the evidence before us does not demonstrate this to be a credible utility. And in any event, it does not demonstrate that the inventors were in possession of the full scope of the claimed polypeptides—which is the relevant inquiry here. We address the parties’ evidence regarding the potential contraceptive effect of these polypeptides below.

(a) *Petitioner’s Evidence*

In a subsection titled “Contraception,” the Specification states that “[m]odified PH20 polypeptides provided herein can be used as vaccines in contraceptive applications.” Ex. 1001, 193:15–16. It further states that “[i]mmunization with PH20 has been shown to be an effective contraceptive in male guinea pigs (Primakoff et al. (1988) *Nature* 335:543-546, Tung et al. (1997) *Biol. Reprod.* 56:1133-1141). It also has been shown to be an effective contraceptive in female guinea pigs.” *Id.* at 193:24–29.

Dr. Kelsoe states that “Tung 1997 (EX1023), reports that the majority of male guinea pigs developed experimental autoimmune orchitis (EAO), and that the observed infertility was due to the absence of sperm in the epididymis.” Ex. 1134 ¶ 50. According to Dr. Kelsoe, this suggests that “the cause of infertility in male guinea pigs arising from immunization with

PH20 was likely due to autoimmune inflammation rather than specific antibody-mediated responses against native PH20.” *Id.* Dr. Kelsoe states: “Similar irregularities between antibody titer and contraceptive effect were observed in female guinea pigs.” *Id.* ¶ 55. Dr. Kelsoe states that “[o]ther groups that tested recombinant PH20 in rabbits (Pomering 2002) and in mice (Hardy 2004) failed to achieve infertility *in vivo*. . . . This demonstrates that merely eliciting a polyclonal antibody response is insufficient to achieve functional neutralization of the target antigen; more is required.” *Id.* ¶ 57.

Dr. Kelsoe states: “a POSA would have understood that there are differences across species in terms of at least PH20’s importance to fertilization, location of PH20 expression, and the predominant structural form of PH20 relevant to fertilization.” *Id.* ¶ 60. Dr. Kelsoe states:

In 2022, a group of scientists with the first author Printz investigated the risk that antibodies reactive to recombinant human PH20 (rHuPH20) would interact with endogenous PH20. . . . Although the mouse monoclonal antibody and rabbit polyclonal antibody bound to separate peptides from human PH20, with the rabbit polyclonal antibody binding to several such peptides, the human polyclonal IgG did not bind to *any* peptide.

Id. ¶ 69. Dr. Kelsoe further states that the “Printz 2022 authors also reported immunogenicity findings from clinical trials where rHuPH20 was co-administered subcutaneously with a variety of therapeutic molecules” and found “[n]o neutralizing antibodies were detected in any subject from this study.” *Id.* ¶ 71 (quoting Ex. 1122, 9) (alteration in original). Dr. Kelsoe states that “[b]oth Printz 2022 and Nolan 2024 confirm what a POSA would have recognized from the totality of evidence available before the relevant timeframe: that PH20 was unlikely to be useful as an antigen in an

immunocontraceptive vaccine in humans or mammals other than guinea pigs.” *Id.* ¶ 73.

In deposition, Dr. Kelsoe acknowledged that “to determine the target of the immunocontraceptive, I would certainly, since that lies outside of my field of expertise, I would rely on a reproductive biologist, yes.” Ex. 2302, 30:13–17.

Exhibit 1189 (Martin-DeLeon) states:

Taken together, the data from non-primate and primate models (where there are no known redundant reproductive hyases) suggest that PH-20 is not a useful antigen for inclusion in immunocontraceptive vaccines. The absence of critical epitopes in recombinant PH-20 has been considered as an explanation for a lack of sterility after immunization in mice (Hardy et al., 2004). However, it is possible that the strong immunocontraceptive effect reported for affinity purified guinea pig PH-20 could reflect a fundamental difference in the autoimmune response in guinea pigs compared to other species.

Ex. 1189, 119.

(b) Patent Owner’s Evidence

Dr. Cherr states that “POSAs would have known that antibodies that bind to sperm (antisperm antibodies) caused infertility.” Ex. 2072 ¶ 32 (citing Ex. 2116, Abstract; Ex. 2114, 3). Dr. Cherr states:

POSAs would have known that the binding of anti-PH20 antibodies to epitopes of PH20 polypeptide on the sperm surface would prevent sperm from fertilizing the oocyte by, e.g., inhibiting sperm motility, inducing sperm agglutination, reducing penetration of cervical mucus by sperm, interfering with sperm capacitation or the acrosome reaction, or stimulating sperm lysis via the complement pathway.

Id. ¶ 33 (citing Ex. 2114, 3, 18–19; Ex. 2117, Abstract; Ex. 2116, 172, 173).

Dr. Cherr states: “POSAs would have further known that the binding of anti-

PH20 antibodies to epitopes of sperm PH20 polypeptide in the female reproductive tract would prevent PH20's hyaluronidase activity by allosteric effects irrespective of where the antibodies bound on PH20 polypeptides.” *Id.* ¶ 34.

Dr. Cherr states that “[i]n *in vivo* studies, female guinea pigs were less fertile when immunized with guinea pig PH20 polypeptide.” *Id.* ¶ 35.¹⁸ Dr. Cherr states that POSAs would have known “that the poor contraception seen after administering PH20 polypeptides via non-mucosal routes in Hardy 2004 (intraperitoneal route in mice) and Pomeroy 2002 (subcutaneous route in rabbits) reflect the reproductive biology of mice and rabbits.” *Id.* ¶ 51; *see also* Ex. 1019 (Hardy 2004); Ex. 1020 (Pomeroy 2002).

Dr. Moon states that “POSAs would have expected that polyclonal antibodies generated in human females in response to vaccination with any one of the modified PH20 polypeptides would bind to the wild-type PH20 polypeptide of human sperm introduced into the female reproductive tract.” Ex. 2074 ¶ 43; *see also id.* ¶ 64.

In deposition, Dr. Cherr responded to a question about the safety of PH20 as a contraceptive, stating that in “the guinea pig males that were injected with PH20 . . . there was epididymitis and orchitis in the testes with massive inflammation. And that was what was deemed to be responsible for the contraceptive effect rather than any sort of antibody binding to cells, *per se.*” Ex. 1129, 38:6–12. In response to being asked “you wouldn’t want to cause epididymitis or orchitis in humans?”, Dr. Cherr stated: “I would

¹⁸ Dr. Cherr cites “EX2010,” which purports to “Primakoff 1988 (which published in the prestigious, peer-reviewed journal *Nature*.” *See* Ex. 2072 ¶ 35. However, no Exhibit 2010 was filed in this proceeding.

not.” *Id.* at 38:13–16. Dr. Cherr was then asked, “So the POSA would not think that modified PH20 polypeptides would be a viable contraceptive vaccine in human [males]?”, and he responded “that is correct.” *Id.* at 38:17–23.

(c) *Review*

As to their potential contraceptive effect, the evidence of record fails to demonstrate an expectation that any human PH20 polypeptide, much less the modified PH20 polypeptides claimed, would function as a contraceptive in humans. The Specification does not identify any particular modified PH20 polypeptide that can be used in a contraceptive, nor does it describe any testing of such. Ex. 1003 ¶ 123. While we acknowledge the expertise of Dr. Cherr and Dr. Moon, the only evidence of any efficacy of a PH20 polypeptide as a contraceptive vaccine was shown in guinea pigs. *See, e.g.*, Ex. 1022, 1146; Ex. 1023, 1133.

We credit the testimony of Dr. Kelsoe disputing the opinions offered by Drs. Cherr and Moon regarding whether a POSA would have expected the modified PH20 polypeptides in the challenged claims to be useful as contraceptives. *See* Ex. 1134 ¶¶ 48–73. In particular, Dr. Kelsoe points to Martin-DeLeon (Exhibit 1189), which includes experimental evidence that PH20 polypeptide vaccines were ineffective as contraceptives in rabbits, mice, and macaques. *See* Ex. 1189, 119. This evidence demonstrates significant interspecies variability, which is underscored by Martin-DeLeon’s observation that the studies showing a contraceptive effect in guinea pig “could reflect a fundamental difference in the autoimmune response in guinea pigs compared to other species.” *Id.*

The failure of PH20 polypeptides as contraceptive vaccines in three of four species tested, and particularly in a primate (macaque) model that is physiologically more similar to humans, shows that a POSA would not have understood even unmodified PH20 polypeptides to provide a contraceptive effect in humans and most other species. Ex. 1189, 119 (reviewing these animal studies and concluding “[t]aken together, the data from non-primate and primate models (where there are no known redundant reproductive hyases) suggest that PH-20 is not a useful antigen for inclusion in immunocontraceptive vaccines”). At most, the references Patent Owner cites show an immunocontraceptive effect for *unmodified* PH20 polypeptides in guinea pigs. Moreover, Patent Owner’s expert Dr. Cherr conceded these guinea pig studies raised safety concerns (epididymitis and orchitis in the testes) that would prohibit PH20’s use as a contraceptive in human males. *See* Ex. 1129, 38:2–23; *see also* Ex. 2072 ¶ 62 (Dr. Cherr limiting his opinion to “female mammals”).

The Specification does not provide any example of a *modified* PH20 polypeptide that can be used for contraception. Ex. 1003 ¶ 123. Dr. Moon testifies that a POSA would have expected that “polyclonal antibodies would be generated in a human female against any of the modified PH20 polypeptides” and that “such polyclonal antibodies would bind to the wild-type human PH20 polypeptide.” Ex. 2074 ¶ 47. But even so, Dr. Kelsoe persuasively explains that “a POSA would have expected the location of amino acid changes to matter to the nature of an immune response elicited by a modified PH20 polypeptide” (Ex. 1134 ¶ 79) and would not have expected all modified PH20 polypeptides to elicit the relevant biological

response. *See id.* ¶¶ 77–98, 101. To the extent their testimony conflicts, we credit Dr. Kelsoe for the reasons explained in his declaration. *Id.*

For these reasons, the record does not show that a POSA in the 2011–2012 timeframe would have understood that the recited modified PH20 polypeptides would provide a contraceptive effect or otherwise be useful in a contraceptive vaccine, notwithstanding the discussion of such in the Specification.

Petitioner cites Exhibit 1190 (Nolan), a 2024 journal article authored by scientists employed by Patent Owner. *See* Reply 40; Ex. 1134 ¶ 72. Nolan is not prior art, but it confirms that PH20 polypeptides (and by extension the modified PH20 polypeptides recited in the challenged claims) are not useful as contraceptives.¹⁹ As such, it further undermines the competing testimony offered by Patent Owner’s experts on this point. In particular, Nolan states that “rHuPH20 exposure and the resulting development of neutralizing ADAs [anti-drug antibodies] did not negatively alter fertility parameters in adults.” Ex. 1190, 373. Nolan further states that after weekly administration of rHuPH20 to obtain antibodies, “[t]reated males were mated with nontreated females and there were no statistically significant differences in fertility.” *Id.* at 375. Nolan concludes by stating:

Administration of rHuPH20 resulted in the generation of ADAs that had no detrimental effects on fertility as measured by sperm concentration and motility, litter size, litter viability, and development. . . . [T]hese studies demonstrate that prolonged exposure to rHuPH20 and circulating anti-rHuPH20 antibodies

¹⁹ We note that neither Patent Owner, nor its experts, appear to have addressed or otherwise responded to Nolan. *See* Sur-Reply.

is well tolerated without impacts on reproduction or development.

Id. at 381.²⁰

Accordingly, even if the term “modified PH20 polypeptides” were interpreted to include inactive polypeptides that can serve as antigens to provide a contraceptive effect, the preponderance of the evidence does not show that a POSA would have understood the inventors to be in possession of the full scope of the recited polypeptides capable of such use.

7. *Analysis*

We find the preponderance of the evidence supports a finding that the claims fail to comply with the written description requirement. “Every patent must describe an invention. It is part of the *quid pro quo* of a patent.” *Ariad*, 598 F.3d at 1345.

In determining compliance with the written description requirement for nucleic acid genus claims, the Federal Circuit has identified two extremes. In *Capon*, claims relying on known nucleotide sequences with known functions were found to satisfy the written description requirement. *Capon v. Eshhar*, 418 F.3d 1349, 1358 (Fed. Cir. 2005). At the other end, *Juno* found that for broad claims to a nucleic acid encoding a chimeric T cell receptor with a functional requirement to bind a target, “the written description ‘must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the

²⁰ While we discuss Nolan in the context of our written description analysis, we note that it also strongly supports a conclusion that, even given the state of the art in 2024, the use of modified PH20 polypeptides as contraceptives has not been enabled.

applicant has invented species sufficient to support a claim to the functionally-defined genus.”” *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330, 1335 (Fed. Cir. 2021) (quoting *Ariad*, 598 F.3d at 1349).

As explained above, claim 1 requires modified PH20 polypeptides with some hyaluronidase activity. *See supra* Section II.B.2. Moreover, the claims recite a broad swath of sequence space, i.e., modified PH20 polypeptides comprising a substitution position 313 and up to 19 additional substitutions within the hyaluronidase domain. However, the Specification only provides examples having single amino acid substitutions. There are no examples of multiply-modified PH20 polypeptides having the recited replacement at position 313 as well as other modifications and hyaluronidase activity. *See* Ex. 1133 ¶ 115 (summarizing deficiencies in the common disclosure).

Based on this limited disclosure and our claim interpretation, we find the evidence in this case closer to *Juno* than *Capon*, and that the written description in the Specification does not disclose sufficient structural features in the PH20 sequences associated with hyaluronidase (or contraceptive activity) to allow a POSA to distinguish which multiply mutated sequences will result in inactive polypeptides and which will retain activity. Indeed, Patent Owner’s own expert conceded that it would not have been possible to experimentally determine properly folded and enzymatically active polypeptides in 2011 or 2012 over the entire claim scope. *See* Ex. 1131, 64:12–17. And then-available computational modeling techniques would have only allowed a POSA to reasonably predict the effect of, at most, five substitutions on the resulting protein’s structure.

See, e.g., Ex. 1004 ¶¶ 167–169; Ex. 1003 ¶ 264; Ex. 1133 ¶¶ 130–133, 260–263, 268, 270–274, 281–284.

Although *Capon* allows some reliance on prior art for written description (*see Capon*, 418 F.3d at 1357–58), Patent Owner is trying to extend that to include that which is at most obvious from the prior art, as opposed to what is actually described. That is, it may have been obvious to a POSA to align PH20 sequences with other known hyaluronidase enzymes and to use the crystal structure of a different hyaluronidase (Hyal-1) in SWISS-MODEL to generate a three-dimensional structure, but none of that is described in the common disclosure itself. “[A] description that merely renders the invention obvious does not satisfy the [written description] requirement.” *Ariad*, 598 F.3d at 1352. While a POSA might be able to embark on their own research program to try to find suitable multiply-modified PH20 polypeptides, the four corners of the written description do not demonstrate possession of such. *See id.* at 1356–57 (recognizing that “[p]erhaps one of ordinary skill could discover this information, but this does not alter our conclusion that the description . . . just represent[s] a wish or arguably a plan for future research”) (internal quotation omitted).

We also recognize that there are no “bright-line rules governing . . . the number of species that must be disclosed to describe a genus claim, as this number necessarily changes with each invention.” *Id.* at 1351. However, the evidence of record discussed above demonstrates activity in only a tiny fraction of the singly-substituted polypeptides in the genus of about $10^{43}+$ polypeptides in the sequence space. The actual genus encompassed by the challenged claims is smaller than the outer boundaries of the sequence space because the claims are limited to polypeptides having

hyaluronidase activity. But that distinction highlights what is a salient point for our written description analysis—an ordinarily-skilled artisan in the 2011–2012 timeframe would not have been able to determine the set or any significant portion of the set of modified PH20 polypeptides having such activity from the disclosure in the Specification. Instead of demonstrating the inventors were in possession of that genus, the written description leaves the POSA to experiment to try to find representative multiply-modified PH20 polypeptides having the required activity.

As our reviewing court explained in *AbbVie*, in instances such as these the written description must show “that one has truly invented the genus, *i.e.*, that one has conceived and described sufficient representative species encompassing the breadth of the genus. Otherwise, one has only a research plan, leaving it to others to explore the unknown contours of the claimed genus.” *AbbVie*, 759 F.3d at, 1300. Here, Patent Owner claims an immense number of possible mutations to various PH20 polypeptide sequences but provides insufficient guidance for a POSA as of 2011–2012 to determine which, if any, of the untested multiply-mutated forms will retain hyaluronidase activity.

In *Teva Pharmaceuticals International GmbH v. Eli Lilly & Co.*, 172 F.4th 1367 (Fed. Cir. 2026), the court distinguished “(1) claims to a method of using humanized anti-CGRP antagonist antibodies *to treat headache* and (2) claims to such antibodies themselves.” *Teva*, 172 F.4th at 1378. The challenged claims here are more akin to this second category because they are directed to the “modified PH20 polypeptides” themselves. Ex. 1001, 301:36–44. With this understanding, the reasoning in *Ariad, University of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 920 (Fed.

Cir. 2004), *AbbVie*, and *Juno* support a finding that disclosure of only a few species within the immense functionally-defined genus of “modified PH20 polypeptides” having the recited position 313 substitution as well as additional modifications permitted by claim 1 is insufficient to satisfy the written description requirement.

Put differently, the written description of the ’345 patent is insufficient because it and the challenged claims merely “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.

For these reasons, we find that Petitioner has demonstrated by a preponderance of the evidence that for challenged claims 1–17 the ’345 patent does not comply with the written description requirement. Similarly, the written description does not demonstrate possession of the full scope of the claims of the ’345 patent in any of the applications in the extensive priority chain, which all appear to have the same specification, including the ’731 application, filed December 28, 2012, or in provisional application 61/631,313, filed December 30, 2011, or provisional application 61/796,208, filed November 1, 2012.

D. Ground II - Enablement

1. 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) (alteration in original;

internal quotations omitted). That is, “there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill 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).

2. *Petitioner’s Position*

Petitioner asserts that

[e]nabling the full scope of the present claims requires enabling the sub-genus of enzymatically active **multiply**-modified PH20 polypeptides that satisfy the claim parameters—because that subgenus is not enabled, the full scope of the claims cannot be. The only method the common disclosure describes for making such multiply-modified “active mutant” PH20 polypeptides requires a skilled artisan to make and test the $10^{43}+$ different modified PH20 polypeptides being claimed to determine which possess hyaluronidase activity—an impossible scale of experimentation.

Pet. 75. Petitioner asserts that “the claims capture a massive number of structurally distinct multiply-modified PH20 polypeptides that have **unknowable** properties absent a skilled artisan producing and testing 10^{43} – 10^{56} distinct mutants per the common disclosure’s prophetic ‘make and test’ methodology.” *Id.* at 79–80 (citing Ex. 1003 ¶¶ 141, 181, 203, 223–24).

Petitioner asserts that “[t]he number of ‘working examples’ of the **claimed** modified PH20 polypeptides that are ‘active mutants’ is tiny—13 of 14 of the position 313 singly-substituted PH201-447 mutants were ‘active mutants.’” *Id.* at 81 (citing Ex. 1001, Tables 8–10). According to Petitioner, none of the working examples “show the effects of making any substitutions in a human PH20 terminating before position 447, or of **concurrent** substitutions at **multiple positions, particularly in sequences associated with secondary structures, structural motifs, or that stabilize the PH20 protein structure.**” *Id.* at 81–82 (citing Ex. 1003 ¶¶ 179–181, 195, 197).

Petitioner asserts that “[t]he common disclosure also describes only a prophetic method that requires a skilled artisan to perform iterative rounds of **randomized** mutations (up to 19 rounds per starting molecule under the broadest claims) to **discover** which of the 10⁴³+ possible modified PH20 polypeptides being claimed might possess hyaluronidase activity.” *Id.* at 84. Petitioner asserts that these “**iterative, trial-and-error process[es]**” “are indistinguishable from those consistently found insufficient to enable comparable genus claims to modified proteins and compounds.” *Id.* (quoting *Idenix Pharm. LLC v. Gilead Sci. Inc.*, 941 F.3d 1149, 1161–63 (Fed. Cir. 2019)).

Petitioner asserts that the skilled artisan “could not have predicted the effects on a protein’s structure from introducing numbers of concurrent modifications that make up the vast majority of the claimed genera (*e.g.*, 5, 10, 15+ modifications).” *Id.* at 89 (citing Ex. 1003 ¶¶ 59–61, 221–22). Petitioner asserts that the “cumulative effects of those multiple changes would have rapidly exceeded the capacity of computer-based techniques to

reliably predict the effects of each change on the protein's structure.” *Id.* (citing Ex. 1003 ¶¶ 183, 196–97; Ex. 1027, 6–10, Fig. 6).

Petitioner asserts that

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 modifications that preserved stability or activity of such proteins.

Id. at 91 (citing Ex. 1003 ¶¶ 183, 196–97, 264; Ex. 1027, 6–10, Fig. 6; Ex. 1011, 812–814; Ex. 1010, 9437–9439).

3. *Patent Owner's Response*

According to Patent Owner, “[t]here is no dispute that POSAs could readily generate claimed PH20 variants with amino acid substitutions and test them for activity using routine molecular biology and biochemistry techniques.” PO Resp. 62 (citing Pet. 55–57). Patent Owner asserts that

POSAs would recognize, within this narrow genus, that the M313 variants and their subvariants are structurally homogeneous in that they share the same hyaluronidase domain primary structure (amino acids 3-339 of SEQ ID NO: 7) comprising no more than 20 total modifications, the M313 mutation, and for those that are active, the same PH20 tertiary structure and several common structural features, such as the same common residues critical for catalysis; moreover, POSAs can distinguish actives from inactives by the absence of the common structural features in the inactives (e.g. changes to “scaffolding” such as disulfide bridges or modification of catalytic residues).

Id. at 63 (citing Ex. 2068 ¶¶ 287–293, 303, 316; Ex. 2070 ¶¶ 49–51, 53, 248–253, 325–342, 389–431). Patent Owner asserts “the patent provides extensive mutagenesis data across a full, mature, soluble PH20 sequence (SEQ ID NO: 3) that give POSAs predictive insight into which substitutions preserve activity and which abolish it.” *Id.* at 64.

Patent Owner asserts that “[t]he invention is modified PH20 variants with a defined set of structures, which the inventors characterized via expansive disclosure in the specification regarding the tolerance of every position in a mature, soluble, active PH20 sequence to modification, making modification (and the nature of the invention) reasonably predictable.” *Id.* at 67. Patent Owner asserts that POSAs

possessed a high degree of skill and the tools and knowledge to model PH20 accurately, assess potential substitutions, and interpret their effects based on well-characterized structural and mechanistic features shared across hyaluronidases. Given this developed state of the art, the specification’s disclosures provided more than sufficient guidance to enable the full scope of the claimed polypeptides without undue experimentation.

Id. at 68–69 (citing Ex. 2068 ¶¶ 362, 371; Ex. 2070 ¶¶ 52, 234, 262). Patent Owner asserts that “the specification supplies detailed instructions on how to make and used the claimed variants and sub-variants.” *Id.* at 69 (citing Ex. 1001, 67:36–70:5, 71:25–33, Tables, 5, 9–10; Ex. 2068 ¶¶ 372–377; Ex. 2070 ¶¶ 248–261).

Patent Owner asserts: “[Dr.] Petsko describes in detail how POSAs could use the functional data in connection with homology models” and also “provided multiple examples of how POSAs could have used the data in connection with the homology model to make modified PH20s using routine methods and illustrating how a POSA would have predictably and easily

used [] the data without trial-and-error experimentation.” *Id.* at 71 (citing Ex. 2070 ¶¶ 297–342). Patent Owner asserts that “Petitioner’s argument that POSAs would need to generate impossibly large libraries and screen them for activity to practice the claims is not credible. Where, as here, the patent teaches POSAs a structure-function map of PH20, including which changes to make and which positions are generally tolerant to change, there is no reason to randomly screen to identify active PH20s with the M313 mutation.” *Id.* at 72.

Regarding contraceptive use, Patent Owner asserts that by December 28, 2012, POSAs would have expected that PH20 polypeptides would be useful as contraceptive vaccines in humans and other mammals, particularly because it was widely known that PH20 plays a vital role in fertility and affects several stages of conception, including the critical final step of allowing the sperm to physically reach the egg.

Id. at 74 (citing Ex. 2072 ¶¶ 19–34).

Patent Owner asserts that

Petitioner argues that “[m]odified PH20 polypeptides that cannot be produced or are not properly folded will not retain the native protein structure of PH20 and cannot be ‘useful’ ‘active’ or ‘inactive mutants’—they have no utility.” Pet., 94. If true (it is not), those embodiments would simply be inoperative, and “[e]ven if some of the claimed combinations [are] inoperative, the claims are not necessarily invalid.”

Id. at 80 (quoting *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984)). Patent Owner asserts that “the specification, together with well-established tools in the art, provided the means to draw that distinction.” *Id.*

4. *Petitioner's Reply*

Petitioner responds that

When **multiple** mutations are made together, they affect a protein's structure, folding capacity, and stability differently than how each does alone. Each can cause effects remote from the mutation that change how the protein reacts to subsequent changes. The unpredictable effects of combinations of mutations ("epistasis") prevent a POSA from predicting whether the vast majority of multiply-modified PH20s will "properly fold."

Reply 23 (citing Pet. 10–11, 67–69; Ex. 1003 ¶¶ 56–62, 194–197; Ex. 1133 ¶¶ 123, 125–126, 222, 232, 252–259, 262, 330; Ex. 1131, 79:15–22, 89:21–90:24; 270:9–17; Ex. 1160, 383–85). Petitioner asserts that "[e]ven **one** mutation can prevent folding, cause misfolding or incomplete folding, or adoption [of a] native fold but that unfolds outside the cell and forms aggregates—Dr. Petsko's textbook illustrates this." *Id.* at 26 (citing Ex. 2164, 160; Ex. 1133 ¶¶ 73–76, 326; Ex. 1003 ¶ 55; Ex. 1131, 41:22–42:11).

Petitioner asserts that "[e]ven positions Dr. Petsko labeled as '100% tolerant' (the **most** predictable in his table) exhibit widely varying effects. That reflects that **each** substitution causes a **unique** effect on **the entire** PH20 protein structure not limited to its position." *Id.* at 28 (citing Ex. 1133 ¶¶ 264–269).

Petitioner further asserts that, contrary to Patent Owner's assertion that the " α/β barrel motif in PH20s makes it possible to predict combinations of changes to them, . . . EX1144 reports an experiment where loops in a **canonical** α/β enzyme (PRAI) were replaced with loops from other α/β proteins with the **same** fold. Positions were chosen to increase odds of being

tolerated.” *Id.* at 30–31 (citing Ex. 2070 ¶¶ 52, 292; PO Resp. 50–53).
Petitioner asserts that “[d]espite the constrained choices, most α/β barrel mutants ***did not fold***.” *Id.* at 32 (citing Ex. 1133 ¶¶ 177–182).

Petitioner asserts:

Experimental design flaws and incomplete reporting of results independently render Dr. Petsko’s ratings unreliable:

- inadequate numerical, structural context, and physicochemical interrogation of positions prevent reliable ratings of tolerance;
- no use of positive/negative controls in the primary assay, and no evidence of proteins in supernatants or their folded state;
- no activities reported for inactives, precluding differentiation of non-secreted mutants from those with residual activity;
- averaging of activities conceals inter-assay variability;
- unusually high (~40%) assay variability (ordinarily ~10-15%) render classifications unreliable.

Dr. Naismith showed that correcting for these limitations and problems paints very different pictures than the ones Dr. Petsko presented.

Id. at 32–33 (citing Pet. 58–63; Ex. 1003 ¶¶ 68–77, 100; Ex. 1133 ¶¶ 291–315, 244–248, 250, 175, 234–237, 304–305, 316–323, 239–242, Appendix B (Ex. 1135)). Petitioner asserts that “the description does not propose selecting positions and substitutions based on ***a proportion*** of active mutants at a position. Where ‘tolerance’ is used to inform changes, the disclosure simply instructs POSAs to ***not include*** inactivating substitutions in active PH20s.” *Id.* at 37 (citing Ex. 1026, 91:30–92:20; Ex. 1133 ¶¶ 206–207, 209).

Petitioner asserts that for several immunological reasons, “[c]ontraceptive utility was not a credible utility for any PH20 polypeptide

in 2011-2012, it was just an invitation for further research.” *Id.* at 42 (citing *In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005); MPEP § 2107.01).

5. *Patent Owner’s Sur-Reply*

Patent Owner asserts that “[t]he patent’s disclosure provides a granular structure/function correlation that teaches, on a position-by-position basis, the effect on activity of substituting different amino acids into every position within the primary structure.” Sur-reply 7. Patent Owner asserts:

To evaluate written description and enablement, Drs. Petsko and Simpson used the same “visualization-based assessment” technique that Petitioner admits was “prevalent” in 2011 and “a consistent, objective methodology for assessing substitutions.” Pet., 113-118. Indeed, Petitioner admits this method can be used to predict the effects of up to five modifications, *without the patent data*.

Id. (citing Ex. 1003 ¶ 196; Ex. 1004 ¶ 169; Ex. 1133 ¶ 258, n.293). Patent Owner cites Dr. Petsko’s testimony that “[a] POSA could select 23 residues to change and reasonably expect to obtain an active PH20 as those changes were based on the data in the patent.” *Id.* at 10 (citing Ex. 2070 ¶ 359). Patent Owner asserts that “with the patent data in hand, the POSA can avoid the billions of PH20s that will be inactivated by changes identified in the patent.” *Id.* at 12.

Patent Owner asserts: “here, the claim specifies a small range of sequences highly similar to mature PH20, and Petitioner’s expert admitted that if active, *they would fold to the PH20 alpha-beta barrel fold*.” *Id.* at 14 (citing Ex. 2301, 213:10–18, 85:19–86:5; 95:9–20, 96:16–98:20, 99:13–18, 101:11–20, 159:13–25). Patent Owner asserts: “if the patent data were as useless as Petitioner claims, Petitioner should have easily been able show multiple examples of sequences within the scope of the claims that produced

results that were not predicted by the patent’s disclosure of tolerance data.” *Id.* at 16.

Patent Owner asserts that “POSAs would be able to practice the full scope of the claims despite Petitioner’s ‘sequence space’: ‘no POSA would start with the theoretical maximum number of potential sequence variants as a starting point for making a comparative analysis of what amino acids would retain activity in a PH20 polypeptide.’” *Id.* at 24 (citing Ex. 1130, 93:20–24). Patent Owner asserts that “[Dr.] Simpson, who has experience with the patent’s assays, explained why variability does not undermine reliability and is consistent with a POSA’s expectation.” *Id.* at 26 (citing Ex. 2068 ¶¶ 202–203, 223–226, 182–183, 186).

Patent Owner asserts that “Petitioner’s expert agrees that no known human contraceptives achieve 100% effectiveness and substantially lower efficacy would still ‘have an important and valuable’ application.” *Id.* at 27 (citing Ex. 2302, 134:5–135:3).

6. *Analysis*

Petitioner has the burden to identify how the specification allegedly fails to enable the claims. We address the *Wands* factors and the parties’ respective arguments and evidence.

a) Breadth of Claims and Nature of the Invention

Dr. Park states that he determined the number of distinct polypeptides within the sequence space of the challenged claims. Specifically, he calculated “the number of distinct polypeptides that have (i) one substitution at a defined position to either one, eight, or one of nineteen alternative amino acids, and (ii) additional substitutions to human PH20 proteins having

varying lengths of C-terminal truncations.” Ex. 1004 ¶ 175. Dr. Park’s table is reproduced below:

<i># Positions that Could be Changed</i>	<i># Changes</i>	<i>Pos. 313 Choices</i>	<i>Add’l Changes</i>	<i># of Distinct Polypeptides</i>
337	20	19	19	1.85×10^{56}
327	20	19	19	1.02×10^{56}
337	15	19	14	3.10×10^{43}
327	15	19	14	2.01×10^{43}
337	20	8	19	7.78×10^{55}
337	20	1	19	9.72×10^{54}

Id. ¶ 176. Dr. Park’s table shows that the “number of distinct peptides is extremely large by all accounts, ranging from 10^{43} to 10^{56} .” *Id.*

Dr. Hecht agrees, stating the “Dr. Park’s calculations yielded immense numbers of distinct modified PH20 polypeptides based on the different sets of parameters used in the claims.” Ex. 1003 ¶ 141. To illustrate how large a number like 10^{43} is, Dr. Hecht states that an “aggregate weight of the smallest set containing one molecule of each of the PH20 mutants would be . . . = 1.80×10^{21} kg. The weight of the Earth is ‘only’ $\sim 5.97 \times 10^{24}$ kg.” *Id.* ¶ 142. That is, Dr. Hecht states that a complete set of one single molecule of protein that comprises all possible mutations in PH20 as recited in claim 1 would weigh about one thousand times more than the entire mass of planet Earth. *See id.*

In deposition, Dr. Hecht stated, “my sense was that the [] patent lists a minuscule and highly biased sample of what would be within [the claims], in

the sense that it only lists single amino acid substitutions while at the same time it's attempting to claim things that have 20 or more substitutions.” Ex. 2076, 203:6–12. When asked if a sequence “gives you enough information to tell whether that amino acid sequence is 95 percent identical to SEQ ID NO. 3”, Dr. Hecht answered “Yes, but that’s all it tells you. It doesn’t tell you anything about active, precipitated, aggregated, folded. It doesn’t tell you anything.”²¹ *Id.* at 204:11–19.

Dr. Simpson disagrees with Dr. Hecht and Dr. Park, stating that “POSAs would not evaluate the scope of the claimed genus by calculating the total number of amino acid sequences that have up to 20 modifications in the hyaluronidase domain. POSAs would evaluate the scope of the claims by considering the variation across the claimed modified PH20s.” Ex. 2068 ¶ 353. Dr. Simpson states that the “enzymatically active claimed variants [] share a common scaffold with common structures (*e.g.*, disulfide bonds) that enable them to fold into this common tertiary structure.” *Id.* ¶ 356. Dr. Simpson states that the “enzymatically active claimed variants and sub-variants share a common active site and common residues involved in facilitating the catalysis reaction.” *Id.* ¶ 357.

Dr. Simpson states that

[a]s to the nature of the invention, the claims cover modified PH20 variants and sub-variants. A POSA would have understood that predictably making and using the claimed PH20 variants and sub-variants required only routine molecular biology and protein biochemistry techniques, particularly in

²¹ The same would apply to amino acid sequences that are 94% percent identical to SEQ ID NO. 3. *See supra* n.12.

view of the extensive structure-function guidance provided in the '345 patent and the knowledge in the art.

Id. ¶ 360.

Dr. Petsko agrees with Dr. Simpson, stating that “POSAs think of the class of modified PH20 proteins with up to 20 modifications within the hyaluronidase domain (including the recited change at position 313) as an extremely limited set of proteins. Those that fold are a limited set of structurally homogeneous proteins.” Ex. 2070 ¶ 391. Dr. Petsko states that “[t]o further illustrate the common structural features shared by the claimed polypeptides, I generated models of several M313K variant PH20s that satisfy the sequence identity requirements of claim 1.” *Id.* ¶ 420. After showing images of one set of these models, Dr. Petsko states that in this example, “all of the M313K models share a common structural feature in that they all form interactions with F29 and E31.” *Id.* ¶ 426.

In deposition, Dr. Simpson acknowledged the accuracy of Dr. Park’s sequence space calculations. *See* Ex. 1130, 90:14–16. However, Dr. Simpson stated that “no POSA would start with the theoretical maximum number of potential sequence variants as a starting point for making a comparative analysis of what amino acids would retain activity in a PH20 polypeptide.” *Id.* at 93:20–24. Dr. Simpson also stated that a POSA “would have internal experimental criteria that they would be seeking to meet in generating a polypeptide that met the claims.” *Id.* at 96:13–15.

Addressing the impact of mutations on the three-dimensional structural integrity of the polypeptide, Dr. Petsko stated: “What I can say is, from years of experience in mutating enzymes and looking at them, just because a mutation has no activity or low activity doesn’t mean it has

disrupted the fold.” Ex. 1131, 79:6–9. In response to being asked whether for “changes that cause a loss of activity . . . is it likely that individual residues have shifted in the spatial positioning of them relative to the native protein?”, Dr. Petsko stated: “Maybe a few, but not many. And the alpha-beta barrel might be completely superimposed.” *Id.* at 92:17–93:2. When asked about nonhuman proteins that would fall within the scope of the claims, Dr. Petsko acknowledged that the chimp, gibbon, and orangutan naturally-occurring sequences fall within the scope of claim 1. *Id.* at 84:10–24.

Dr. Naismith disagrees with Dr. Petsko’s and Dr. Simpson’s attempt to “portray the claims of the ’345 Patent as covering a ‘narrow’ and ‘structurally homogeneous’ set of proteins,” stating:

If the set of polypeptides being claimed includes any polypeptide with an amino acid sequence that meets only the above three claim requirements^[22], it is both enormous and highly heterogeneous. Even if the set is restricted to enzymatically active modified PH20 polypeptides, a POSA would expect there to be variations in the structural features of that set of proteins, albeit in ways that permit substrate recognition and catalysis. Dr. Hecht illustrated these points in his declaration.

Ex. 1133 ¶ 40 (citing Ex. 1003 ¶¶ 44–46, 56–62, 194–197). Dr. Naismith notes that “Dr. Petsko said he uses enzymatic activity and the ability to be secreted as ‘proxies’ for PH20 proteins that have ‘properly folded’” but that

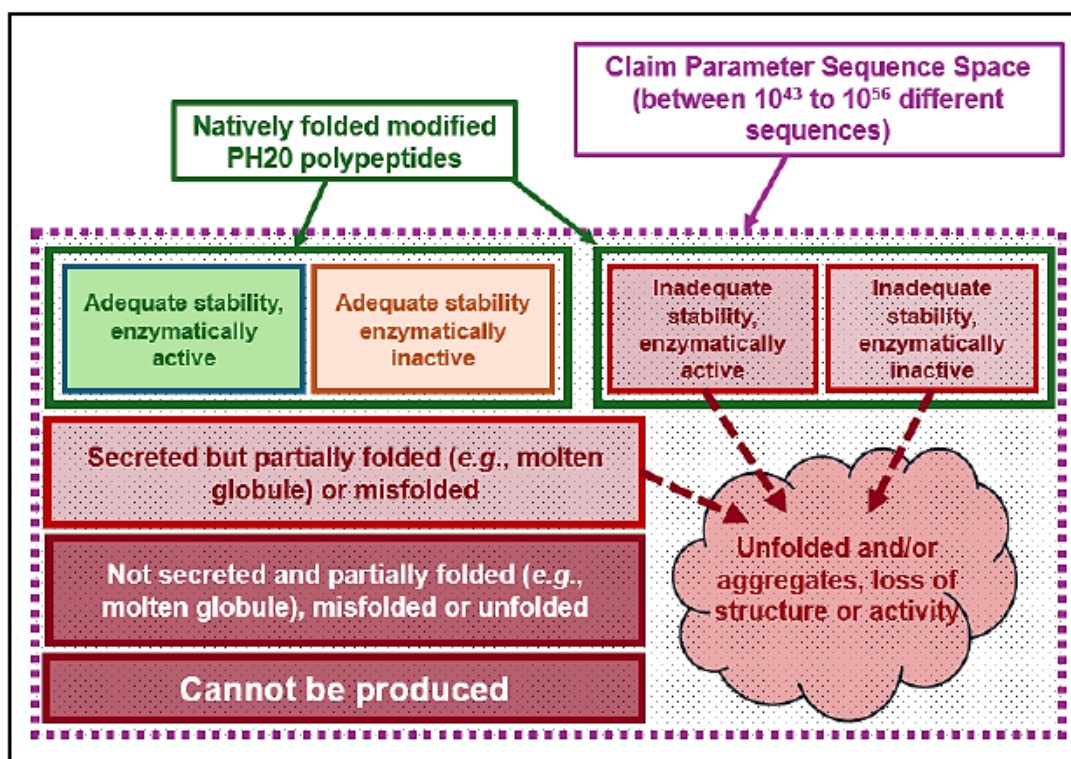
²² The three claim requirements Dr. Naismith identifies are (i) “a hyaluronidase domain that corresponds to positions 3-339 of the mature human PH20 protein (*i.e.*, SEQ ID NO: 7),” (ii) “an amino acid substitution at position 313 with reference to SEQ ID NO: 7,” and (iii) “up to 20 total modifications within the hyaluronidase domain.” Ex. 1133 ¶ 40.

“a POSA would not believe an enzyme had ‘properly folded’ if it did not maintain activity over a meaningful period or if it formed aggregates within a short period.” *Id.* ¶¶ 58–59.

According to Dr. Naismith, sequences within the recited sequence space will adopt many different three-dimensional structures according to a complex folding process, and mutations to their amino acid sequence increase obstacles to them successfully folding to adopt their native (active) state. *See* Ex. 1133 ¶¶ 60–80. As evidence, Dr. Naismith cites “a series of articles by Dr. Christopher Dobson at Cambridge University before 2011” regarding “the complexity and challenges of protein folding, and the diversity of confirmations an amino acid sequence can adopt.” *Id.* ¶ 62. Dr. Naismith states:

As Dobson 2004a explains, native (not mutant) sequences have been specifically selected by evolution to fold. Of particular note is that only these “special” evolutionarily selected amino acid sequences will induce the “correct (native-like) interactions between different residues [that] are on average more stable than the incorrect (nonnative) ones.” Mutated sequences do not benefit from this evolutionarily conferred advantage, which is why so many of them cannot find the pathway to the native state of the folded protein.

Id. ¶ 69 (citing Ex. 1136, 4). Dr. Naismith states that “a POSA would not view the sequence space defined by the sequence identity claim parameters as being structurally homogeneous. That is because it contains many unfolded sequences that can adopt an immense number of conformational states, all of which are different from the native fold” and impact activity. *Id.* ¶ 77. Dr. Naismith explains this will result in distinct sets of three-dimensional structures within the sequence space, as illustrated in the figure reproduced below:



Id. ¶ 78. Dr. Naismith’s figure reproduced above shows what Dr. Naismith describes as distinct sets or categories of sequences within the claimed sequence space (dotted line), including stable, active polypeptides (shown in green) and others that suffer from various problems (shown in red). *See id.* ¶¶ 77–80. Dr. Naismith states that “[i]n the 2011-2012 timeframe, a POSA would have no reliable method of assigning sequences to the various categories [in the figure above] except by extensive experimentation.” *Id.* ¶ 80.

Dr. Naismith states: “I do not agree that the 94% sequence identity requirement is a ‘structural feature’ of a modified PH20 polypeptide. It is a claim requirement that is determined mathematically.” *Id.* ¶ 83.

Dr. Naismith states that percent identity “does not define any particular physical characteristic of a modified PH20 molecule. It functions solely to limit the size of the sequence space of the modified PH20 polypeptides.” *Id.*

In deposition, Dr. Naismith observed with respect to the structural comparisons of Hyal1 and PH20 that “what is really interesting . . . is despite the fact that they have the same fold, they actually have some differences in function, which shows you it is quite difficult to detect.” Ex. 2301, 86:14–17.

Based on the evidence of record, we find that the breadth of claim 1 and the dependent claims is immense, comprising a sequence space ranging from $\sim 10^{43}$ distinct polypeptides for the narrowest claims to 10^{56} for the broadest. Ex. 1003 ¶¶ 141; Ex. 1004 ¶ 176. While we appreciate that the sheer number of distinct polypeptides as calculated by Dr. Park is larger than the scope of the claims (which is limited to active polypeptides), the number of active polypeptides encompassed by the challenged claims is still very large even if its precise breadth is unknown. *See, e.g.*, Ex. 1131, 61:19–64:11 (Dr. Petsko testifying that the number of properly folded proteins in the genus of claim 1 is large and that it would not be possible to calculate the number of such proteins that are not properly folded).

We also disagree with Patent Owner’s attempt, through its experts, to characterize the claim scope as “structurally homogenous.” *See, e.g.*, PO Resp. 3, 63–67. In particular, we credit Dr. Naismith’s testimony regarding a POSA’s understanding of protein folding and the three-dimensional structure formed by enzymatically-active polypeptides. *See* Ex. 1133 ¶¶ 52–80. That testimony is well-supported by the references Dr. Naismith cites, including a textbook from Patent Owner’s expert Dr. Petsko. *See id.* (citing Ex. 1136, 11; Ex. 1137, 888, Ex. 1138, 11; Ex. 1139, 351; Ex. 1140, 329 (Dobson articles); 1140, 329; Ex. 2164, 3, 160 (Petsko Textbook); Ex. 1014, 91–92).

We find Dr. Naismith's testimony in this regard to be more persuasive than the competing testimony offered by Drs. Simpson and Petsko to show that the claims are directed to a "limited set of structurally homogeneous proteins." *See, e.g.*, Ex. 2068 ¶¶ 33, 317, 354–359; Ex. 2070 ¶ 58, 391–430. At most, the testimony of Drs. Simpson and Petsko shows that at least some of the claimed polypeptides may have some broad structural features in common, but Dr. Naismith shows that protein folding is extremely complex, resulting in many different subsets of polypeptides within the claims' immense sequence space (Ex. 1133 ¶ 78) and that even a single mutation can affect the net free energy such that the protein does not fold properly (*see, e.g., id.* ¶¶ 75–76).

We also agree with Dr. Naismith's criticism that Dr. Petsko's testimony regarding a common "alpha-beta barrel fold" exhibited by the recited polypeptides is imprecise and does not predict whether a particular amino acid sequence within the recited sequence space will possess that feature. *See, e.g.*, Ex. 1133 ¶¶ 153–163. Therefore, it cannot be said to be "a 'common structural feature' of the entire set of 10^{43} to 10^{56} polypeptides within the claim parameter sequence space" because, as Dr. Naismith persuasively explains, within that "space will be many sequences that cannot be produced, will not properly fold, or will unfold because they are unstable" and without "a stable tertiary structure, they will not contain the 'PH20 α/β barrel' motif present in the tertiary structure of the PH20 protein." *Id.* ¶ 170. We therefore agree with Petitioner and Dr. Naismith that the challenged claims are directed to very broad, "structurally heterogenous genera." *See* Reply 3–6; Ex. 1133 ¶ 80 (a POSA would

recognize “there is an incredible amount of structural diversity” with the “claim parameter sequence space”).

b) Skill in the Art

We find that the skill in the art is high, as indicated by both parties. *See supra* Section II.A.

c) State of the Prior Art

Dr. Hecht acknowledges that protein expression is routine, stating that the “conventional procedures relating to production of the wild-type PH20₁₋₄₄₇ . . . protein could be applied to produce forms of human PH20₁₋₄₄₇ that incorporate a single amino acid substitution . . . with little effort.” Ex. 1003 ¶ 239. Dr. Hecht further states that “[t]he first experimentally determined structure of a hyaluronidase was of bvH [bee venom hyaluronidase], 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.” *Id.* ¶ 81 (citing Ex. 1033, 1028–31).

However, Dr. Hecht also states “[d]ata in the ’429 Patent and a 2007 paper by Frost (EX1013) identified seven C-terminally truncated human PH20 proteins that retained >40% activity of the 1-447 PH20 sequence Additional truncations of varying length at the C-terminus of PH20 caused significant variations in hyaluronidase activity.” *Id.* ¶ 94. Dr. Hecht states that 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.* ¶ 96. Dr. Hecht states that “[n]either the scientific literature existing by 2011 nor the common disclosure provides an explanation why these PH20

truncation mutations that differ by one residue (i.e., PH20₁₋₄₄₆ vs. PH20₁₋₄₄₇ vs. PH20₁₋₄₄₈) exhibit variability in their activity.” *Id.* ¶ 98.

Dr. Hecht states “[t]here were limits to using rational design techniques in the 2011-timeframe.”²³ *Id.* ¶ 51 (citing Ex. 1018, 378; Ex. 1059, 1225–26). “The complexity of the structure/function relationship in enzymes has proven to be the factor limiting the general application of rational design.” *Id.* at ¶ 51 n.21 (quoting 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.* ¶ 53 (citing Ex. 1018, 378; Ex. 1059, 1227). Dr. Hecht states that “changing many amino acids simultaneously risks disrupting the pattern necessary to induce formation of the original secondary structure . . . and [can] be highly destabilizing to the overall protein structure.” *Id.* ¶ 56. Dr. Hecht states that in a ten amino acid substitution situation, “[t]here are approximately 6×10^{12} different scenarios of 10 substitutions.” *Id.* ¶ 59.

²³ “At a conceptual level, there are two approaches for creating engineered proteins, referred to as ‘rational design’ and ‘directed evolution.’” Ex. 1003 ¶ 48 (citing Ex. 1059, 1225–1227; Ex. 1018, 378–379; Ex. 1017, 223). “‘Rational design’ involves an in-depth study of the structural features of a protein and their contribution to stability and function” using computational tools, e.g., sequence alignments and structural modeling such as SWISS-MODEL. *Id.* ¶¶ 49–50 (citing Ex. 1017, 224–230 Ex. 1018, 378). “In ‘directed evolution,’ one generates large libraries of mutant proteins with randomly distributed mutations” and “then screens those libraries to find mutants having the desired properties.” *Id.* ¶ 52 (citing Ex. 1059, 1225–1226).

In deposition, Dr. Hecht referred to differences in present day computational modeling tools such as AlphaFold as compared to the tools available to a POSA in the 2011–2012 timeframe, explaining: “Now AlphaFold is -- you know, it’s an AI thing. People pop it in, and magic happens and something comes out. That’s very different from what was going on 15 years ago.” Ex. 2076, 33:19–22.

Dr. Simpson states that, as of the 2011–2012 timeframe, the “crystal structures of bee venom hyaluronidase and human Hyal-1 had been solved” and that “made it possible to generate accurate homology models of PH20’s tertiary structure.” Ex. 2068 ¶¶ 366–367. Dr. Simpson states that “[m]utagenesis studies in both Hyal-1 and PH20 also had confirmed the importance of certain residues for enzymatic activity and structural stability.” *Id.* ¶ 369 (citing Ex. 1010; Ex. 1011; Ex. 1033, 1029; Ex. 2070 ¶¶ 167–217). Dr. Simpson states that “as of December 28, 2012, a POSA would have had in-hand a PH20 homology model to evaluate potential substitutions.” *Id.* ¶ 370.

In deposition, regarding the sequence alignment in Figure 3 of Chao (Ex. 1006), Dr. Simpson stated that

a POSA would use the information about this structure, use the sequence alignment, and model PH20 according to this new structural information, and evaluate whether the blue invariant residues were located in a position of critical -- of a critical nature to the folded structure of PH20, and evaluate them individually, potentially, for their location in the structure, if they wanted absolute certainty about their role in maintaining the structure.

It’s also my opinion, though, that if I have this information about invariant residues in an alignment and about functional data that implicates certain of those invariant

residues in maintaining enzymatic activity of the enzyme, that a POSA would avoid residues that are invariant if they wish to maintain activity of the polypeptide.

Ex. 1130, 121:8–24.

Dr. Petsko states that “PH20, Hyal-1 and bee venom hyaluronidase all achieve the function of cleaving HA using a common structure—the active site in all three proteins is a long groove and the same critical residues (oriented in about the same positions) catalyze the reaction in all three proteins.” Ex. 2070 ¶ 139. Dr. Petsko states that “this common structural feature was recognized in the literature”:

Stern teaches that “HA-degrading enzymes” share a “common structural feature,” which is an “elongated cleft for accommodating substrate” EX1008 (Stern), 833. Consistent with this, Marković-Housley reports that the “dominant feature of the [bee venom hyaluronidase] protein surface is a large groove” that forms the active site and “would be large enough to accommodate a hexasaccharide” of HA.

Id. ¶ 140 (citing Ex. 1033, 1028).

Dr. Naismith states: “By 2011-2012, it had been demonstrated that the five human hyaluronidase enzymes exhibit distinct profiles of biological activities and expression patterns.” Ex. 1133 ¶ 183 (citing Ex. 1008, 825). For example, Stern (Ex. 1008) states: “Hyal-2 of human origin degrades high molecular mass HA to an approximately 20 kDa product (~50 saccharide unites), whereas Hyal-1 can degrade high molecular weight HA to small oligomers, primarily to tetrasaccharides.” Ex. 1008, 825.

Dr. Naismith states that “[u]sing Dr. Petsko’s high level perspective, all appear have the same ‘alpha-beta barrel’ motif. Despite this similarity, the

five proteins exhibit subtle but meaningfully different substrate preferences and activity.” Ex. 1133 ¶ 184.

Dr. Naismith states that Zhang (Ex. 1010), a paper co-authored by Dr. Simpson, “highlights the limits of homology models in predicting mutation effects.” Ex. 1133 ¶ 195. Dr. Naismith explains that

Dr. Simpson confirmed that her group used a Hyal-1 structural model to predict catalytic residues, then tested those predictions experimentally, with mixed results—for example, mutating Glu131 abolished activity, while mutating Asp129 did not. This reflects the understanding of a POSA in 2011-2012: that one could make a limited number of reasonable predictions using a homology or structural model but experimental confirmations are needed to test those predictions.

Id. ¶ 195 (citing Ex. 1130, 130:9–16; Ex. 1010, 9436–9437). Indeed, Zhang itself states that “[a]nalogy to point mutations in both sperm hyaluronidase, PH-20, and bacterial *N*-acetylglucosaminidase H, further suggested Asp¹²⁹ and Glu¹³¹ would be critical for catalytic activity of the enzyme. . . . Interestingly, Asp¹²⁹ was not essential, because significant activity was retained.” Ex. 1010, 9436–37.

In deposition, when asked, “Did you look at the experimentally determined PH20 structure?”, Dr. Naismith stated: “I don’t believe there is experimentally. There certainly wasn’t one at 2011/2012.” Ex. 2301, 87:19–23.

Based on the evidence of record, we find that simply making and expressing modified PH20 polypeptides was well within the state of the prior art. The evidence also shows that molecular modeling of a putative PH20 structure, using a then-available tool such as SWISS MODEL, would have been routine as well, and that there was information about several

amino acid locations within the protein that were involved in catalytic activity. Ex. 1033, 1028–31; Ex. 2070 ¶¶ 139–140. However, the evidence of record also demonstrates that it was known that mutations, whether conservative or non-conservative, may impact protein function and physical shape. *See, e.g.*, Ex. 1003 ¶¶ 96, 101, 181–182 (discussing references showing disparate effects from modifying hyaluronidases and evidencing uncertainty regarding the effect of changes, particularly to certain regions of PH20, e.g., changes to the Hyal-EGF domain); Ex. 1133 ¶¶ 185–195, 221–222 (similar). The evidence demonstrates that identifying which of the 10^{43} to 10^{56} members of the PH20 polypeptide genus would either retain functional hyaluronidase activity (or otherwise be useful as antigens in contraceptive vaccines) was not known in the prior art. This is evidenced for example by Zhang, which teaches that Asp¹²⁹ was predicted to be critical for activity based on homology, but was determined experimentally by making and testing the modified PH20 polypeptide to not be essential. *See* Ex. 1010, 9436–9437. A POSA would have understood this unpredictability was even more pronounced when multiple mutations were introduced. Ex. 1003 ¶¶ 55–62, 196; Ex. 1004 ¶ 169; Ex. 1133 ¶¶ 252–259 (discussing epistasis²⁴ and concurring with Petitioner’s other experts “that after about 5 mutations, a POSA could no longer predict enzyme behavior by simple linear combinations of single site mutations” (¶ 258)).

²⁴ Dr. Naismith explains that “epistasis refers to a non-additive interaction of an additional mutation, where the functional effect of the functional mutation is context-dependent,” meaning that when combined two singly beneficial mutations may be deleterious. Ex. 1133 ¶¶ 253–254 (citing Ex. 1160, 383–385).

Accordingly, the evidence of record demonstrates that methods of accurately identifying which of the 10^{43} to 10^{56} members of the challenged claims' sequence space would retain functional hyaluronidase activity aside from actually making and testing particular polypeptides was not known in the prior art as of the 2011–2012 timeframe.

Finally, addressing Patent Owner's argument that the claimed polypeptides could also be used antigens in contraceptive vaccines regardless of whether or not they exhibited hyaluronidase activity, we find that the extent to which PH20, much less the recited "modified PH20 polypeptides," could be credibly used as contraceptives was not demonstrated in the prior art. *See supra* Section II.C.6.b.2.

d) Presence of Working Examples

According to Dr. Hecht, Table 8 of the Specification provides a compilation of the 6,753 mutants produced by the inventors, which were all generated by substituting one amino acid from PH20₁₋₄₄₇. Ex. 1003 ¶ 107. Dr. Hecht states that Table 10 contains a compilation of tested "inactive mutants" with 3,380 entries. *Id.* ¶ 112. Dr. Hecht calculates that based on the data in the Specification, "57.1% were inactive, and 29.4% others had activity <100%." *Id.* ¶ 115. Dr. Hecht states the Specification "does not identify any *mutated* PH20 proteins that were effective when used in a contraceptive vaccine." *Id.* ¶ 123.

Dr. Petsko states that "[t]he '345 patent provides a comprehensive and systematic analysis of each position on PH20, achieved through large-scale

mutagenesis and enzymatic activity testing of thousands of variants, with up to 18 mutations per position.” Ex. 2070 ¶ 44. Dr. Petsko states:

The patent data show, for each of the 447 positions in SEQ ID NO: 3, the tolerance of each position to substitution. The data show which positions are critical to activity, which are generally intolerant in that they permit only very limited substitution, and which are generally tolerant in that they permit a broad range of substitutions. The data also identify tolerant positions that retain activity when different types of residues are substituted (*e.g.*, negatively charged, positively charged, large, small, hydrophobic, hydrophilic).

Id. ¶ 54. Dr. Petsko states that “[i]n addition to providing data on 5847 single substitution variants, the patent also provides proof of principle for several multiply modified PH20s, including N47A/N131A, N47A/N219A, N131A/N219A and N47A/N131A/N219A, which were shown to be active.”

Id. ¶ 57.

Dr. Simpson states that the “patent provides a structure-function map of PH20 that informs a POSA, position by position, which residues are invariant, which tolerate little change, and which are amenable to substitution.” Ex. 2068 ¶ 373. Dr. Simpson states:

The inventors provide experimental data for the exemplary M313 variants in the patent. . . . [T]he patent also teaches the activity levels for various PH20 polypeptide lengths (*i.e.*, C-terminal truncation variants) recited in the claims. Given the breadth of experimental data establishing a structure-function map of PH20, POSAs would not have required further working examples of every possible sub-variant to make and use the claimed sub-variants.

Id. ¶ 377.

Dr. Cherr and Dr. Moon identify no working examples of PH20 functioning as a contraceptive in the Specification. *See generally* Ex. 2072, Ex. 2074.

Based on the evidence of record, we find that the Specification includes fifteen working examples of “modified PH20 polypeptides” with a single substitution at position 313, twelve of which were shown to have hyaluronidase activity, one of which was inactive, and two of which were not classified as either active or inactive. *See* PO Resp. 23; Ex. 1003 ¶ 147.

The common disclosure also discloses data for most of the other modified polypeptides having a single substitution at one position in PH20, classifying such mutants as either “inactive” or “active” and for the latter disclosing data showing their activity relative to the unmodified protein.²⁵ *See, e.g.*, Ex. 1003 ¶¶ 109, 113, 115 (referring to Tables 8–10 in the Specification). This evidence shows that more than half of the single substitution variants tested in the Specification’s working examples resulted in what the common disclosure describes as “inactive mutants.” Ex. 1003

²⁵ Dr. Hecht observes that the Specification provides no data for 836 of the 6,753 single substitution mutants listed in Table 8. Ex. 1003 ¶ 106. Dr. Petsko does not disagree and apparently excluded them from his positional analysis. *See* Ex. 2070 ¶ 264 n. 19 (“I understand there are additional substitutions in Table 8 that are not identified in Table 9 or 10 . . . it is not possible to tell why they were not included in either Table. Accordingly, I do not consider them in my analysis.”). Accordingly, while it is true that the Specification provides data for most of these single substitution PH20 mutants, we disagree with Patent Owner’s suggestion that the data is “comprehensive” for all such mutants. *See, e.g.*, PO Resp. 16 (characterizing the patent disclosure as “a comprehensive and systematic analysis of each and every position within the primary structure of PH20 (SEQ ID No: 3)”).

¶ 115; *cf.* Ex. 2070 ¶¶ 263–274 (Dr. Petsko tabulating data by position and noting that by that measure “about 48% of positions in PH20 are generally intolerant of substitution” (¶ 268)). This suggests there is substantial variability in the activity resulting from just a single modification to one of the residues in PH20. Patent Owner’s experts also refer to a handful of examples of multiply-modified PH polypeptides disclosed in the ’457 publication. *See, e.g.*, Ex. 2068 ¶¶ 189–192, 321. But none of these contain a substitution at position 313. *See id.*; Ex. 2165.

Finally, to the extent Patent Owner contends that a POSA could use the claimed modified PH20 polypeptides as antigens in a contraceptive vaccine, we note that none of the working examples in the Specification relate to such a use. *See supra* Section II.C.6.b.2.

e) Amount of Direction or Guidance Presented

The Specification states that “one or more modified . . . PH20 polypeptides are tested for a desired activity or property, such as increased stability.” Ex. 1001, 134:5–9. The Specification states the following regarding processes to make mutations in hyaluronidase enzymes such as PH20:

Libraries or collections of modified hyaluronan-degrading enzymes can be screened. Hyaluronan-degrading enzymes can be modified by any process known to one of skill in the art that can alter the structure of a protein. Examples of modifications include replacement, addition, and deletion of one or more amino acids of the protein to form libraries or collections of modified hyaluronan-degrading enzymes. It is within the level of one of skill in the art to generate modified or variant proteins for use in the methods herein. Methods of mutagenesis are well known in the art The mutations can be made rationally or randomly.

Id. at 135:18–43. Regarding testing the resultant mutations, the Specification states:

For purposes of selecting or identifying a modified hyaluronan-degrading enzyme that exhibits stability or increased stability under the denaturation condition, activity can be compared to activity of the modified hyaluronan-degrading enzyme in the absence of the denaturation condition and/or activity of the corresponding unmodified hyaluronan-degrading enzyme in the presence of the denaturation condition.

Id. at 136:19–26. The Specification states that “[c]ritical residues can be identified because, when mutated, a normal activity of the protein is ablated or reduced. For example, critical residues can be identified that, when mutated in a hyaluronan-degrading enzyme, exhibit reduced or ablated hyaluronidase activity.” *Id.* at 141:3–8. The Specification states that “[p]roteins, such as modified PH20 polypeptides, can be purified using standard protein purification techniques known in the art.” *Id.* at 151:4–9.

Dr. Hecht states that the Specification “uses the 40% activity threshold to classify a mutant as an ‘active mutant’” and that “‘inactive mutants’ are mutants with 20% or less of the activity of unmodified PH20.” Ex. 1003 ¶¶ 104–105. Dr. Hecht states that the data in the Specification shows that “most of the single-replacement PH20₁₋₄₄₇ mutants that were tested exhibited less activity than the unmodified PH20₁₋₄₄₇ (*i.e.*, 57.1% were inactive, and 29.4% others had activity <100%).” *Id.* ¶ 115.

Regarding potential contraceptive use, Dr. Hecht states that the Specification

does not identify any *mutated* PH20 proteins that were effective when used in a contraceptive vaccine. . . . The common disclosure does not provide any guidance that would allow a skilled artisan to determine whether any active or inactive

mutants are useful as contractive vaccines (such as by identifying common structural or functional characteristics shared by those inactive mutants), without making and testing all $\sim 10^{43}$ (or more) modified PH20 polypeptides within the parameters of each claim.

Id. ¶ 123.

Dr. Hecht further states “the data for testing the 409 mutants reported in Tables 11 and 12 [of the Specification] 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 PH20₁₋₄₄₇ form specifically.” *Id.* ¶ 77.

Regarding multiply-modified peptides, Dr. Hecht states that the Specification

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

Id. ¶ 206. Dr. Hecht characterizes the Specification’s disclosure as “best described as a research plan, as it generally outlines the types of steps one might take to carry out a mutagenesis and screening research program.” *Id.* ¶ 207.

In deposition, Dr. Hecht stated: “if you’re trying to take a protein -- this protein, PH20 -- and you’re planning to make 10 mutations, in many

cases even having the data here would not allow you to predict whether that protein would be active.” Ex. 2076, 264:7–12. Dr. Hecht stated that “the data in these tables is not going to always solve your problems if you’re attempting to make 10 changes. You can get into a situation where two changes give rise to a cooperative result, which means they’re not just the additive sum of the two.” *Id.* at 270:7–12.

Patent Owner’s experts characterize the Specification’s disclosure differently. For example, Dr. Simpson states that the “specification provides the POSA detailed information for literally every position in the protein, so the POSA can proceed position by position, or region by region, make the desired changes, depending on the POSA’s goals.” Ex. 2068 ¶ 375.

Similarly, in deposition, Dr. Simpson stated that

this patent discloses an enormous amount of data that help them beyond what was published in the literature at the time, which was the sequence, the sequence alignment to other hyaluronidases for PH20, as well as the knowledge of where it can be truncated to make it a soluble polypeptide, the fact that it retained activity as a soluble PH20 polypeptide.

And now, in addition, mutagenesis at every single residue of the polypeptide that gives data on whether or not that single substitution remained active.

Ex. 1130, 97:16–98:2.

Dr. Petsko states that “[w]ith the ’345 patent in hand, the POSA knows what positions tolerate substitution and which do not. The POSA would use that information to obtain modified PH20 polypeptides with the desired properties. The POSA would then make and test the desired polypeptide.” Ex. 2070 ¶ 348. Dr. Petsko states that a “POSA seeking to make a modified PH20 with the ’345 patent in hand would not make a

randomly generated combinatorial library of billions of sequences that happen to have up to 20 modifications within the hyaluronidase domain and then screen it for activity, because it makes no sense to do so.” *Id.* ¶ 347.

Dr. Petsko also states that the Specification

provides valuable data for identifying potential rescue mutations. To determine likely candidates for rescue mutations, a POSA would have examined the PH20 model to determine why activity was lost for a particular substitution. If the interactions that were lost can be replaced by simultaneously making another substitution (*i.e.*, a “rescue mutation”), then activity may be restored.

Id. ¶ 374.

In deposition, when asked whether “the patent provides examples of particular combinations of mutations that are correlated to PH20 proteins with desired properties such as increased activity or increased stability?”, Dr. Petsko stated:

The main combinations referred to have to do with the glycosylation, I don’t remember that any of those increased the activity. I don’t know if the stability was measured. Solubility of those can [a]ffect -- I think that might have been looked at but I don’t remember that either. So no, I don’t think so.

Ex. 1131, 110:22–111:8.

Dr. Naismith responds to Dr. Simpson’s and Dr. Petsko’s characterization of the Specification’s disclosure, stating that it

does not explain how any of the experimental results reported in the common disclosure relate to any of the structural observations reported in the Stern, Markovic-Housley, Chao or Zhang publications. It also does not tell a POSA how to [] use those findings in combination with the mutagenesis data when designing modified PH20 polypeptides to preserve the unique

α/β barrel motif or other structural features in the tertiary structure of the wild-type PH20 protein.

Ex. 1133 ¶ 151. Dr. Naismith states: “Dr. Petsko’s view of what a POSA would do directly contradicts the instructions of the common disclosure. The *only* description in the common disclosure for producing PH20 polypeptides with multiple substitutions is an iterative, directed evolution technique.” *Id.* ¶ 204 (citing Ex. 1003 ¶¶ 207–213; Ex. 1026, 141:30–34, 150:1–26). Dr. Naismith states that “the common disclosure leaves POSAs no practical alternative to the iterative mutagenesis approach that Dr. Petsko claims a POSA would avoid, notwithstanding that it necessarily entails generating and screening enormous numbers of largely nonfunctional variants.” *Id.* ¶ 205 (citing Ex. 1003 ¶¶ 218–222).

Dr. Naismith states that there “is no technique or passage in the common disclosure that could provide a basis for Dr. Petsko’s theory that a POSA could reliably identify rescue mutations to restore activity in inactive modified PH20 mutants” and “there was no reliable way to predict in advance which, if any, additional mutations would restore activity in a given protein, or PH20” particularly since “such mutations are often distributed throughout a protein and act through indirect effects on stability or dynamics, rather than through obvious local structural corrections.” *Id.* ¶¶ 210–211.

In deposition, Dr. Naismith stated that “the data in the patent show that single site mutations are perturbing the active site. Most of them perturb the structure function relationship at the active site. So we know that they are having some, I think Dr. Petsko’s phrase was, ‘action at a

distance.” Ex. 2301, 110:8–14. Dr. Naismith states that the “patent doesn’t give any teaching about combining multi-mutations at all.” *Id.* at 133:8–9.

Based on the evidence of record, we find that a POSA would have significant guidance on synthesis and expression of modified PH20 polypeptides, including most (but not all) of the single substitutions within the native PH20 structure.

However, the evidence also shows that the Specification provides very limited guidance regarding effective methods to identify which of the immense number of distinct polynucleotides having both the recited position 313 substitution and other modifications (i.e., multiply-modified polypeptides) are likely to have activity other than actually making and testing them. *See* Ex. 1003 ¶¶ 206–207; Ex. 1133 ¶¶ 204–205. To the extent computational tools and modeling might have been used along with the data in the Specification to help guide the discovery of specific multiply-modified polypeptides, we credit Petitioner’s evidence that the tools available to a POSA in the 2011–2012 timeframe did not allow for accurate predictions for five or more mutations. *See infra* Section II.D.6.g.

Finally, to the extent Patent Owner contends the ability to provide a contraceptive effect is relevant, we find there is essentially no guidance, either in the Specification or the prior art of record demonstrating which, if any, of the recited modified PH20 polypeptides are useful for providing such an effect. *See supra* Section II.C.6.b.2.

f) Quantity of Experimentation

Dr. Hecht states:

the effects on the local structure of a protein at the site of a single amino acid substitution will not necessarily be observed when multiple modifications are made at or near that position

(or even when they are made remote from the site of the first substitution). Consequently, even if one had insights on the effects of a single substitution on the local structure of a PH20 polypeptide at the site of that substitution, that information would not provide insights into the effects on the protein structure that might result when different combinations of 5, 10, 15, or more modifications are made to the protein. Consequently, the results observed for the single-replacement human PH20₁₋₄₄₇ polypeptides reported in the common disclosure would not be considered to be representative of all mutated forms of human PH20₁₋₄₄₇ polypeptides with that substitution (*e.g.*, at position 313) plus between 1 to 19 *additional* substitutions at any of hundreds of positions within the “hyaluronidase domain” of the PH20 protein. Instead, a skilled artisan would have had to discover which combinations of substitutions to the PH20 protein would result in mutants that exhibit hyaluronidase activity by making and testing all of them, which is an *an impossibly large undertaking*.

Ex. 1003 ¶ 197 (emphasis added). Dr. Hecht states that “[t]he examples of single-replacement human PH20₁₋₄₄₇ mutants are not representative of the incredible diversity of possible modified PH20 polypeptides having different sets of 1 to 14 or 1 to 19 *additional* substitutions within the common hyaluronidase domain that meet the parameters of the claims.” *Id.* ¶ 184.

Dr. Hecht states that “[m]aking and identifying all of the multiple-modified PH20 polypeptides within the immense set of polypeptides (between at least 10⁴³ and 10⁵⁶ distinct mutants) defined by the claims’ parameters and that are enzymatically active would require not only an undue amount of experimentation, it likely is impossible.” *Id.* ¶ 204. Dr. Hecht states that the directed evolution methods of the ’345 patent are “the quintessential ‘make and test’ trial and error technique. By definition, the scientist carrying out a directed evolution protocol does not know which of the potentially trillions of possible mutants might incorporate a

substitution that causes the protein to exhibit a particular characteristic, whether that is measured as increased stability, activity or something else.” *Id.* ¶ 223.

Dr. Simpson counters that “a POSA could have used the patent data to generate multiply modified PH20s with combinations of 5, 10, 15, or more substitutions. . . . The POSA would have expected those proteins to be active in view of the disclosure in the patent.” Ex. 2068 ¶ 387. Dr. Simpson also states that a “POSA seeking to generate the claimed modified PH20 variants and sub-variants actually using the data in the patent (*i.e.*, without randomly screening large libraries) could have done so.” *Id.* ¶ 389.

In deposition, in response to a question of “how would you identify which positions were important or necessary for folding of the protein?”, Dr. Simpson explained that

[b]y looking at the alignments, there are a number of invariant residues. A knowledge of which invariant residues are the active site residues allows us to exclude those from consideration as active site residues. There are a number of other invariant residues using the structure that can be deduced to be responsible for substrate docking. Those may or may not be folding determinants, but additional residues that don’t appear to be directly in contact with the substrate and are not directly defined as active site residues within 5 angstroms of a docked substrate are likely candidates for structural determinants.

Ex. 1130, 76:19–77:18. When asked, “Did you perform that analysis you just described of comparing the possible sequences to some smaller number of them that match the structure of the model of PH20?”, Dr. Simpson stated: “I need to say that no POSA would start with the theoretical maximum number of potential sequence variants as a starting point for

making a comparative analysis of what amino acids would retain activity in a PH20 polypeptide.” *Id.* at 93:13–24.

Dr. Petsko stated that “[a]s of 2012, the structure for PH20 had not been solved. As Dr. Park explains in his Declaration, however, the ‘absence of an experimentally determined structure for a protein does not preclude the use of structure-based modeling methods.’ EX1004, ¶ 37. That is because the PH20 structure can be modeled.” Ex. 2070 ¶ 117. Dr. Petsko states:

A POSA seeking to make a modified PH20 with the ’345 patent in hand would not make a randomly generated combinatorial library of billions of sequences that happen to have up to 20 modifications within the hyaluronidase domain and then screen it for activity, because it makes no sense to do so. It is difficult to imagine why anyone would do such a thing. If the sequences truly are random, then it is likely that a substantial number would include substantial modifications to residues known to be invariant because they are involved in catalysis, the active site, or in protein structure. . . . [T]hanks to the ’345 patent, the POSA has a much more sensible strategy.

Id. ¶ 347. However, Dr. Petsko does not identify any teaching in the Specification that suggests the use of molecular modeling. *See generally* Ex. 2070.

In deposition, when asked, “Is it possible to experimentally determine which ones are properly folded and enzymatically active in 2011 or 2012?”, Dr. Petsko stated: “Not from experimenting on the entire ensemble.” Ex. 1131, 64:12–17. When asked whether “a person of ordinary skill in the art in the 2011-2012 timeframe would be able to predict the change to a protein’s net free energy of stabilization associated with a set of 10 or 15 or 20 mutations?”, Dr. Petsko answered: “No. They would not be able to

predict the number. They would be able to get a sense of whether those were likely to be destabilizing or not.” *Id.* at 102:1–9.

Dr. Naismith states: “I agree with Dr. Hecht and Dr. Park that after about 5 mutations, a POSA could no longer predict enzyme behavior by simple linear combinations of single site mutations.” Ex. 1133 ¶ 258. Dr. Naismith states: “[t]hat is also the practical limit for screening enzyme libraries in the 2012 timeframe. Even using the most sophisticated screening technologies, the largest library that could be screened was around $\sim 10^9$ proteins.” *Id.*

After reviewing the record, we find the evidence and expert testimony offered by Petitioner to be more persuasive than the competing evidence from Patent Owner and its experts. That is, the record shows that an ordinary artisan would have been able to align and computer model the PH20 sequence in combination with other known hyaluronidase sequences to identify amino acids implicated in structure and function. This could provide some measure of guidance to identify polypeptides having both multiple modifications and activity, but in the 2011–2012 timeframe, the computerized techniques for making such predictions quickly became unreliable as more modifications were introduced. *See, e.g.*, Ex. 1004 ¶¶ 166–169; Ex. 1003 ¶ 264; Ex. 1133 ¶¶ 130–133, 260–263, 268, 270–274, 281–284.

The only “methods for identifying a modified or variant hyaluronan-degrading enzyme, such as a . . . modified PH20 polypeptide, that exhibits an altered activity of property compared to an unmodified hyaluronan-degrading enzyme” disclosed in the Specification follow directed evolution approaches. Ex. 1001, 132:48–53; Ex. 1003 ¶¶ 207–212. In such

approaches, libraries of modified polypeptides are prepared by random or site-directed mutagenesis and screened for activity. Ex. 1001, 133:11–17. Multiply-modified mutants can be identified by iterative screening, e.g., introducing single amino acid changes to create a first library, screening it to identify mutants that exhibit a particular property, and then introducing additional modifications to those mutants to create a second library for screening. Ex. 1001, 133:62–67, 140:45–52; Ex. 1003 ¶¶ 211–213. As Petitioner’s experts credibly explain, the problem with such approaches is scale—meaning it would require making and testing very large amounts of multiply-modified mutants to identify those within the recited sequence space that exhibit hyaluronidase activity. Ex. 1003 ¶¶ 218, 220–221; Ex. 1133 ¶¶ 204–205 (“the common disclosure leaves POSAs no practical alternative to the iterative mutagenesis approach that Dr. Petsko claims a POSA would avoid, notwithstanding that it necessarily entails generating and screening enormous numbers of largely nonfunctional variants”).

We find that it would not have been possible to make and test all of the polypeptides within the sequence space of the challenged claims for hyaluronidase activity. *See, e.g.*, Ex. 1003 ¶¶ 204, 223–226. Both Dr. Simpson and Dr. Petsko acknowledge that an ordinary artisan would not consider it possible to perform testing on the complete claimed set of PH20 mutations recited in claim 1, suggesting that the quantity of experimentation exceeded that feasible or possible at the time of invention. *See* Ex. 1130, 93:13–24; Ex. 1131, 64:12–17. And Dr. Naismith confirmed that neither the computer analysis nor screening technologies available in the 2011–2012 timeframe would have been capable of testing the full scope of the challenged claims. Ex. 1133 ¶ 258.

We are unpersuaded by Patent Owner’s attempt to sidestep the directed evolution experiments taught in the Specification though its expert’s testimony that the Specification’s experimental data provides a “structure-function map of PH20” that teaches “which positions are tolerant and intolerant of substitution, including what types of changes are tolerated and not tolerated” such that a POSA could pick and choose modifications to combine with a reasonable expectation that the resulting polypeptide would have activity. *See, e.g.*, Ex. 2068 ¶¶ 377, 379; Sur-reply 5–7 (urging the “patent’s disclosure provides a granular structure/function correlation” a POSA could use to “visualize” multiply-modified species and predict activity). First, as Dr. Naismith explains, the predictive analyses and residue-selection strategies asserted by Patent Owner’s experts are not taught, and in some respects run contrary to, the teachings in the Specification. Ex. 1133 ¶¶ 202–222. Second, Dr. Naismith also identifies a number of errors in Dr. Petsko’s positional tolerance table that undermine the credibility of Patent Owner’s experts’ analysis in this regard. *Id.* ¶¶ 238–242.

Third, we credit Dr. Naismith’s substantive criticisms of Dr. Petsko and Dr. Simpson’s opinions that the Specification data provides a “functional map”²⁶ that would allow a POSA to predict which multiply-modified mutants would have hyaluronidase activity without actually making and testing them. *See* Ex. 1133 ¶ 232 (summarizing points of disagreement). In particular, we credit Petitioner’s showing that the effects observed from single amino acid modifications are not necessarily

²⁶ *See, e.g.*, Ex. 2070 ¶ 44.

additive when combined in same polypeptide and that a POSA could not reliably identify “rescue mutations” (i.e., mutations that restore activity lost from deleterious ones) from the data in the Specification. Ex. 1133 ¶¶ 210–211; 252–269; *see also* Ex. 1003 ¶¶ 58–62, 180; Ex. 1004 ¶¶ 167–169.

Patent Owner suggests such evidence can be overlooked because instances of epistasis are “rare” and an inactive PH20 polypeptide “will stay inactive . . . absent intentional ‘rescue’ mutations.” *See* Sur-reply 12–14. But the claims encompass far more than combinations of just two substitutions, and even Dr. Petsko concedes there are “billions” of sequences within the recited sequence space that will not properly fold. *See* Ex. 2070 ¶ 347; *see also* Ex. 1133 ¶ 237 (“While some [residues critical to protein structure] can be predicted (*e.g.*, highly conserved positions), many others cannot without experimentation.”). Accordingly, we find Petitioner’s position more persuasive than Patent Owner’s competing position and evidence.

The facts here are similar to those in *Idenix*, 941 F.3d at 1156 where, in a genus of billions, the “key enablement question is whether a person of ordinary skill in the art would know, without undue experimentation, which [species] would be effective.” *Idenix* states that because of the “many thousands of [species] which need to be screened for . . . efficacy, the quantity of experimentation needed is large and weighs in favor of non-enablement.” *Id.* at 1159. Here, where the number is not thousands but at least some representative number of the multiply-modified PH20 polypeptides within the 10^{43+} sequence space sufficient to enable the full scope of the challenged claims, the quantity of experimentation would be many orders of magnitude more than that needed in *Idenix*.

Regarding potential contraceptive use, we find that the same problems would plague the quantity of experimentation needed to determine which, if any, of the modified PH20 polypeptides could be used in a contraceptive vaccine. As explained above, the Specification does not provide any substantial guidance or examples related to contraceptive use. And the prior art at the time evidences that a POSA would not have believed contraception to be a credible use. *See supra* Section II.C.6.b.2.

For these reasons, we find that a very large amount of experimentation would be necessary to enable the full scope of the challenged claims.

g) Predictability of the Art

Dr. Hecht states that the

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

Ex. 1003 ¶ 62. Dr. Hecht states, citing the '429 patent, that the “varying effects of changing residues in the Hyal-EGF region of PH20 show that a skilled artisan’s belief that changes in this region would be unpredictable were warranted and would be more so if multiple changes were made concurrently.” *Id.* ¶ 100. Dr. Hecht states that “[i]t would not have been scientifically plausible to suggest, before the advances in computational prediction of protein structure around 2020, that a skilled artisan could have predicted the effects of making the myriad possible sets of 2-14 or 2-19 additional changes (plus one substitution at position 313) on the enzymatic activity or other characteristics of a PH20 polypeptide.” *Id.* ¶ 180.

Dr. Hecht notes that “[a]nother problem caused by the claims’ parameters is that they capture many multiply-modified PH20 polypeptides with changes that the common disclosure says are deleterious or eliminate hyaluronidase activity in PH20 enzymes.” *Id.* ¶ 198. For example, Dr. Hecht explains that “the claims (other than claims 4-5) include multiply-mutated PH20 polypeptides having C-terminal truncations that truncate the sequence below position 429.” *Id.* ¶ 201. Dr. Hecht observes that the common disclosure “does not report any examples of singly- or multiply-modified ‘active mutant’ PH20 polypeptides having fewer than 447 residues, and provides no guidance about making enzymatically active PH20 mutants based on sequences terminating before position 447 [i.e., truncated sequences] and containing 2 or more substitutions.” *Id.* ¶ 201.

Dr. Hecht states that the “skilled artisan also could not predict whether any combinations of substitutions could be made in [] truncated forms of the native human PH20 would restore hyaluronidase activity with the M313K mutant.” *Id.* ¶ 202. Dr. Hecht continues:

In other words, the common disclosure not only does not help the skilled artisan identify which of the $10^{43}+$ possible PH20 polypeptides of varying length with 2 to 20 substitutions have hyaluronidase activity; to make and use all such enzymatically active PH20 polypeptides meeting the parameters of the different claims would require the skilled artisan to ignore what little guidance is in the specification about single-substitutions and truncations that render PH20 polypeptides inactive.

Id. ¶ 203. Dr. Hecht states that the artisan following the Specification’s “iterative mutagenesis and screening research plan cannot know in advance of conducting multiple rounds of experiments, whether multiply-modified PH20 polypeptides will be produced that retain sufficient activity will be

selected for the next round of the process.” *Id.* ¶ 220. Dr. Hecht’s testimony as supported by record evidence demonstrates that it is highly unpredictable which polypeptides would have hyaluronidase or contraceptive activity. *See, e.g., id.* ¶¶ 185, 189, 202–222.

Dr. Park states:

In 2011, a second or third substitution could possibly be considered, but modeling multiple substitutions is more challenging and predictions can quickly become unreliable. This is especially true if the mutated residues are close to each other, either in sequence or in space, so that they interact with each other. That is because one needs to model interaction between substituted residues as well as interaction between a substituted residue with constant neighbors. Because this is difficult to visualize, it becomes necessary to model individual combinations through homology modeling, which becomes combinatorial intractable.

Ex. 1004 ¶ 168. Dr. Park states that “a skilled artisan in 2011 could not have used SWISS-MODEL to reliably predict the effects on the structure of a modified PH20 polypeptide of many substitutions (*e.g.*, 5 or more) in the PH20 sequence, if each position is allowed to vary independently to one of several amino acids.” *Id.* ¶ 169.

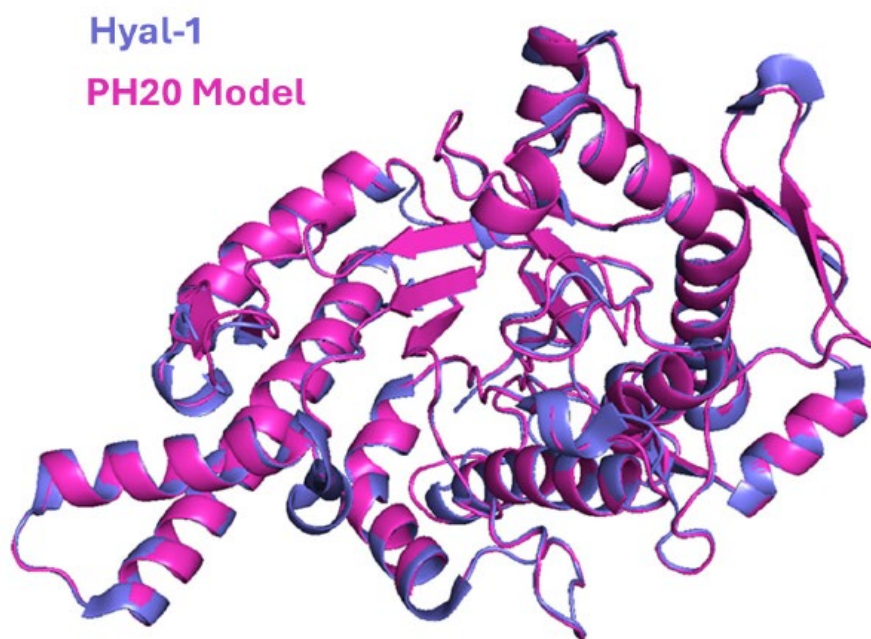
In deposition, Dr. Park, addressing single mutations, stated: “The problem is when you’re looking at one substitution, there are only so many interactions that a single amino acid can make, and those are relatively straightforward to discern for an expert.” Ex. 2077, 198:12–16. Dr. Park then stated that for multiple mutations,

if those substitutions happen to be very close to each other, what happens is now suddenly you have to deal with many more possible changes in the interactions, because the individual substitutions would now alter their interactions with their neighbor, and there would be interactions between them as well.

So now that results in both positive and negative interactions, all of which need to be tracked and estimated. Unfortunately, a person viewing the structure would not be able to differentiate many of these subtle changes, especially if there are multiple mutations nearby.

Id. at 199:7–19. Dr. Park stated regarding multiple mutations that “[a]s you introduce more and more mutations, the number of possible favorable and unfavorable interactions increases exponentially, and can quickly overwhelm a person’s ability to evaluate them.” *Id.* at 202:9–13. Dr. Park stated that “SWISS-MODEL doesn’t put a number on – it doesn’t tell you anything about the energetics of those substitutions. . . . It may be a horrendous combination of mutations. SWISS-MODEL would not know the difference between that and the best sequence.” *Id.* at 204:19–205:5. Dr. Park stated that the inability to model multiple mutations “was not a solved problem back in 2011. I don’t think it’s a solved problem as of today.” *Id.* at 212:17–19.

Dr. Petsko states that “Hyal-1 and PH20 also share a common alpha-beta barrel fold, with bee venom hyaluronidase adopting a similar fold. These three proteins are considered homologous with high sequence identity (30-40%).” Ex. 2070 ¶¶ 126–127. Dr. Petsko presents the figure reproduced below:



The figure above shows the PH20 model superimposed on the Hyal-1 structure. *Id.* ¶ 132. Dr. Petsko states: “When the PH20 model is superimposed on the Hyal-1 structure in PyMOL, as in the figure [above], it is evident that both proteins adopt essentially the same alpha-beta barrel fold.” *Id.* Dr. Petsko states that “PH20, Hyal-1 and bee venom hyaluronidase share a common mechanism of action in that they all cleave HA through the same chemical reaction.” *Id.* ¶ 135.

Dr. Petsko states that another “common structural feature shared by Hyal-1 and PH20 is the EGF motif. . . . [T]he EGF region is required for enzymatic activity in both proteins” but also states that “bee venom hyaluronidase does not include an EGF domain at all.” *Id.* ¶¶ 207, 210. Dr. Petsko states that “PH20, Hyal-1 and bee venom hyaluronidase all achieve the function of cleaving HA using a common structure—the active site in all three proteins is a long groove and the same critical residues (oriented in about the same positions) catalyze the reaction in all three proteins.” *Id.* ¶ 139.

Dr. Petsko states that

Zhang, on which Dr. Simpson is an author, contains mutagenesis data and provides insight regarding Hyal-1 residues required for activity.

. . . Those data can be mapped onto the Hyal-1 structure and PH20 model And the POSA seeking to evaluate structure/function correlations and common structural features among enzymatically active hyaluronidases in 2012 would have performed this analysis.

Id. ¶ 167. Dr. Petsko states that, as shown by his analysis,

POSAs expect that homologous proteins with high sequence similarity adopt the same fold because they share critical residues that adopt essentially the same positions and interactions (which in turn is what allows them to adopt the same fold). Because this principle holds for 40% identical homologous (but different) hyaluronidases, it certainly applies for 94% identical (properly folded) PH20 variants.

Id. ¶ 206.

In deposition, Dr. Petsko stated, “just because a mutation has no activity or low activity doesn’t mean it has disrupted the fold.” Ex. 1131, 79:7–9. Dr. Petsko stated that

the most common things are more complicated and more subtle. They involve, for example, action at a distance. You could have a mutation that changes the electrostatic potential of the protein at the active site even though it’s not in the active site, for example. But it would still have exactly the same fold.

Id. at 79:15–21. When asked whether a POSA in 2012 “would be able to predict the change to a protein’s net free energy of stabilization associated with a set of 10 or 15 or 20 mutations?”, Dr. Petsko answered “No. They would not be able to predict the number. They would be able to get a sense of whether those were likely to be destabilizing or not.” *Id.* at 102:1–9.

Despite that statement, when asked whether “you would be able to predict whether that mutated 15 or 20 residue-mutated PH20 will exhibit the activity that you are hoping to get?”, Dr. Petsko answered: “My opinion is that you could do so.” *Id.* at 111:9–16. However, when asked “do you think that in 2011 or 2012, a POSA using only a homology model could have predicted the effect of making five changes that are close together in a -- in the PH20 protein?”, Dr. Petsko stated: “I cannot answer that without knowing which five changes and where they are. . . . It will be context dependent to a large extent.” *Id.* at 207:15–24.

Dr. Simpson states: “in my opinion the specification gives a POSA the tools to make and use active (and inactive) PH20 variants and sub-variants and to distinguish between active and inactive PH20 variants using routine techniques.” Ex. 2068 ¶ 378. Dr. Simpson states that the “patent data allows POSAs to reasonably predict what changes will maintain activity, abrogate activity, reduce activity, or improve activity.” *Id.* ¶ 380 (citing Ex. 2070 ¶¶ 44, 54–56, 233–388). Dr. Simpson states that the “immense disclosure in the specification makes generating and using the modified PH20 variants and sub-variants in the claims predictable.” *Id.* ¶ 384.

Dr. Simpson states that

a POSA could have used the patent data to generate multiply modified PH20s with combinations of 5, 10, 15 or more substitutions. In fact, Dr. Petsko provided examples of such modified PH20s, including chimpanzee, gibbon and orangutan PH20s with the M313K substitution. EX20270, ¶¶ 420–439. The POSA would have expected those proteins to be active in view of the disclosure in the patent.

Id. ¶ 387.

In deposition, Dr. Simpson states: “Given the amount of activity data and the amount of structural homology and the sequence information, you would be able to predict the vast majority of activity structure, function relationships, for that family of modified PH20s.” Ex. 1130, 100:5–9. But when asked about a specific mutation characterized in the Zhang paper (Ex. 1010), specifically, “is the result for the D129N mutation – that’s not consistent with your hypothesis because it retained 5% of the activity. Right?”, Dr. Simpson answered: “It isn’t that it’s inconsistent with our hypothesis. . . . But we did not actually expect, necessarily, that it would fully abolish activity.” Ex. 1130, 130:23–131:20.

Dr. Naismith states:

Dr. Petsko’s textbook references Dr. Dobson’s work and provides an illustration of the impact of even a single mutation to the structure and stability of a globular protein (*e.g.*, PH20). In this example, the single mutation does not prevent secretion of the globular protein but disrupts its stability to the degree that the original folded protein partially or completely unfolds in the extracellular environment.

Ex. 1133 ¶ 76 (citing Ex. 2164, 160 (Fig. 4-53)). Dr. Naismith states: “Dr. Petsko suggests a POSA would expect that if the M313K substitution was introduced in three primate sequences, they would properly fold and be enzymatically active”, however,

[n]one of these proteins Dr. Petsko described were made or tested. It is important to note that they represent special cases. Dr. Petsko’s experiment of introducing the M313K change in chimp, orangutan or gibbon PH20 is simply introducing a single mutation into a naturally occurring sequence that has been shaped by evolution to stably fold and be active. Dr. Petsko’s hypothetical mutants represent an infinitesimally small portion of the patent’s enclosed sequence space. There is no teaching in the patent or modelling software that would allow

sets of 42 combined substitutions that differ by more than around five changes from a known stably folded active PH20 to be predictably active.

Id. ¶¶ 116–117 (citing Ex. 2070 ¶¶ 361–365, 420–429).

Dr. Naismith states: “I do not believe a POSA in the 2011-2012 timeframe could have visualized from the common disclosure the set of modified PH20 polypeptides with more than about 5 changes within the claim parameter sequence space that will fold and be enzymatically active.”

Id. ¶ 123. Dr. Naismith states:

If a POSA cannot accurately predict the effect of a set of mutations to a protein’s free energy of stabilization (and particularly the overall magnitude of those effects), that person cannot predict whether that set of mutations will collectively increase, have no net effect on or decrease the stability of the folded protein (and if it folds). As Dr. Petsko’s textbook explains, “the net free energy of stabilization of most folded proteins—the difference in free energy between the folded and unfolded states—is actually rather small, about 21-42 kJ/mole, or only about 10 times the average thermal energy available at physiological temperature.” Changes that cause even modest reductions in the net free energy of stabilization of a modified PH20 polypeptide can slow or prevent folding or result in rapid unfolding of the protein after it has folded and/or been secreted.

Id. ¶ 129 (quoting Ex. 2164, 26).

Dr. Naismith states that

[t]he 2024 Chemistry Nobel Price Background paper [i.e., Scientific Background] that Dr. Hecht references in his declaration provides an accurate historical perspective on the capabilities of computational tools to accurately predict a protein’s tertiary structure from its amino acid sequence. As that paper shows, those computational tools did not reach predictive accuracy levels comparable to experimental determination of structure until around 2019.

Id. ¶ 133 (citing Ex. 1027, 8).

According to Dr. Naismith, the alpha-beta barrel motif that Patent Owner's experts point to in PH20 is a common motif. *See* Ex. 1133 ¶ 137. Dr. Naismith states: "Many α/β barrel proteins are enzymes. In his textbook, Dr. Petsko estimated that ~10% of all enzymes share this protein structural fold." *Id.* ¶ 139. Dr. Naismith states that the "actual structural fold of each protein containing an α/β barrel motif may have considerably more structural size, diversity and complexity beyond what the term 'alpha-beta barrel' might suggest. Those structural differences also translate into functional diversity." *Id.*

Dr. Naismith explains that "the phrase 'PH20 alpha-beta barrel fold' as it is being used by Drs. Petsko and Simpson" is not a precise description nor does it identify the structural features shared by enzymatically active forms of the PH20 protein. *See* Ex. 1133 ¶ 152; *see also id.* ¶¶ 152–163. Dr. Naismith states "[i]f Dr. Petsko is suggesting that positions 3 to 339 correspond to the α/β barrel motif in PH20, that would be misleading." *Id.* ¶ 162. Dr. Naismith states "[t]hat is because several loops in PH20 are much more extensive and contain additional and elongated secondary structural elements when compared to the canonical α/β barrel Similar observations were made by Chao (EX1006)." *Id.* (citing Ex. 1006, 6913).

Dr. Naismith notes discrepancies in the patent data and Dr. Petsko's positional analysis thereof. *See* Ex. 1133 ¶¶ 238–251. For example, Dr. Naismith states that "[s]everal individual mutants are classified as both 'active' and as 'inactive' mutants in the common disclosure (e.g., mutants listed in both Tables 9 and 10)." *Id.* ¶ 239; *see also id.* ¶ 240 (identifying 50 such double counted mutants). Dr. Naismith states: "These double counted

mutants create an ambiguity that cannot be resolved using the information only in the common disclosure. . . . A POSA would have found the classifications of these mutants to be unreliable and would not have used them in analyzing the tolerability of a position to change.” *Id.* ¶ 241.

Dr. Naismith further identifies flaws in the hyaluronidase assay design and reporting in the Specification that limit the information a POSA can draw from it. *Id.* ¶¶ 248–251. Dr. Naismith states:

The active/inactive classifications that are the foundation of Dr. Petsko’s tolerance assessments do not differentiate reasons for loss of activity. For example, they do not differentiate between mutations that cause loss of activity between those that impair expression or secretion, induce aggregation, impair folding, or disrupt positioning of residues involved in catalysis, substrate binding or unknown biological functions. They also do not evaluate how the effects of individual substitutions change when combined—there is no investigation in the common disclosure of epistatic effects which manifest only when multiple residues are changed in one polypeptide. Narrowing the analysis to a smaller subset of positions that appear tolerant to single substitutions does not resolve these limitations, because the data still provides no reliable basis for predicting how multiple substitutions distributed across the protein will interact to affect folding, stability, solubility or activity.

Id. ¶ 276.

Based on the record as a whole, we again find the expert testimony and other evidence offered by Petitioner to be more persuasive than the competing evidence from Patent Owner and its experts. Patent Owner’s experts identify four approaches that an ordinary artisan would have had available to identify PH20 polypeptides within the scope of claim 1 with hyaluronidase or contraceptive activity during the relevant time frame:

sequence alignment, computer homology modeling, screening libraries of randomly mutated PH20 polypeptides, and site directed mutation of PH20 polypeptides. However, we are persuaded by Petitioner's experts and the other evidence Petitioner cites that none of those four approaches would allow one to reasonably predict the effect of changes for the full scope of claim 1.

As explained above, the Specification itself discusses only library screening and site directed mutation approaches. *See* Ex. 1001, 135:18–43. Both Petitioner's and Patent Owner's experts testified that library screening or site directed mutation at all positions would not be possible over the scope of claim 1. *See, e.g.*, Ex. 1003 ¶ 196; Ex. 1131, 64:12–17; Ex. 1133 ¶ 258.

As to the use of homology modeling, we credit Drs. Hecht, Park, Naismith, and Petsko that even with the '345 patent data in hand, the technology as of the 2011–2012 timeframe would not have allowed a POSA to reasonably predict the impact of more than about five changes to the PH20 protein on hyaluronidase activity. Ex. 1003 ¶¶ 56, 59, 196–197, 205; Ex. 1004 ¶¶ 166–169; Ex. 1133 ¶¶ 125, 260–265, 323; Ex. 1131, 207:15–24. That testimony is supported by the Scientific Background for the 2024 Chemistry Nobel Prize. *See, e.g.*, Ex. 1027, 7 (“Despite the progress outlined above, the average GDT score for the best *ab initio* predictions was stuck below 40% up until and including CASP12 in 2016.”). And even Dr. Petsko, when asked whether a homology model in 2012 could have predicted the effect of making five changes that are close together in the PH20 protein, was unable to refute Petitioner's experts' consistent testimony that such models at the time could not do so. *See* Ex. 1131, 207:15–24

(“I cannot answer that” because “[i]t will be context dependent to a large extent.”).

As to sequence alignment, Chao provided an alignment of the human hyaluronidases that is reproduced below:

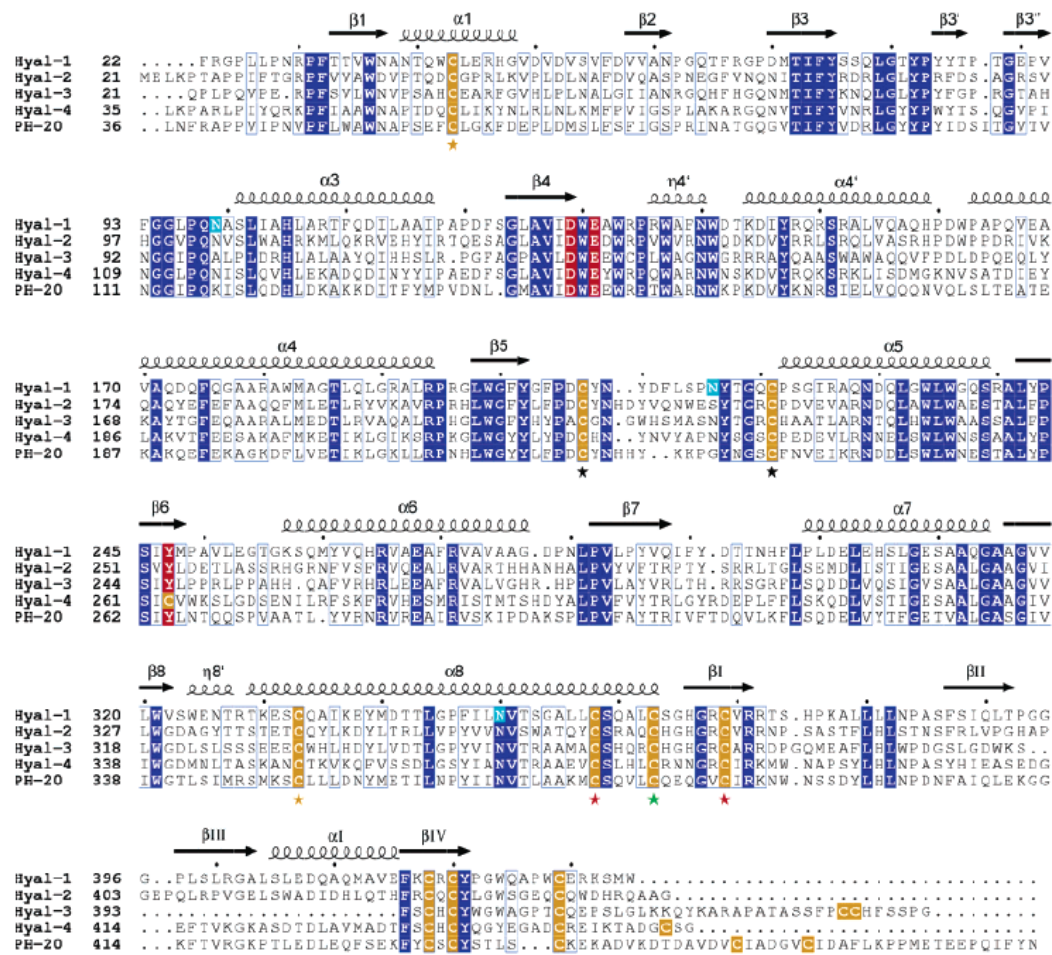


Figure 3: Structure-based sequence alignment of human hyaluronidases. Invariant residues are shown in blue except for three key catalytic residues that are colored red. Cysteine residues are colored yellow. The hHyal-1 N-glycosylated asparagines residues are colored turquoise. Residues exhibiting conservative 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 as in Figure 2B.

Ex. 1006, 6916. This alignment shows that only a small fraction of the alignment identifies amino acids that are invariant (blue or red), and therefore the alignment information would not be sufficient to predictably identify which residues for the full scope of claim 1 would allow for mutation without loss of hyaluronidase activity.

Therefore, based on the evidence of record, we find it is unpredictable which modified PH20 polypeptides within the scope of the claims of the '345 patent would retain hyaluronidase activity.

As for potential contraceptive use, nothing in the Specification or prior art suggests that it would have been predictable for a POSA to determine which, if any, of the modified PH20 polypeptides within the claimed sequence space might be useful for that purpose. *See supra* Section II.C.6.b.2.

7. Conclusion

Based on our review of the *Wands* factors and the record as a whole, we find that undue experimentation would have been required to practice the full scope of the challenged claims. The claims are extremely broad and the “number of distinct peptides is extremely large by all accounts, ranging from 10^{43} to 10^{56} .” Ex. 1004 ¶ 176. The skill in the art is agreed as very high. But while the prior art was developed in the field of hyaluronidases with alignments and projected three dimensional folding proposals (*see, e.g.*, Ex. 1003 ¶ 81), the evidence also shows that structural modeling and other computational techniques were not yet reliable to predict the effect of multiple mutations. *E.g.*, Ex. 1004 ¶¶ 167–169. The Specification provides a significant number of working examples of single mutations, but provides essentially no examples of multiple mutations and no detailed approach to

address how to reliably obtain multiply-mutated PH20 polypeptides having hyaluronidase activity. *See, e.g.*, Ex. 1003 ¶¶ 180–181.

The evidence discussed in our analysis of the quantity of experimentation and predictability factors demonstrates that undue experimentation would have been required to practice the full scope of the challenged claims. *Supra* Section II.D.6.f-g. Indeed, as noted above, most of the experts acknowledge that actually making and testing the full scope of the potential genus of multiply-modified polypeptides would not be possible. Ex. 1003 ¶¶ 204, 223–226; Ex. 1133 ¶ 258; *see also* Ex. 1130, 93:13–24; Ex. 1131, 64:12–17. Lastly, while there appears to be some agreement that modeling might allow predictability for modifications with two or three amino acid changes, the record shows that the computational techniques available as of December 2012, even when used in combination with the single substitution data in the '345 patent, could not be used to reasonably predict the effect of five or more amino acid changes on protein structure and activity. *See, e.g.*, Ex. 1003 ¶¶ 62, 180–181, 197, 205; Ex. 1004 ¶¶ 167–169; Ex. 1133 ¶ 123.

To the extent Patent Owner contends the claims are not limited to polypeptides having hyaluronidase activity and that the recited polypeptides may also be used to provide a contraceptive effect, we find that identifying which, if any, modified polypeptides are useful for that purpose would also have required undue experimentation.²⁷ Again, while we acknowledge the expertise of Dr. Cherr and Dr. Moon, the only evidence of any efficacy of a

²⁷ To be clear, this is an alternative finding premised on Patent Owner's claim construction that we do not adopt because it is not supported by the intrinsic evidence. *See supra* Section II.B.2.

PH20 polypeptide as a contraceptive vaccine was in guinea pigs and was an outlier from studies in other animals showing no such efficacy. *See supra* Section II.C.6.b.2. As explained above, a POSA at the time would not have regarded the potential use of *modified* PH20 polypeptides as contraceptives to be a credible utility. *Id.* Even if the record did show that a *native* PH20 polypeptide could be used for this purpose, we credit Dr. Kelsoe’s testimony explaining that a POSA would have needed to make and test modified PH20 polypeptides to determine if they could cause infertility over the competing testimony from Patent Owner’s experts. *See* Ex. 1134 ¶¶ 70–118, 124. Thus, a POSA seeking to make and use the recited polypeptides as antigens in a contraceptive vaccine would still need to engage in undue experimentation to identify polypeptides suitable for that purpose.

Therefore, considering all of the *Wands* factors and the totality of the record, we find by a preponderance of the evidence that undue experimentation would have been required to enable the full scope of the challenged claims and therefore they fail to comply with the enablement requirement of 35 U.S.C. § 112(a).

E. Ground III – Indefiniteness

1. Principles of Law

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

2. *Petitioner's Position*

Petitioner argues that “[t]he claims define only a portion of the claimed modified PH20 polypeptides—a mutated ‘hyaluronidase domain’ *within* each” modified PH20 polypeptide. Pet. 97. According to Petitioner, “[p]er the common disclosure’s definitions, the remainder of the modified PH20 polypeptide must derive from the starting PH20 polypeptide sequence that is modified to yield it. The claims, however, do not identify with reasonable certainty what those sequences are.” *Id.* at 98.

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

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

Id. at 99–100.

3. *Patent Owner's Response*

Patent Owner argues that “the ’345 patent expressly defines ‘modified PH20 polypeptides’” and “even though the parties dispute what specific disclosure in the ’345 patent constitutes the definition of ‘modified PH20 polypeptide,’ that is not enough for indefiniteness.” PO Resp. 82 (citing, e.g., Ex. 1001, 47:3–18; Ex. 2068 ¶¶ 263–264; Ex. 2076, 178:21–179:10; Pet. 98; Inst. Dec. 32). Patent Owner further argues that “[t]he metes and bounds of the claimed set of modified PH20 polypeptides are clear: claim 1 is directed to a set of modified PH20 polypeptides with a substitution at position 313, and a narrow set of subvariants of those modified PH20 polypeptides with no more than 20 total modifications in the hyaluronidase domain (amino acids 3-339 of SEQ ID NO: 7).” *Id.*

Patent Owner argues that “Petitioner does not contend that, when provided a particular sequence, a POSA would not be able to tell whether that sequence satisfies the claims,” and “[i]nstead, Petitioner appears to contend that a POSA could not reasonably envision all of the sequences that have a hyaluronidase domain with up to 20 modifications.” *Id.* at 82–83. Patent Owner asserts that “these arguments at best relate to the *breadth* of the claim, not indefiniteness.” *Id.*

4. *Petitioner's Reply*

Petitioner reiterates that “the claims do not define ‘modified PH20 polypeptides’ outside the ‘hyaluronidase domain’ beyond requiring use of a ‘PH20,’ which includes neutral-active non-human PH20s and over 10⁵⁰⁰ other possible (not-yet-discovered) sequences that would need to be tested for neutral activity.” Reply 42 (citing Pet. 41–43, 49–52, 82–84, 97–100;

PO Resp. 82–83; Ex. 1004 ¶ 177). According to Petitioner, “POSAs could not realistically determine whether all such sequences fall within the claims.” *Id.*

5. *Patent Owner’s Sur-reply*

Patent Owner asserts that although “Petitioner argues (at 42) that the claims are indefinite because they do not define ‘modified PH20 polypeptides’ outside the ‘hyaluronidase domain,’” Petitioner admits that the Specification expressly defines the term “modified PH20 polypeptide.” Sur-reply 29. Patent Owner reiterates that “Petitioner’s argument improperly conflates claim breadth with indefiniteness.” *Id.*

6. *Analysis*

We find that Petitioner has not demonstrated by a preponderance of the evidence that the challenged claims are indefinite.

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

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

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

These definitions undermine Petitioner’s indefiniteness argument. Indeed, Petitioner’s complaints, e.g., that the claims embrace “*non-human* PH20 polypeptides,” truncated forms, and “starting PH20” polypeptides of varying length go to the breadth of the claims, rather than to indefiniteness. *See, e.g., In re Miller*, 441 F.2d 689, 693 (CCPA 1971) (“breadth is not . . . indefiniteness”). For this reason, we find that Petitioner has not demonstrated by a preponderance of the evidence that the challenged claims are indefinite.

F. Ground IV - Obviousness

1. 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;²⁸ and (4) considering objective evidence indicating obviousness or non-obviousness. *KSR*, 550 U.S. at 406.

2. Overview of the Asserted Prior Art

a) 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

²⁸ *See supra* Section II.A.

the soluble, neutral active Hyaluronidase Glycoprotein family, particularly the human soluble PH-20 Hyaluronidase Glycoproteins (also referred to herein as sHASEGPs).” *Id.* at 3:51–54.

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

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

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

b) Chao (Ex. 1006)

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

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

Chao states that “[h]uman hyaluronidases exhibit 33-42% sequence identities and even higher conservation of active site residues. Yet, the enzymes differ in their catalytic efficiencies and pH profiles.” *Id.* at 6914. Figure 3 of Chao is reproduced below:

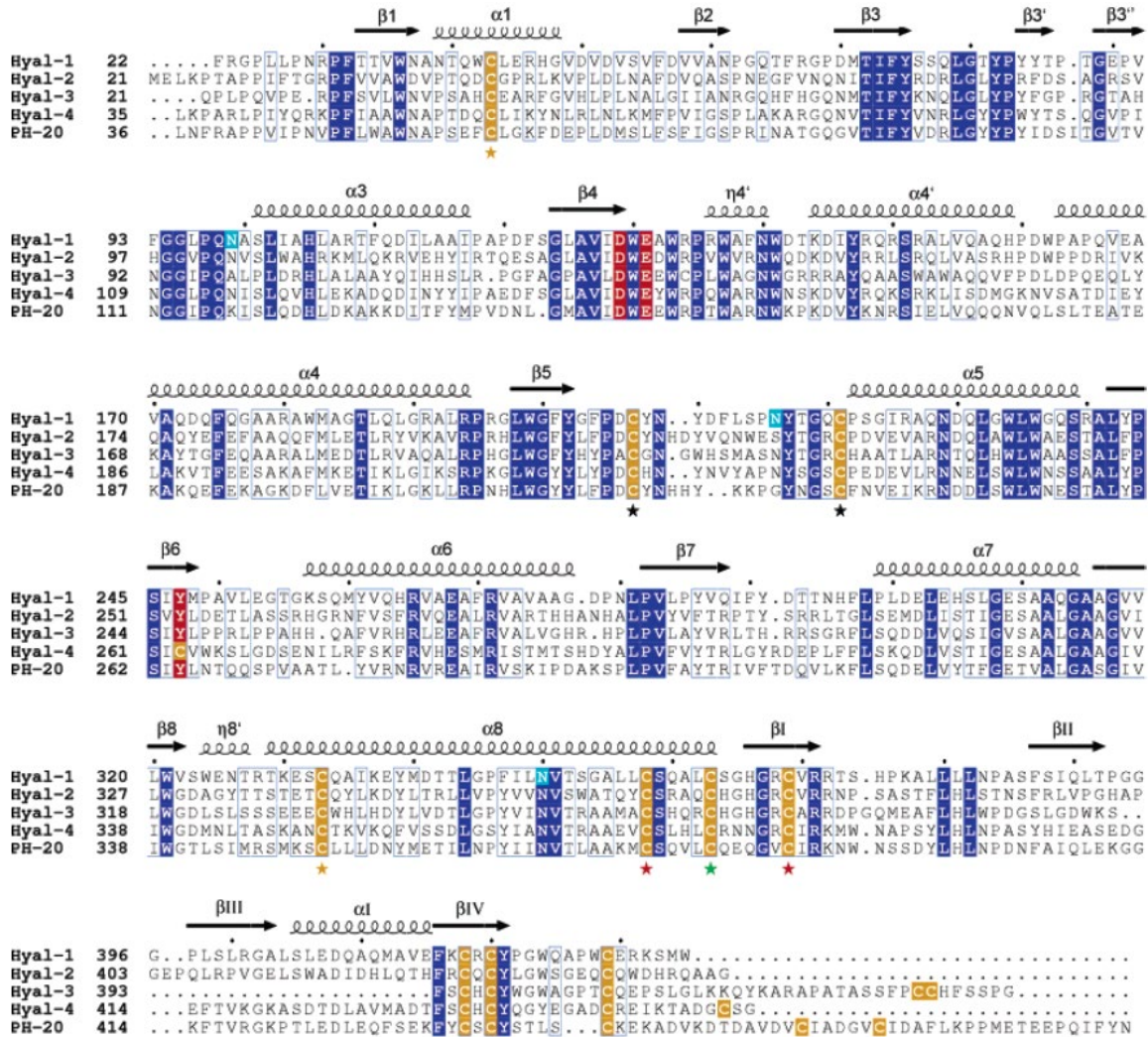


Figure 3 shows

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

stars with matching colors. Secondary structure units are labeled.

Id. at 6916.

3. *Asserted Obviousness over the '429 Patent and Chao*
a) Petitioner's Position

Petitioner asserts that the '429 patent “teaches making a *particular* type of modification (a single amino acid substitution) in *particular* locations (all of the non-essential regions of PH20) in a *particular* PH20 sequence (PH20₁₋₄₄₇) to yield equivalents of PH20₁₋₄₄₇ (*i.e.*, those that do not substantially alter the activity or function of PH20₁₋₄₄₇).” Pet. 103 (citing Ex. 1003 ¶ 242; Ex. 1004 ¶ 33). Petitioner asserts that Chao “described ‘a novel, EGF-like domain’ in the C-terminal region of human hyaluronidases ‘closely associated’ with the catalytic domain (in PH20 at 337-409), with a characteristic pattern of residues.” Pet. 105 (citing Ex. 1006, 6911; Ex. 1004 ¶¶ 98–99; Ex. 1003 ¶¶ 85, 88).

Petitioner asserts that “a skilled artisan looking to implement the '429 Patent's teachings would have (i) identified all of the non-essential regions in PH20₁₋₄₇₇, and (ii) determined which substitutions to make within those non-essential regions.” Pet. 104 (citing Ex. 1003 ¶¶ 287–89). Petitioner asserts that Dr. Park performed such an analysis and, consistent with Chao's Figure 3, identified “position 313 as being within a non-essential region [in] PH20₁₋₄₄₇.” *Id.* at 107–08 (citing Ex. 1003 ¶¶ 252, 256; Ex. 1004 ¶¶ 32–33, 104, Appx. D-2; Ex. 1006, 6916; Ex. 1005, 16:14–22, 16:24–36).

Petitioner asserts that in Dr. Park's alignment, “[m]ethionine (M) occurs at position 313 in human PH20 and at positions corresponding to

position 313 in ~14% of homologous proteins, while lysine (K) is the most prevalent amino acid found at those positions (~40%) (*i.e.*, 35 different proteins).” *Id.* at 110 (citing Ex. 1004 ¶¶ 106–07, 114; Ex. 1003 ¶ 253).

Petitioner asserts that a “skilled artisan would have viewed lysine (K) as an obvious single substitution at position 313 in PH20₁₋₄₄₇.” *Id.* at 110. Petitioner asserts: “First, the ’429 Patent explicitly identifies lysine as being one of the conservative substitutions for methionine as a single amino acid substitution in PH20 proteins.” *Id.* (citing Ex. 1005, 16:4–32, Table 1, 10:9–13). Petitioner asserts that, “[s]econd, lysine occurs at this position in many homologous proteins and in 2 of 5 human hyaluronidases.” *Id.* (citing Ex. 1004 ¶¶ 44, 107, 114; Ex. 1003 ¶ 253, 256–57). Petitioner asserts: “Third, lysine has a high helix propensity, meaning it is favored in sequences that form α -helix structures, while Chao reports position 313 as being in an α -helix sequence (‘ $\alpha 8$ ’).” *Id.* at 111 (citing Ex. 1050, 422–24, Table 2; Ex. 1004 ¶¶ 32, 70–71, 109, 118; Ex. 1003 ¶¶ 43, 254; Ex. 1006, 6916, Figure 3).

Petitioner asserts that in prosecuting the ’429 patent, Patent Owner relied on “its statements that a skilled artisan would have expected *any* single amino acid substitution in *any* non-essential position of PH20₁₋₄₄₇ to not substantially affect the activity of the enzyme.” *Id.* at 112. Petitioner also asserts that “a skilled artisan would have reasonably expected the M313K substitution to not substantially alter the hyaluronidase activity of PH20₁₋₄₄₇.” *Id.* at 112.

b) Patent Owner’s Response

Patent Owner asserts that “[b]ased on the teachings of Chao and the ’429 patent, POSAs would not have had a reason to introduce substitutions

at position 313.” PO Resp. 88 (citing Ex. 2068 ¶¶ 405–416). Patent Owner asserts that while Chao provides insight into human hyaluronidase structures, “[n]one of this alleged useful information provides a reason to modify position 313 in PH20.” *Id.* at 89 (citing Ex. 1006, 6912, 6916–17; Ex. 2068 ¶¶ 400–404).

Patent Owner asserts that “Petitioner’s expert [Dr.] Park’s analysis confirms that nothing in the art would have motivated POSAs to modify position 313. . . . Nothing in [Dr.] Park’s results provides a reason to elevate M313 above the hundreds, if not thousands, of other substitutions he predicts would have been tolerated.” *Id.* at 90–91 (citing Ex. 2068 ¶¶ 404–416). Patent Owner asserts that “Petitioner has not provided any reason why POSAs, who have in hand a working enzyme, would tinker with that enzyme with the sole purpose of maintaining the same activity profile.” *Id.* at 91.

Patent Owner asserts that “[e]ven if position 313 were somehow selected (it would not be), there is no reason POSAs would have substituted methionine (M) with lysine (K). EX2068, ¶¶ 417–18. Neither Chao nor the ’429 patent suggests replacing M313 with lysine.” *Id.* at 92.

c) Petitioner’s Reply

Petitioner asserts that Dr. Park “identif[ied] M313K as *one of ~750 such substitutions* suggested by the ’429 Patent before 2011” and “identified M313K’s favorable effects, which confirms a POSA’s motivation to make that substitution. Reply 43 (citing Ex. 2176; Ex. 1133 ¶ 344; Ex. 1003 ¶¶ 265–270; Ex. 1004 ¶¶ 114–121). Petitioner asserts that “Dr. Park’s objective and unbiased assessment found M313K tolerated,” and that “he

and Dr. Petsko identified the same M313:F29 interaction.” *Id.* at 45 (citing Ex. 1004 ¶¶ 114–121; Ex. 2070 ¶¶ 408–410; Ex. 1133 ¶¶ 349–351).

d) Patent Owner’s Sur-Reply

Patent Owner asserts:

Petitioner abandons any articulated motivation by asserting—without support—that all ~750 positions [Dr.] Park identifies for substitution would have been obvious candidates for substitution. But the claims require substitution ***at position 313***, and “there must be some reason to select a species from the genus.” Petitioner offers none beyond impermissible, attorney-driven hindsight. Reply, 42-47; ID, 38; POR, 88-92.

Sur-reply 29.

4. *Analysis*

Based on the evidence of record, we agree with Patent Owner that Petitioner has not provided any persuasive reason to particularly target the methionine at position 313 of a PH20 polypeptide for modification with lysine, as recited by claim 1 of the ’345 patent. It is undisputed that neither the ’429 patent nor Chao specifically identifies or discusses position 313 of the PH20 polypeptide.

We are not persuaded by Petitioner’s argument that multiple sequence alignments identify amino acids that are tolerated at particular positions (*see* Pet. 108), 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 F. App’x 728, 733 (Fed. Cir. 2019).

Dr. Park identified 379 positions in “PH20₁₋₄₄₇ other than the 68 essential residues” (i.e., ~85% of the protein) with evolutionary variation, meaning that “homologous proteins have tolerated different amino acids at those positions.” Ex. 1004 ¶ 32. Dr. Park also evaluated the “compatibility with the predicted secondary structure” for the possible substitutions at those positions by categorizing 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.* ¶¶ 70–71. But nothing in the prior art or Dr. Park’s analysis directs the ordinary artisan to position 313 itself. Moreover, Dr. Hecht states that “[r]eplacing, inserting or deleting amino acids indiscriminately in this[α8] region could disrupt that [alpha helical] pattern, which could have a range of effects in this region of the helical structure.” Ex. 1003 ¶ 229.

And while Dr. Hecht asserts that the ’429 patent suggests conservative mutations—including substituting lysine for methionine—Petitioner did not point us to any specific teaching or suggestion to modify position 313 of PH20 in the first place. *See, e.g., id.* ¶¶ 242–244 (asserting a POSA would expect that “a single amino acid substitution in a non-essential region would retain much of its activity”).²⁹ Petitioner did not point us to anything in

²⁹ Indeed, in support of his testimony that a POSA would not be able to predict the effects of multiple modifications, Dr. Hecht observes that position 313 is located within the “‘α8’ α-helix structure in PH20” and “[r]eplacing, inserting or deleting amino acids indiscriminately in this region could disrupt that pattern, which could have a range of effects in this region of the helical structure.” Ex. 1003 ¶ 229. This seems to contradict aspects of Dr. Hecht and Dr. Park’s obviousness analysis.

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 are also not persuaded by Petitioner's arguments that a person of ordinary skill in the art would have substituted methionine with lysine at position 313 because "lysine has a high helix propensity, meaning it is favored in sequences that form α -helix structures." Pet. 111. This statement is not a reason for the substitution, but rather a statement as to the properties of lysine. Dr. Park identified seven different amino acids that favor alpha helix formation. *See* Ex. 1004 ¶ 71. Figure 3 of Chao shows a number of different alpha helical regions, $\alpha 1$, $\alpha 3$, $\eta 4'$, $\alpha 4'$, $\alpha 4$, $\alpha 5$, $\alpha 6$, $\alpha 7$, 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 amino acids found within alpha helices might be subject to substitution by one of the seven preferred amino acids identified by Dr. Park, but it is Petitioner's "burden to show that the 'prior art would have suggested making the *specific molecular modifications* necessary to achieve the claimed invention.'" *Amerigen Pharm. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1089 (Fed. Cir. 2019) (citing *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007)).

Petitioner's other rationale for substituting lysine at position 313 is that this residue is found at the corresponding position in some homologous hyaluronidase sequences. *See* Pet. 108–10. But that rationale assumes that an ordinarily-skilled artisan would have already had a reason to target position 313 and Petitioner offers no reason to do so other than Dr. Park's observation that it is among the overwhelming majority (~85%) of positions

in PH20 that are apparently in non-essential regions of the protein. *See* Ex. 1004 ¶ 32.

In sum, we find that Petitioner has not shown by a preponderance of the evidence that the combination of the '429 patent and Chao with the knowledge and teaching described by Drs. Hecht and Park demonstrate that the challenged claims are unpatentable as obvious.

III. CONCLUSION

After considering the evidence and arguments before us on the complete trial record, we conclude that Petitioner has demonstrated by a preponderance of the evidence that challenged claims 1–17 are unpatentable.³⁰

³⁰ Should Patent Owner wish to pursue amendment of the Challenged Claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner's attention to the April 2019 Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding, 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. §§ 42.8(a)(3), (b)(2).

In summary:

Claims	35 U.S.C. §	Reference(s)/Basis	Claim(s) Shown Unpatentable	Claim(s) Not shown Unpatentable
1–17	112(a)	Written Description	1–17	
1–17	112(a)	Enablement	1–17	
1–17	112(b)	Indefiniteness		1–17
1–17	103	The '429 patent, Chao		1–17
Overall Outcome			1–17	

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–17 of U.S. Patent 12,264,345 B2 are determined to be unpatentable; and

FURTHER ORDERED that, because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

PGR2025-00052
Patent 12,264,345 B1

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