UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,
Petitioner

v.

HALOZYME, INC.,
Patent Owner

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

PATENT OWNER'S NOTICE OF APPEAL

Mail Stop "PATENT BOARD"
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Pursuant to 35 U.S.C. §§ 141(c) and 142 and 37 C.F.R. § 90.2(a), Patent Owner Halozyme, Inc. ("Patent Owner") hereby appeals to the U.S. Court of Appeals for the Federal Circuit from the Patent Trial and Appeals Board's ("Board") Final Written Decision, entered June 24, 2026 (Paper 135) (a copy of the decision is attached), and from the order Denying Director Review of the Board's Final Written Decision, entered July 22, 2026 (Paper 142) (a copy of the decision is attached), and from all underlying and related findings, orders, decisions, rulings, and opinions.

For the limited purpose of providing the Director with the information requested in 37 C.F.R. § 90.2(a)(3)(ii), Patent Owner further indicates that the issues on appeal may include, but are not limited to:

1. Whether the Board erred in construing the term "modified PH20 polypeptide."
2. Whether, under the proper construction of "modified PH20 polypeptide," Petitioner failed to demonstrate by a preponderance of the evidence that claims 1, 2, 6–14, and 16–29 of U.S. Patent No. 12,123,035 are unpatentable under 35 U.S.C. § 112(a) for lack of written description.
3. Whether, under the Board's construction of "modified PH20 polypeptide," Petitioner failed to demonstrate by a preponderance of

the evidence that claims 1, 2, 6–14, and 16–29 of U.S. Patent No. 12,123,035 are unpatentable under 35 U.S.C. § 112(a) for lack of written description.

4. Whether, under the proper construction of "modified PH20 polypeptide," Petitioner failed to demonstrate by a preponderance of the evidence that claims 1, 2, 6–14, and 16–29 of U.S. Patent No. 12,123,035 are unpatentable under 35 U.S.C. § 112(a) for lack of enablement.

5. Whether, under the Board's construction of "modified PH20 polypeptide," Petitioner failed to demonstrate by a preponderance of the evidence that claims 1, 2, 6–14, and 16–29 of U.S. Patent No. 12,123,035 are unpatentable under 35 U.S.C. § 112(a) for lack of enablement.

Patent Owner further reserves the right to challenge any finding or determination supporting or relating to the issues above.

Pursuant to 37 C.F.R. § 90.2(a), Patent Owner is electronically filing one copy of this Notice of Appeal with the Director, and electronically filing a copy of this Notice Appeal with the U.S. Court of Appeals for the Federal Circuit with the requisite filing fee, in addition to filing this Notice of Appeal with the Board.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX PLLC

/Eldora L. Ellison/

Eldora L. Ellison, Ph.D.
Registration No. 39,967
Attorney for Patent Owner

Date: September 21, 2026

1101 K Street, NW, 10th Floor
Washington, DC 20005
(202) 371-2600

CERTIFICATION OF FILING

The undersigned hereby certifies that, in addition to being electronically filed through P-TACTS, a true and correct copy of the above-captioned **PATENT OWNER'S NOTICE OF APPEAL** is being filed by electronic mail with the Director on September 21, 2026, at the email address efileSO@uspto.gov, in accordance with 37 C.F.R. § 90.2(a)(1)(i).

The undersigned also hereby certifies that a true and correct copy of the above-captioned **PATENT OWNER'S NOTICE OF APPEAL** and the filing fee is being filed via CM/ECF with the Clerk's Office of the United States Court of Appeals for the Federal Circuit on September 21, 2026.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX PLLC

/Eldora L. Ellison/

Eldora L. Ellison, Ph.D.
Registration No. 39,967
Attorney for Patent Owner

Date: September 21, 2026

1101 K Street, NW, 10th Floor
Washington, DC 20005
(202) 371-2600

CERTIFICATE OF SERVICE

I certify that the above-captioned **PATENT OWNER'S NOTICE OF APPEAL** was served in its entirety on September 21, 2026, upon the following parties via electronic mail:

Jeffrey P. Kushan (Lead Counsel)	jkushan@sidley.com
Leif Peterson (Back-up Counsel)	leif.peterson@sidley.com
Sue Wang (Back-up Counsel)	sue.wang@sidley.com
Katherine A. Helm (Back-up Counsel)	khelm@dechert.com
Amy Mahan (Back-up Counsel)	Amy.mahan@sidley.com
Blaine Hackman (Back-up Counsel)	Blaine.Hackman@dechert.com
Christine M. Engen (Back-up Counsel)	christine.engen@sidley.com
Amit Bhatla (Back-up Counsel)	abhatla@sidley.com
Brian M. Goldberg (Back-up Counsel)	Brian.Goldberg@dechert.com
Mark Stewart (Back-up Counsel)	mark.stewart@merck.com

HalozymePGRs@sidley.com
Merck-Halozyme-Dechert@dechert.com

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX PLLC

/Eldora L. Ellison/

Eldora L. Ellison, Ph.D.
Registration No. 39,967
Attorney for Patent Owner

Date: September 21, 2026

1101 K Street, NW, 10th Floor
Washington, DC 20005
(202) 371-2600
27705746.1

Trials@uspto.gov
Tel: 571-272-7822

Paper 135
Entered: June 24, 2026

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,
Petitioner,

v.

HALOZYME, INC.,
Patent Owner.

PGR2025-00009
Patent 12,123,035 B2

Before JEFFREY N. FREDMAN, SUSAN L. C. MITCHELL, and CYNTHIA M. HARDMAN, Administrative Patent Judges.

MITCHELL, *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, 2, 6–14, and 16–29[1] of U.S. Patent No. 12,123,035 B2 (Ex. 1001, "the '035 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, 2, 6–14, and 16–29 are unpatentable.

A. Procedural History

Petitioner Merck Sharp & Dohme LLC filed a Petition requesting post grant review of all claims of the '035 patent. *See* Paper 1 ("Pet."). Patent Owner Halozyme, Inc. filed a Preliminary Response ("Prelim. Resp."), Petitioner filed an authorized Reply ("Prelim. Reply"), and Patent Owner filed an authorized sur-reply ("Prelim. Sur-Reply"). Papers 14, 20, 23, respectively.

We determined, based on the information presented by the parties, that the '035 patent was eligible for post-grant review and that at least one of the challenged claims was more likely than not unpatentable. Paper 29 ("Inst. Dec."). Pursuant to 35 U.S.C. § 324, the Board instituted trial on July 11, 2025, of all remaining challenged claims (claims 1, 2, 6–14, and 16–29). *Id.*; *see supra* n.1.

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[1] Although the Petition was directed to claims 1–34 of the '035 patent, Patent Owner filed a statutory disclaimer of claims 3–5, 15, and 30–34 of the '035 patent, leaving claims 1, 2, 6–14, and 16–29 at issue. Ex. 2003.

Following institution, Patent Owner filed a Director Review Request (Paper 33), and Petitioner filed an Authorized Response (Paper 37), and the then-Acting Director issued a denial of the Director Review Request. Paper 40.

Patent Owner then filed a Patent Owner's Response to the Petition (Paper 46, "PO Resp."), Petitioner filed a Reply to Patent Owner's Response (Paper 71, "Pet. Reply"), and Patent Owner filed a Sur-reply (Paper 84, "PO Sur-reply"). Patent Owner filed a motion for additional discovery (Paper 62), Petitioner opposed the Motion for Discovery (Paper 63), and the Board denied the Motion for Discovery (Paper 77).

Patent Owner filed a Motion to Terminate (Paper 82), and Petitioner filed an Opposition to the Motion to Terminate (Paper 89). The Board denied Patent Owner's Motion to Terminate. Paper 130. Patent Owner filed a Request for Director Review of this denial under seal.

The parties filed, and the Board resolved, various motions to seal.

We held an oral hearing March 2, 2026, a transcript of which is of record. Papers 108, 121.

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 5, 1.

C. Related Matters

The '035 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; 12,195,773; and 12,264,345. Paper 124, 1.

The '035 patent is also related to a number of 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	Nov. 26, 2024	Yes
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
12,264,345	PGR2025-00052	Jun. 27, 2025	Yes
12,195,773	PGR2025-00053	Jun. 6, 2025	Yes
12,371,685	PGR2025-00087	Nov. 20, 2025	No
10,865,400	IPR2026-00312	Mar., 23, 2026	Yes
11,041,149	IPR 2026-00313	Mar. 23, 2026	Yes
11,066,656	IPR2026-00314	Mar. 23 2026	Yes

See Paper 124, 2.

Patent Owner states that the '035 patent is related to the following pending U.S. Patent Applications and patents:

U.S. Patent 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
19/546,132	Feb. 20, 2026
19/550,132	Feb. 25, 2026

U.S. Patent Application No.	Filed
19,550,136	Feb. 25, 2026
19/551,393	Feb. 26, 2026
19,551,420	Feb. 25, 2026

Paper 124, 2.

D. The '035 Patent

The '035 patent issued October 22, 2024, from U.S. Application 18/068,327, filed December 19, 2022. Ex. 1001, codes (21), (22), (45). The '035 patent is a division of application of U.S. Application 17,327,568, filed on May 21, 2021, which is a continuation in a lengthy set of applications claiming continuity to U.S. Application 13/694,731 ("the '731 Application"), filed on Dec. 28, 2012, now U.S. Patent No. 9,447,401 B2. *Id.* at code (60). The '731 Application claims the priority benefit of provisional applications U.S. 61/796,208, filed November 1, 2012, and U.S. 61/631,313, filed Dec. 30, 2011. Id.

The '035 patent is drawn to "[m]odified PH20 hyaluronidase polypeptides, including modified polypeptides that exhibit increased stability and/or increased activity." Ex. 1001, 4:16–18. The '035 patent teaches "[h]yaluronan (hyaluronic acid; HA) is a polypeptide that is found in the extracellular matrix of many cells, especially in soft connective tissues." *Id.* at 4:23–25. The '035 patent teaches "[c]ertain diseases are associated with expression and/or production of hyaluronan. Hyaluronan-degrading enzymes, such as hyaluronidases, are enzymes that degrade hyaluronan. By catalyzing HA degradation, hyaluronan-degrading enzymes (e.g., hyaluronidases) can be used to treat diseases or disorders associated with accumulation of HA or other glycosaminoglycans." *Id.* at 4:30–36. The '035 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 4:41–47.

The '035 patent states that modifications for PH20 polypeptides include amino acid replacements, deletions, and/or insertions. Ex. 1001, 4:56–58. With regard to modified PH20 hyaluronidase polypeptides, the '035 patent further teaches:

> [P]rovided are modified PH20 polypeptides that contain one or more amino acid replacements that result in a PH20 polypeptide that retains activity and/or exhibits increased or altered stability under a variety of conditions. . . . Exemplary modifications are amino acid replacements. For purposes herein, amino acid replacements are denoted by the single amino acid letter followed by the corresponding amino acid position in SEQID NO:3 in which the replacement occurs. Single amino acid abbreviations for amino acid residues are well known to a skilled artisan . . . and are used herein throughout the description and examples. For example, replacement with P at a position corresponding to position 204 in a PH20 polypeptide with reference to amino acid residue positions set forth in SEQ ID NO:3 means that the replacement encompasses F204P in a PH20 polypeptide set forth in SEQ ID NO:3, or the same replacement at the corresponding position in another PH20 polypeptide.

Id. at 4:54–5:15.

The '035 patent teaches "modified PH20 polypeptides provided herein exhibit altered activities or properties compared to a wildtype, native or reference PH20 polypeptide." *Id.* at 75:45–47. The '035 patent further provides:

> Included among the modified PH20 polypeptides provided herein are PH20 polypeptide that are active mutants, whereby the polypeptides exhibit at least 40% of the hyaluronidase activity of the corresponding PH20 polypeptide not containing the amino acid modification (e.g., amino acid replacement). In

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

Id. at 75:47–58.

E. Illustrative Claims

Claim 1 is illustrative of the challenged claims in the ’035 patent, and is reproduced below.

> 1. A modified PH20 polypeptide, comprising one or more amino acid modifications in an unmodified PH20 polypeptide, wherein:
>
> the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID Nos: 3, 7 and 32–66;
>
> amino acid modifications are selected from the group consisting of amino acid replacements(s), deletion(s), and/or insertion(s);
>
> the modified PH20 polypeptide comprises an amino acid replacement at a position corresponding to residue 312, with reference to amino acid positions set forth in SEQ ID NO:3;
>
> the replacement at the position corresponding to residue 312 is selected from the group consisting of G, K, L, N, and T;
>
> corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the amino acid sequence of SEQ ID NO:3; and

> the modified PH20 polypeptide has at least 91 % sequence identity to a polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7 and 32–66.

Ex. 1001, 317:2–25.

F. Asserted Grounds of Unpatentability

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

Ground	Reference(s)/Basis	35 U.S.C. §	Claim(s) Challenged
1	Written Description	§ 112	1, 2, 6–14, 16–29
2	Enablement	§ 112	1, 2, 6–14, 16–29
3	The '429 patent,[2] Chao[3]	§ 103	1, 2, 6–14, 16–29

Petitioner also relies on the Declarations of Michael Hecht, Ph.D., Sheldon Park, Ph.D., James Naismith, Ph.D., and Garnett Kelsoe, Ph.D. 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.[4] 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

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[2] US 7,767,429 B2, issued Aug. 3, 2010 (the "'429 patent") (Ex. 1005).

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

[4] Patent Owner withdrew the Declaration of Dr. Triggs-Raine. PO Resp. 10 n.6.

herein as "POSA") as of the effective filing date of the challenged claims. Petitioner contends that one of ordinary skill in the art would

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

Pet. 15–16.

Patent Owner responds "[s]olely for the purposes of the analysis herein, there is no significant difference between Petitioner's POSA definition (Pet., 15-16; EX1003, ¶13) and Patentee's, both of which were addressed in the Institution Decision (ID, 9-18)." PO Resp. 31. Patent Owner notes that "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.'" *Id.* (citing Ex. 2076, 63:8–64:2).

Accordingly, we find that Petitioner's proposal is sufficiently comprehensive to encompass the prior art relevant to the '035 patent as Patent Owner agreed. 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 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. 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. *See, e.g.*, PO Resp. 11 n.7 (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 and enablement 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 and enablement challenges, "Petitioner and its experts erroneously rely upon a December 30, 2011 date (Pet., 26-84; *see also,* Pet 39, 55, 74; EX1003, ¶11), rather than the proper December 28, 2012 date." PO Resp. 45 n.12. Petitioner explains the disclosure of "the '731 Application (including subject matter incorporated by reference [the earlier-filed provisionals]) does not provide written description support for and does not enable any claim of the '035 Patent," and that "[t]he same is true for the '035 Patent, whose disclosure relative to the claims is generally identical to the '731 Application." Pet. 5–6. Therefore, Petitioner assessed the relevant disclosures, and the record does not reflect any material difference in the state of the art between the 2011 and 2012 priority dates that would change our opinions 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 relied upon the Declarations of record and upon the intrinsic evidence in a definitional sentence in the '035 Specification cited in part by Patent Owner's expert (Ex. 2001 ¶ 67) that 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, 48:38–46.

Based on the evidence of record at that time, we determined that

> the evidence of record shows the '035 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 '035 patent to encompass polypeptides with some hyaluronidase activity.

Inst. Dec. 16–17. We now address the parties' contentions on the complete record.

1. Petitioner's Position

Petitioner asserts that the "terms used in the claims are either expressly defined in the common disclosure[5] or are used with their common and ordinary meaning. Consequently, no term requires an express construction to assess the grounds in this Petition" (in addition to those terms expressly defined in the Specification). Pet. 16. Petitioner asserts "the specification describes two mutually exclusive categories of 'modified PH20 polypeptides' (*i.e.*, 'active mutants' vs. 'inactive mutants') but the claims are limited to one (*i.e.*, 'active mutants')." *Id.* at 21. Petitioner asserts that the claims are limited to "active mutants" for three reasons:

> First, every claim requires modified PH20 polypeptides with one of five replacements at position 312 that yielded an "active mutant" as a single-replacement $PH20_{1\text{-}447}$ polypeptide (*i.e.*, S312G, S312K, S312L, S312N, or S312T). All 5 mutants are identified as "Active Mutants" in Table 3, and have at least ~40% activity per Table 9.
>
> Second, claim 4 restricts the genus of active mutants in claim 1 (*i.e.* those with hyaluronidase activity) to modified PH20 polypeptides that have at least 100% of the activity of unmodified PH20.
>
> Third, the specification defines a "modified PH20 polypeptide" as "a PH20 polypeptide that contains at least one modification," but can also "have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide ***exhibits hyaluronidase activity***."

[5] Petitioner uses the term "common disclosure" to refer to the Specifications of the '035 patent and "its ultimate parent," U.S. Application No. 13/694,731, filed on December 28, 2012. *See* Pet. 1.

Id. at 24–25 (citations omitted).

Petitioner further asserts that even if the claims include inactive mutants, "every claim still necessarily includes (and thus must describe and enable) the full subgenus of 'active mutants' in claim 1 defined by claim 4." *Id.* at 25–26; *cf. id.* at 80 ("[T]he common disclosure provides no guidance about which epitopes on the PH20 protein must be preserved in an 'inactive mutant' . . .'").

2. Patent Owner's Response

Patent Owner asserts that it "does not dispute that the claims encompass PH20s with hyaluronidase activity," but that it "does contend that the claims are defined by structure only, and encompass ***both*** enzymatically active and enzymatically inactive PH20s." PO Resp. 31. 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.* at 33 (citing Ex. 2076, 172:21–173:9).

Regarding the Specification, Patent Owner asserts that

> The 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.

Patent Owner asserts that "the term 'modified PH20 polypeptides' is used throughout the specification as encompassing enzymatically active and inactive polypeptides, so construing the term as limited to active polypeptides contradicts the disclosure." *Id.* at 37 (citing Ex. 1001, 79:27–29, 115:59–63, 75:47–49, 75:56–58, 116:9–57, 116:66–117:6, 185:3–6, 259:11–260:20; Ex. 2068 ¶¶ 266–268). Patent Owner asserts "Petitioner's expert, Dr. Hecht, admitted that he understood the claims could only cover 'useful' PH20s, and thus he interpreted the claims as limited to enzymatically active polypeptides because he considered those to be useful. But Dr. Hecht's analysis is wrong as a matter of law and science." *Id.* at 39 (citing Ex. 2076, 213:1–21, 137:12–139:13). Patent Owner asserts that "inactive PH20s do have a credible utility," e.g., as antigens in contraception vaccines. *Id.* at 40 (citing Ex. 2068 ¶ 392; Ex. 2074; Ex. 2072).

3. Petitioner's Reply

Petitioner responds that:

> The claim construction dispute is narrow: are the claims limited to a "***structurally and functionally distinct genus***" of PH20s (*i.e.*, "properly folded" and enzymatically active modified PH20 polypeptides), or do they ***also*** include 10^{59+} other PH20 sequences in the claim parameter's "sequence space" (*i.e.*, a genus weighing more than Earth)?

Pet. Reply 1–2 (citing PO Resp. 31; Ex. 2068 ¶ 33; Ex. 2070 ¶¶ 51, 58, 128 n.12; Ex. 1130, 62:13–23; 68:6–69:5; Ex. 1133 ¶¶ 44–46, 55–58; Pet. Reply § III.C.1(b); Ex. 1003 ¶¶ 122–123). Petitioner asserts "the Board should reject Halozyme's perspective, as the claims ***as a whole*** require modified PH20s that are 'properly folded and enzymatically active.'" *Id.* at 2 (citing PO Resp. 42–43; Ex. 1130, 55:23–56:7, 90:1–16).

Petitioner asserts that Patent Owner "cannot dispute the preamble is limiting—its arguments rest on the ***preambular*** phrase 'modified PH20 polypeptide.' Halozyme's expert (Dr. Simpson) testified that 'PH20' ***provides context*** to 'modified PH20 polypeptide.'" *Id.* at 2 (citing PO Resp. 32–42; Prelim. Resp. 16–22; Ex. 1130, 57:9–58:4; *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 952 (Fed. Cir. 2006)). Petitioner asserts Dr. Petsko stated "***POSAs think of PH20 as a folded protein***.' Dr. Simpson also testified PH20's definition led POSAs to view 'PH20s' as properly folded and enzymatically active proteins. Giving effect to both defined terms, the preamble requires a '***properly folded*** PH20 polypeptide with ***at least one modification***.'" *Id.* at 3 (citing Ex. 2070 ¶¶ 50, 345; Ex. 1026, 50:31–32; Ex. 1130, 60:14–61:12, 61:19–23; Ex. 2070 ¶ 128 n.12; Ex. 1133 ¶¶ 92–101, 104; Ex. 1133 ¶¶ 87–89; Ex. 1131, 32:8–37:20; Ex. 2068 ¶¶ 283, 353, 376).

4. Patent Owner's Sur-Reply

Patent Owner asserts that the "claimed modified PH20 polypeptides are defined by their structure—a[n] S312 mutation and 91% sequence identity—not by their function. Petitioner's expert, Dr. Kelsoe, admitted as much: 'Q So you don't read claim 1 to require any hyaluronidase activity, right? **A. To the best of my understanding, no.**'" PO Sur-reply 1 (quoting Ex. 2302, 41:6–12; 48:1–4). Patent Owner asserts "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). Patent Owner asserts "Dr. Naismith admits that 'the definition of "modified PH20 polypeptide" in the common disclosure considered in

isolation does not explicitly state that each modified PH20 polypeptide is enzymatically active.'" *Id.* at 2 (citing Ex. 1133 ¶ 109).

Patent Owner asserts that Petitioner's argument that proper folding is required for a "modified PH20 polypeptide" conflicts with the Specification, specifically asserting:

> First, "PH20" is itself a defined term, and the definition does not mention proper folding: "As used herein, PH20 refers to a type of hyaluronidase that occurs in sperm and is neutral-active." EX1001, 45:56–57. Second, like "modified PH20 polypeptide," the specification uses "PH20" to refer to both active and inactive polypeptides, so Petitioner's construction is inconsistent with the specification. EX1001, 116:59–117:12; 79:27–29. Third, Petitioner contends that because wild type PH20, which is a membrane-bound sperm cell protein, is active and properly folded, "PH20" must be too. But the claims are directed to ***modified*** PH20 polypeptides which are C-terminally truncated and not membrane-bound or in sperm.

Id. at 2–3.

5. 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).

a) Intrinsic evidence

Our analysis begins with the claims and Specification of the '035 patent. Claim 1 recites a "modified PH20 polypeptide" that also requires the polypeptide sequence is 91% identical to one of the 37 recited SEQ ID NOs and with at least one of five amino acids at position 312 of the reference sequence. The '035 patent states "PH20 refers to a type of hyaluronidase that occurs in sperm and is neutral-active."[6] Ex. 1001, 45:56–57; *cf. id.* at 68:46–50. The '035 patent further explains that "[r]eference to PH20 includes precursor PH20 polypeptides and mature PH20 polypeptides (such as those in which a signal sequence has been removed), truncated forms thereof that have activity, and includes allelic variants and species variants, variants encoded by splice variants, and other variants." *Id.* at 46:6–11. The '035 patent states that "PH20 polypeptides also include those that contain chemical or posttranslational modifications and those that do not contain chemical or posttranslational modifications." *Id.* at 46:15–18.

[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, 50:39–42.

The ’035 patent has a detailed “Definitions” section (*id.* at 44:57–68:42) that provides a definition of the term “modified PH20 polypeptide” stating:

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

Id. at 48:39–53 (emphasis added). The “Definitions” section states “[a]s used herein, PH20 refers to a type of hyaluronidase that occurs in sperm and is neutral-active.” *Id.* at 45:56–57. The “Definitions” section further addresses a number of other terms that relate to the “modified PH20 polypeptide.” 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 50:9–17.

The "Definitions" section also 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 51:15–18. The "Definitions" section 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 52:41–47 (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(s) or under elevated temperatures, respectively. *Id.* at 55:2–8, 55:17–23. The "Definitions" section 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 57:58–61. 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 61:66–62:1.

The "Definitions" section also states "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 63:37–44 (emphasis added). The "Definitions" section 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 64:14–19.

After the "Definitions" section, in a different section discussing the PH20 polypeptide, the '035 patent states, "[d]ue to the role of PH20 in fertilization, PH20 can be used as an antigen for immunocontraception." *Id.* at 72:60–62. The '035 patent also states "provided are modified PH20 polypeptides that are inactive, and that can be used, for example, as antigens in contraception vaccines." *Id.* at 75:56–58.

Analyzing all of the intrinsic evidence, a consistent reading of the term "modified PH20 polypeptide" in the '035 patent supports the understanding that some type of activity is required for a polypeptide to be a "modified PH20 polypeptide," and that the enzymatic activity of hyaluronidase is the most frequently identified activity recited in the definitions section of the '035 patent. *See e.g., id.* at 45:56–57, 46:15–18, 48:39–53, 52:41–47, 61:66–62:1, 63:37–44, 64:14–19. In contrast, the discussion regarding the potential use of "modified PH20 polypeptides that are inactive" as antigens in contraception vaccines appears only in a non-definitional sections of the '035 patent. *Id.* at 72:60–62, 75:56–58. Accordingly, this discussion does not modify the definition's explicit

requirement that the claimed "modified PH20 polypeptide" exhibit hyaluronidase activity. *Id.* at 48:39–53.

b) 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.

"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. 2035, 33654 ("Among the six HAases [hyaluronidases], HYAL1, HYAL2, and PH20 are well characterized"); 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 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 ("immunization of male guinea pigs with PH-20 reproducibly results in infertility"); Ex. 2013, 10075 ("hPH-20 should be a good candidate antigen for developing a contraceptive vaccine for humans.").

Turning to the expert testimony, when asked "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.

Ex. 2076, 181:9–18. When a further question asked "the specification, in fact, uses the termed modified PH20 polypeptides to refer to inactives?", Dr. Hecht recognized a distinction in the '035 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,[7] Dr. Simpson, disagrees with Dr. Hecht. Dr. Simpson states, "[i]n my opinion, a POSA would have understood the claims do not require hyaluronidase enzymatic activity, let alone ≥ 40% hyaluronidase enzymatic activity." Ex. 2068 ¶ 256. Dr. Simpson relies upon the absence of a recitation of function in claim 1 and on recitations in the '035 patent of "inactive mutants" that were not found in the "Definitions" section to support the position that "a POSA would understand that modified PH20 polypeptides with a S312G, S312K, S312L, S312N, or S312T substitution 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.

In deposition, when asked "if claim 1 requires the modified PH20 polypeptides to contain any hyaluronidase activity?," Petitioner's expert Dr. Kelsoe stated "It does not. It simply claims 95 percent identity." Ex. 2302, 41:6–12.

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

[7] 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.

expressly defined in the common disclosure to have a form a POSA would understand is folded and is enzymatically active." *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.

c) Analysis

The instant claims, after Patent Owner's disclaimer of claim 4, 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 '035 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, 45:56–57. And the second sentence of the definition of "modified PH20 polypeptide" in the '035 patent allows mutations in the PH20 polypeptide "so long as the resulting modified PH20 polypeptide ***exhibits hyaluronidase activity***." *Id.* at 48:44–46. Thus, we

agree with Petitioner that the term, interpreted in light of the Specification, requires at least some hyaluronidase activity.

We recognize Patent Owner's argument that the claims do not exclude the use of such peptides as contraceptives (the only other activity possible utility recited in the '035 patent). PO Resp. 42–44; *cf.* Ex. 1001, 115:59–63. We note, however, that "[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)). In other words, the Specification's observation that a modified PH20 polypeptide may also be useful to provide a contraceptive effect (even when it is inactive) does not 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***." *Id.* at 48:43–46 (emphases added).

As cited above, the extrinsic evidence also supports that "PH20" is understood by ordinarily-skilled artisans in this field to refer to activity, and not just structure. Indeed, as virtually every publication cited by both parties reference hyaluronidase activity, and several also mention contraceptive activity. And while we recognize that Patent Owner's expert Dr. Simpson finds that "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 '035 patent, Patent Owner chose to inform the ordinary artisan that the claimed polypeptides would have the properties that the '035 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.

The record also reflects that the Examiner allowed claim 1 with the understanding that it encompassed modified PH20 polypeptides with hyaluronidase activity, as shown by disclaimed claim 4.[8] *See* Ex. 1001, 317:34–37. This claim recites that the modified PH20 polypeptide has "increased hyaluronidase activity" as compared to the unmodified PH20 polypeptide (SEQ ID NO: 3), which assumes that the underlying "modified PH20 polypeptide" recited in the base claim has activity. *See id.*[9]

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[8] Claims 4 in the '035 patent as issued are reproduced below:

> 4. The modified PH20 polypeptide of claim 1 that exhibits increased hyaluronidase activity compared to the unmodified PH20 polypeptide not containing the amino acid replacement at position 312.

Ex. 1001, 317:34–37.

[9] Given that this claim has been disclaimed, the extent to which it continues to bear on claim construction is unclear. We cite it simply to note that it is consistent with the other evidence supporting our claim interpretation.

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.

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 challenged claims fail to comply with the written description requirement.

2. Petitioner's Position

Petitioner asserts "the claim language defines enormous genera: between 10^{59} and 10^{112} distinct polypeptides. . . . Testing every polypeptide within the claims' scope in search of 'active mutants' is impossible—literally." Pet. 26–27 (citing Ex. 1003 ¶¶ 123, 135, 189; Ex. 1039, 136–37). Petitioner asserts that:

> The sequence identity language in claims 1–2, 6–14, and 24–25 define genera of modified PH20 polypeptides of varying size that are not only immense, but are structurally and functionally diverse. These genera capture PH20 mutants with 2 substitutions, 3 substitutions and so on up to a number set by the sequence identity boundary (*i.e.*, 21 for the narrowest claims (*e.g.* claims 24 and 25) to 42 for the broades (claim 1). . . . Each claim also encompasses substitutions within C-terminally truncated forms of PH20 of varying lengths. Claim 1 does this explicitly, specifying 37 alternative sequences ranging from 430 to 474 residues.

Id. at 32–33 (citing Ex. 1003 ¶¶ 119–20).

Petitioner asserts the '035 patent "directs the skilled artisan to blindly make-and-test all such candidate mutants using trial-and-error experimentation." *Id.* at 34 (citing Ex. 1003 ¶ 193). Petitioner acknowledges that the '035 patent identifies six double mutations to avoid and indicates "the substitutions listed in Tables 5 and 10 should not be included in enzymatically active multiply-modified PH20 polypeptides," but

Petitioner notes that "nothing in the claim language excludes such combinations." *Id.* at 34–36 (citing Ex. 1003 ¶¶ 146–151, 161–162, 169).

Petitioner asserts that based on the prior art and the common disclosure, "a skilled artisan in 2011 would have believed that C-terminal deletions yielding PH20 polypeptides terminating before position 430 would be inactive," but asserts that the '035 patent "provides no examples of (or guidance concerning) PH20 mutants truncated below position 447 with one or more substitutions and that are enzymatically active. It thus ignores the uncertainty existing in 2011 about PH20 truncation mutants that terminate between positions 419 to 433." *Id.* at 39–40 (citing Ex. 1003 ¶¶ 92, 93, 97, 143, 159, 165–169).

Petitioner asserts that of 5,917 tested single amino acid changes, "~87% of the single-replacement $PH20_{1-447}$ polypeptides had ***less*** activity than unmodified $PH20_{1-447}$." *Id.* at 41 (citing Ex. 1003 ¶ 105). Petitioner asserts that the data shows the unpredictability of mutations where "introducing different amino acids at the same position in $PH20_{1-447}$ resulted in (i) increased activity, (ii) decreased activity, or (iii) inactive mutants." *Id.* at 42 (citing Ex. 1001, Tables 3, 5, 9, 10). Petitioner asserts that multiple concurrent mutations

> can cause complex and unpredictable effects on a protein's structure and resulting function. The patent's empirical test results thus provide no guidance to a skilled artisan about which of the many possible PH20 mutants with different sets of 2–42 substitutions will be enzymatically active.

Id. at 44 (citing Ex. 1003 ¶¶ 139–40, 142–43). Petitioner asserts that the '035 patent does "not identify which ***combinations*** of substitutions improve stability. [The examples provide] no probative insight regarding

multiply-modified PH20 polypeptides with increased stability." *Id.* at 45 (citing Ex. 1003 ¶¶ 75–76).

Petitioner asserts that the '035 patent fails to "identify ***any*** actual multiply-modified PH20 polypeptides (*i.e.*, particular sets of specific amino acid substitutions), much less provide results from testing any. They simply draw boundaries around a theoretical and immense genus of modified PH20 polypeptides." *Id.* at 48–49. Petitioner asserts that the '035 patent "outlines an prophetic, 'iterative' make-and-test research plan for discovering modified PH20 polypeptides with multiple substitutions that might exhibit hyaluronidase activity," but that:

> The guidance in this research plan is effectively meaningless. It says to make mutants, test them to find activity and/or stability, and keep repeating the process until you find something via screening. It does not indicate that any useful multiply-modified PH20 polypeptides will be found, much less what their specific characteristics or activities are.

Id. at 49 (citing Ex. 1003 ¶¶ 187–90; Ex. 1001, 42:48–55, 125:27–32, 132:13–26).

Petitioner asserts the '035 patent does not identify

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

Id. at 51–52 (citing Ex. 1003 ¶¶ 139–40, 151).

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

between ***2 and 22 substitutions*** at any of hundreds of positions within the protein." *Id.* at 54 (citing Ex. 1003 ¶¶ 61, 143, 159). Petitioner asserts that the "effects of those numerous substitutions on a protein's various secondary structures and structural motifs within the protein is not described in the common disclosure." *Id.* at 54 (citing Ex. 1003 ¶ 228).

Petitioner asserts that the figure below illustrates "how ***non-representative*** the examples are: all of the examples of single-replacement $PH20_{1-447}$ mutants fit into one box of the array below (claim 2)":

	Number of Changes																						
SEQ	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
3																							
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The figure depicts a 23 x 37 array with a single shaded red box representing all of the tested single nucleotide mutations in SEQ ID NO: 3. *Id.* at 57–58. Petitioner further states that "[u]like claim 2, which requires 95% sequence

identity, claim 1 permits 91% sequence identity, thus capturing an even ***larger*** genus (up to 42 permitted changes) than depicted above." *Id.* at 58.

Petitioner asserts that the remaining challenged claims in the '035 patent lack written descriptive support for the same or similar reasons. *See id.* at 60–65.

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 five S312 variants and 91% identical subvariants." 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 91% identical subvariant polypeptides as of December 28, 2012.

Id. at 44–45.

Patent Owner asserts that "[t]he specification describes and characterizes the common structural features of the five S312 variants recited in the claims (S312G, S312K, S312L, S312N, and S312T) and their 91% identical subvariants." *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 46. Patent Owner asserts that

> Dr. Petsko generated homology models of multiply modified PH20s identified in the patent with the claimed S312 mutation, including chimpanzee PH20, gibbon PH20, orangutan PH20. EX2070, ¶¶57, 413-434. 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[10] teaches is active).

Id. at 46. Patent Owner points out that the Specification identifies specific amino acids necessary for enzymatic activity, amino acids involved in disulfide bridges, and sites involved in substrate binding. *Id.* at 49–50 (citing Ex. 1001, 70:46–54, 70:14–26; 70:34–41; Ex. 2068 ¶ 303). Patent Owner asserts "because the specification discloses the structural features necessary for activity, POSAs would have understood them as common to active S312 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 50.

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.

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[10] The "'457 publication" is U.S. Patent Application Publication No. 2010/0143457 A1 to Wei et al., published June 10, 2010. It is referenced in the '035 patent. *See, e.g.*, Ex. 1001, 69:66–70:8, 70:64–71:1, 71:40–45, 74:4–15, 126:6–12.

Id. at 52 (citing Ex. 2070 ¶¶ 44–56, 268–388; 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 in actives." *Id.* at 54 (citing Ex. 2068 ¶ 311). Patent Owner asserts that unlike the situations in *Ariad* and *AbbVie*, 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 S312 mutation and 91% identity—to be covered. And, as the inventors identified by sequence and structure-function mapping the full scope of the narrow set of claimed S312 variants and subvariants, they in fact possessed the full scope of the genus.

Id. at 55.

Patent Owner asserts that "Dr. Petsko's and Dr. Simpson['s] analyses show that in fact the claimed subvariants are structurally homogeneous. And the large number of inactivating mutations are not evidence of unpredictability. EX2068, ¶¶379-380." *Id.* at 58. Patent Owner asserts "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

> 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 '035 patent as set forth in footnote 10] provides activity data for all of the SEQ IDs listed in the claims.

> As Drs. Simpson and Petsko further explain, POSAs would have reasonably known based on '457 publication's results what the activity would be for each recited sequence in the '035 claims.

Id. at 60 (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 312) were active." *Id.* at 63 (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 five variants and their 91% identical sub-variants. Moreover, the working examples comprehensively characterize the structure-function of PH20 (SEQ ID NO: 3) through the mutagenesis data." *Id.* at 63–64.

4. Petitioner's Reply

Petitioner responds their "reading of the 'sequence space' of the claims is not a 'parlor trick'— Halozyme's experts ***confirmed*** it (~10^{59} to ~10^{112} sequences). The Petition also explained (and Halozyme's experts agree) the claims permit (i) modifications at any position, (ii) additions/deletions, and (iii) substitutions to any of 19 other amino acids." Pet. Reply 4–5 (citing Ex. 1003 ¶¶ 119–122; Ex. 1004 ¶¶ 150–154; Ex. 1130, 90:1–16, 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).

Petitioner asserts "[p]roperly folded PH20s are the only 'subgenus' of PH20s in the sequence space that could have a common set of structural features, but the disclosure fails to identify what they are and which of the 10^{59}+ sequences will fold to have them." *Id.* at 11. Petitioner asserts that "[a]s a ***claim element***, the 91% identity requirement 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 structural 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 (much less explain) how the "distorted" (α/β) barrel motif in human PH20 differs from its canonical structure, or describe its relationship to PH20's active site.

Id. at 14 (citing Ex. 1133 ¶¶ 151–158, 165–170; Ex. 1008, 824–25, 829, 833; Ex. 1006, 6911–13; Ex. 1033, 1027). Petitioner asserts that a "POSA could not have used knowledge of the ***canonical*** 'α/β barrel' motif to visualize the ***distinct*** structure of PH20's α/β motif because the two ***are materially different***." *Id.* at 15 (citing Ex. 1133 ¶¶ 136–139, 144, 150–152). Petitioner asserts that the "common disclosure refers to a 'common core hyaluronidase domain' shared by PH20 hyaluronidases (3-339 of PH20). That does not identify the Hyal-EGF domain in PH20 (it terminates 4-5 residues into it), and is not a 'common structural feature' of active PH20s because it cannot 'properly fold.'" *Id.* at 18 (citing Ex. 1026, 79:20–31; Ex. 1133 ¶¶ 161–163).

Petitioner asserts:

> First, effects on PH20 folding and activity from single-substitutions cannot predict effects of ***combinations*** of changes. *See* § III.D.1. Even positions Dr. Petsko labeled "100% tolerated" exhibited extensive variation, demonstrating the unpredictability of single substitutions.
>
> Second, listing options and leaving to a POSA the task of figuring out which combinations yield active PH20s does not describe species of PH20s.

Id. at 20 (citing Ex. 1003 ¶¶ 54–61, 140–143; Ex. 1133 ¶¶ 115, 232–233, 252–259, 264–269) (also noting experimental data problems and lack of description of the PH20 tertiary structure).

Petitioner asserts that Patent Owner "points to 14 alleged 'examples' of 'S312 modified PH20s.' None are described in its disclosure. Three are based on native ***primate*** sequences with known activity, while four were tested. None of the fourteen illustrate the unpredictability of making 5, 10, or 15 changes to a native sequence." *Id.* at 21 (citing PO Resp. 55–57, Ex. 2070 ¶¶ 429–432; Ex. 1133 ¶¶ 114–119).

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.

PO Sur-reply 4. Patent Owner asserts "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 (citing Pet. 11–15, 74, 101–108; Ex. 1004 ¶¶ 36, 104–149; Ex. 2077, 176:2–5; Ex. 1130, 97:14–99:10; Ex. 2070 ¶¶ 112–230, 343–434; 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 6. 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 '035 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 9–10 (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 10 (citing Ex. 2070 ¶¶ 61–67, 343–434). 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 Section 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. Patent Owner asserts that

Petitioner "has not shown any evidence, from prior art or post-filing, that cumulative effects of combining mutations (whether through epistasis or otherwise) renders visualizing, making, and using multiply-mutated PH20s unpredictable ***when actually considering 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 18–19.

Patent Owner asserts that the

> specification discloses the common structural features based on that primary structure and the related mutagenesis data:
> • 91% sequence identity to the primary structure of the recited SEQ IDs;
> • The S312 mutation;
> • 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 21. Patent Owner asserts "[t]here is no dispute that there are several highly active representative species disclosed in the specification. Moreover, Petitioner's new expert 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 24 (citing Ex. 2301, 213:10–18, 85:19–99:18, 101:11–20, 159:13–25).

6. Evidence and Analysis

a) Description in the '035 patent

Our review begins with the claims and Specification of the '035 patent. Claim 1 recites a "modified PH20 polypeptide" that also requires the polypeptide sequence is 91% identical to one of the 37 recited

SEQ ID NOs and with at least one of five amino acids at position 312 of the reference sequence. *See* Ex. 1001, 317:1–25. As we note above, we interpret the claim to require hyaluronidase activity. *See supra* Section II.B.

The ’035 patent generally recites polypeptides with single point mutations at a variety of positions. *See, e.g.*, Ex. 1001, 13:3–18:42. The ’035 patent 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 73:2–10. Significantly, the ’035 patent details single modifications at every position of the mature, soluble PH20 polypeptide with analysis showing whether the modification impacted hyaluronidase activity. *See id.* at 192:4–222:18, 224:33–259:9. The ’035 patent also references an earlier patent application publication (the ’457 publication) that disclosed three double mutations and a single example of a triple mutation in the PH20 hyaluronidase enzyme, which all show hyaluronidase activity, that are within the scope of the claims. *See* Ex. 2068 ¶¶ 336–342; *see* Ex. 2165, Table 16.

However, the ’035 patent 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 PH20 polypeptide or any hyaluronidase enzyme. *See generally* Ex. 1001; Ex. 1003 ¶¶ 103, 131 (“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”), 228 (“[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.”).

The ’035 patent states that “[m]odified PH20 polypeptides provided herein can be used as vaccines in contraceptive applications.” Ex. 1001, 193:15–16. The ’035 patent 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 193:24–28.

b) Expert testimony

There is agreement among the experts, and we find, that the claims encompass (i) modifications at any position, (ii) additions/deletions, and (iii) substitutions to any of nineteen other amino acids. *See* Ex. 1003 ¶ 119; Ex. 1130, 90:25–91:12; Ex. 1131, 54:15–56:23. There is also agreement, and we find, that these modifications result in approximately 10^{112} different polypeptide sequences within the genus of claim 1 (i.e., permutations based on as many as 41 changes to the longest of the PH20 backbones in the recited SEQ ID NOs). Ex. 1003 ¶ 122; Ex. 1004 ¶¶ 150–152; Ex. 1131, 60:24–61:3; Ex. 1133 ¶ 112.

(1) Hyaluronidase activity

The experts disagree, however, on the scope of the impact of the claimed 10^{112} different polypeptide sequences on hyaluronidase activity and enzyme structure.

(a) Petitioner's Evidence

Dr. Hecht states that "[t]he effects of these myriad sets of combinations of multiple substitutions within PH20 could not have been predicted by a skilled artisan in the 2011 timeframe using the tools that were available then." Ex. 1003 ¶ 158. Dr. Naismith concurs with Dr. Hecht, stating that "[t]here is no teaching in the patent or modelling software that would allow sets of 17 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 continues, stating that "[o]ther than these hypothetical mutants, neither Dr. Petsko nor Dr. Simpson 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.* ¶ 119.

Dr. Hecht notes that claim 1 allows "21-42 changes, with each additional change (except at position 312) being to 1 of 19 other amino acids. But the up to 21-42 changes also can be at any of between 430 and 465 (or, in the case of the broadest claims, 474) different positions depending on which unmodified PH20 sequence is used." Ex. 1003 ¶ 120. Dr. Park calculates that "95% sequence identity to $PH20_{1\text{-}465}$ means that the protein can have 23 total changes," and that where one of those changes is one of five choices at position 312 as required by claim 1, the number of possible PH20 polypeptides with twenty-two additional changes is 2.59×10^{66}. *See* Ex. 1004 ¶¶ 153–154. Dr. Hecht characterizes the number of possible mutations as "astronomical in size." Ex. 1003 ¶ 125.

In the context of structure modeling, Dr. Park states that "the PH20 model from SWISS-MODEL that I used in my analysis should be very

similar to what a skilled artisan would have obtained in 2011." Ex. 1004 ¶ 141. 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.* ¶ 143. Dr. Park cites Zhang (Ex. 1010), which states, "analysis of Hyal1 point mutants highlights the importance of specific conserved residues in catalytic function, but also identifies active site conformation as a critical factor. Disrupted activity resulted from the R265L mutation but not from N216A or global disulfide reduction." Ex. 1010, 9441. Dr. Park notes that Zhang found "a mutation at Asn350 in the 'c-terminal EGF-like domain' abolished hyaluronidase activity but one at Asn216 did not." Ex. 1004 ¶ 96; Ex. 1010, 9438–39. Dr. Park also cites Ex. 1011 (Arming), which states:

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

Ex. 1011, 813; Ex. 1004 ¶ 101. According to Petitioner, these prior art references demonstrate that even conservative mutations may significantly impact the PH20 polypeptide hyaluronidase function. *See* Reply 16–18.

Dr. Naismith states that "[i]f the set of polypeptides being claimed includes any polypeptide with an amino acid sequence that meets only the . . . two 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.* (citing Ex. 2164, 160 (Fig. 4-53)) (alteration in original). Dr. Naismith states "[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 91% sequence identity requirement is a "structural feature" of a modified PH20 polypeptide. It is a claim 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 (for each of S312T and S312N) of PH20 polypeptides with more than one change . . . . These limited examples do not meaningfully probe the combinatorial sequence space covered by the claims and are not

representative of the breadth of modified PH20 polypeptides claimed." *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 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 ¶¶ 49–50; Ex. 1004 ¶ 144).

In deposition, when Dr. Hecht was asked "what is your interpretation for why the inventors used a 95 percent sequence identity claim language?", Dr. Hecht answered: "[t]he inventors are trying to capture a genus. They're not giving a substantial, written description of that genus, but they're attempting to capture that." Ex. 2076, 196:10–18. Dr. Hecht further stated: "my sense was that the [] patent lists a minuscule and highly biased sample of what would be within that fence, 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." *Id.* at 203:6–12. When asked what "the skilled person would expect that if they made five changes in HYAL1", Dr. Hecht stated: "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 in 2011 would have performed "that 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 characterizing 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 PBD [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 PBD 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 would impact protein folding and stated: "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 remained low for many years, until

CASP12[11] in 2016, when the accuracy suddenly 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 stated 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.

(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.

Id. ¶¶ 126–127. Dr. Petsko states: "a POSA would have expected that a folded modified PH20 that is 91% identical in sequence to wild type ('WT')

[11] 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.

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, 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, 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 stabilization[12] 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 is enormous. And when combined with the structural information from modeling the PH20 structure, it allows you to visualize and make predictions about much more of the dataset than just what you see here." *Id.* at 113:2–18.

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[12] In explaining the term "free energy of stabilization", Ex. 1014 states:

> Every biochemist or molecular biologist who has worked with proteins knows by experience that they are unstable. Slight changes in pH or temperature can convert a solution of biologically active protein molecules in their native state to a biologically inactive denatured state. The energy difference between these two states in physiological conditions is quite small, about 5–15 kcal/mol, not much more than the energy contribution of a single hydrogen bond, which is of the order of 2–5 kcal/mol. . . . The total energy difference between the native and the denatured state of 5–15 kcal/mol, which is called the free energy difference, is thus a difference between two large numbers, the enthalpy difference and the entropy difference.

Ex. 1014, 90.

In deposition, Dr. Simpson stated that a POSA "would have all the information they needed with respect to its 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." Ex. 1130, 99:5–10.

(c) Review

As to hyaluronidase activity, the evidence of record shows that a POSA, in 2012, would not have predictably been capable of determining which PH20 polypeptides having modifications in addition to the recited modification at position 312 would have retained hyaluronidase activity, i.e., we credit Petitioner's evidence above that is more consistent with the evidence of record over Patent Owner's competing evidence. In particular, as Dr. Park noted, SWISS-PROT would not reliably provide such information. *See* Ex. 2077, 202:9–13. And this is confirmed by Scientific 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 '035 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. Ex. 1003 ¶ 171; Ex. 1004 ¶¶ 62, 144; Ex. 1131, 102:1–9; Ex. 1133 ¶¶ 59, 76.

Patent Owner's evidence does not overcome Petitioner's showing. While Dr. Petsko testified that the single substitution data in the Specification shows that there are a number of 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, quoting Dr. Petsko's textbook as teaching that 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 Dr. Petsko and Dr. 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"[13]) for finding the recited polypeptides rather than demonstrating the inventors were in possession of the full scope claimed. 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; Ex. 2068 ¶¶ 123–125) do not appear in the written

[13] Ex. 2068 ¶ 157.

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. For these 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 hyaluronidase activity, even with the single substitution data provided by the '035 patent.

(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. 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

Dr. Kelsoe states regarding Tung, cited in the '035 patent for contraceptive activity, 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. Dr. Kelsoe states 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 "[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 (citing Ex. 2010). Dr. Cherr states: "POSAs would have known, as Hardy 2004 and Pomering 2002 also acknowledge, that the poor contraception seen after administering PH20 polypeptides via non-mucosal routes in Hardy 2004 (intraperitoneal route in mice) and Pomering 2002 (subcutaneous route in rabbits) reflect the reproductive biology of mice and rabbits." *Id.* ¶ 51.

Dr. Moon states "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.

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 not." *Id.* at 38:13–16.

(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 contraceptives

in humans. 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. 2010, Abstract. But in addition to the expert testimony by Dr. Kelsoe disputing their positions, Exhibit 1189 (Martin-DeLeon) cites extensive experimental evidence that PH20 polypeptide vaccines were ineffective as contraceptives in rabbits and mice. *See* Ex. 1189, 119. This evidence showing significant interspecies variability is further supported by the statement in Exhibit 1189 (Martin-DeLeon) that "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." *Id.* Exhibit 1189 further states:

> In a primate model, *Cynomolgus macaques*, combinations of adjuvant and antigens derived from synthesized and recombinant proteins all produced significant immune responses in females, with circulating antibodies recognizing macaque sperm surface PH-20 (Deng et al., 2002). However, there was a lack of sterility following immunization in this model also.

Id.

The failure of PH20 polypeptides as contraceptive vaccines in three of four species tested, and particularly in a primate 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. The data Patent Owner relies upon at most shows an immunocontraceptive effect for unmodified PH20 polypeptides limited to guinea pigs. It does not evidence that a POSA would have understood that the recited modified polypeptides would provide such

an effect or otherwise be useful in a contraceptive vaccine. 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 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, 1337 (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. Based on this claim interpretation, we find the evidence in this case closer to *Juno* than

Capon, and that the ’035 patent does not disclose sufficient structural features in the PH20 sequences associated with hyaluronidase or contraceptive activity to allow an ordinary artisan 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 on the entire claim. *See* Ex. 1131, 64:12–17.

And while *Capon* expressly allows reliance on prior art for description (*see Capon*, 418 F.3d at 1357–58), Patent Owner is trying to extend that to include that which is obvious from the prior art, not just that which is described. That is, it may have been obvious to a POSA to align PH20 sequences with other known hyaluronidase enzymes and obvious to use the crystal structure of a different hyaluronidase in SWISS-PROT to generate a three-dimensional structure, but neither that alignment nor a structure for PH20 is disclosed in the ’035 patent. “[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 (recognizing that “[p]erhaps one of ordinary skill could discover this information, but this does not alter our conclusion that the description . . . just represent 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^{112} polypeptides claimed.

We find this is consistent with *AbbVie*, which required an inventor to 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 Deutschland GmbH v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300 (Fed. Cir. 2014). Here, Patent Owner claims an immense number of mutations in the PH20 polypeptide, but provides insufficient guidance for a POSA as of 2012 to determine which, if any, of the untested multiple mutated forms will retain hyaluronidase activity.

In the recent case *Teva Pharm. Int'l 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 distinction rested on difference between claims that didn't require function and those that did. And we recognize that while claim 1 does not recite a function in the claim language itself, here the Specification defines the term "modified PH20 polypeptide" to require hyaluronidase activity. *See supra* Section II.B. 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 the structure of a small

number of species in an immense genus is insufficient to satisfy the written description requirement.

A preponderance of the evidence shows that the claims of the ’035 patent fail to satisfy the written description requirement because they “recite a description of the problem to be solved while claiming all solutions to it and . . . cover any compound later actually invented and determined to fall within the claim’s functional boundaries—leaving it to the pharmaceutical industry to complete an unfinished invention.” *Ariad*, 598 F.3d at 1353.

Accordingly, we find that Petitioner has demonstrated by a preponderance of the evidence that for challenged claims 1, 2, 6–14, 16–29 of the ’035 patent does not comply with the written description requirement. Similarly, the current record does not appear to provide evidence of possession of the full scope of the claims of the ’035 patent in any of the applications in the extensive priority chain, which all have the same specification, including the provisional application 61/631,313, filed Dec. 30, 2011, provisional application 61/796,208, filed Nov. 1, 2012, or non-provisional application 13/694,731, filed Dec. 28, 2012, for the reasons given above.

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) (bracketing in original; internal quotations omitted). That is, “there must be sufficient disclosure,

either through illustrative examples or terminology, to teach those of ordinary skill [in the art] how to make and how to use the invention as broadly as it is claimed." *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991) (footnote omitted).

> 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

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

Pet. 67 (citing Ex. 1003 ¶¶ 170–71, 190). Petitioner asserts that the "claims capture a massive genera of modified PH20 polypeptides, most of which would have unknowable properties absent individual production and testing." *Id.* at 69 (citing Ex. 1003 ¶ 158).

Petitioner asserts that the '035 patent "provides an extremely narrow set of working examples: ~5,916 randomly generated single-replacement $PH20_{1\text{-}447}$ polypeptides, of which ~2500 were 'active mutants.' Those

examples are a tiny fraction of the 10^{59} to 10^{112} modified PH20 polypeptides covered by the claims." *Id.* at 70 (citing Ex. 1003 ¶ 103).

Petitioner asserts that the "prospective research plan in the common disclosure demands that a skilled artisan engage in undue experimentation to practice the full scope of the claims. First, it requires manually performing iterative rounds of ***randomized*** mutations" and "provides no meaningful guidance in producing 'active mutant' modified PH20 polypeptides." *Id.* at 71 (citing Ex. 1003 ¶¶ 188–90; Ex. 1018, 382). Petitioner asserts that the "disclosure is indistinguishable from the '***iterative, trial-and-error process[es]***' that have consistently been found to not enable broad genus claims to modified proteins." *Id.* at 72–73 (quoting *Idenix Pharm. LLC v. Gilead Sci. Inc.*, 941 F.3d 1149, 1161–63 (Fed. Cir. 2019)).

Petitioner asserts "the skilled artisan could ***not*** have predicted the effects of making more than a few concurrent amino acid replacements within a PH20 polypeptide in 2011." *Id.* at 74 (citing Ex. 1003 ¶ 228). Petitioner asserts that the "cumulative effects of multiple changes would also have rapidly exceeded the capacity of computer-based, rational design protein engineering techniques to reliably predict the effects of each change on the protein's structure." *Id.* at 75 (citing Ex. 1003 ¶¶ 158, 190, 228; Ex. 1004 ¶¶ 143–144).

Petitioner asserts:

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

Id. at 76–77 (citing Ex. 1003 ¶¶ 158, 228).

3. Patent Owner's Response

Patent Owner asserts "[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. 64 (citing Pet. 36–37). Patent Owner asserts that

> POSAs would recognize, within this narrow genus, that the five variants and their subvariants are structurally homogeneous in that they share at least 91% identical primary structure, the S312 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 65 (citing Ex. 2068 ¶¶ 287–293, 303, 316; Ex. 2070 ¶¶ 49–51, 53, 248–253, 325–342, 389–432). 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 66.

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 68–69. 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 modified PH20 polypeptides without undue experimentation.

Id. at 70 (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 71 (citing Ex. 1001, 69:13–71:48, 73:2–10, Tables 5, 9–10; Ex. 2068 ¶¶ 372–377; EX2070 ¶¶ 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 72–73 (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 S312 mutation." *Id.* at 73–74. 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 76 (citing Ex. 2072 ¶¶ 19–28).

Patent Owner asserts that

> Petitioner argues that "the vast majority of 'inactive mutant' PH20 polypeptides would have no utility at all." Pet., 82. 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 81 (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.* at 81–82.

4. Petitioner's Reply

Petitioner responds that

> When ***multiple*** mutations are made together they affect a protein's structure, capacity to fold, 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."

Pet. Reply 23 (citing Pet. 10–11, 51–53; Ex. 1003 ¶¶ 55–61, 156–159; Ex. 1133 ¶¶ 123, 125–126, 222, 232, 252–259, 262; Ex. 1131, 79:15–22,

89:21–90:24; 270:9–17; Ex. 1160, 383–85). Petitioner asserts "[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; Ex. 1003 ¶ 54; 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 (citing Ex. 2070 ¶¶ 52, 292; PO Resp. 53–55). Patent Owner asserts that "[d]espite the constrained choices, most α/β barrel mutants ***did not fold***." *Id.* at 31 (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.
>
> Correcting for these limitations and problems paints very different pictures than the ones Dr. Petsko presented.

Id. at 32–33 (citing Pet. 45–47; Ex. 1003 ¶¶ 72, 76; Ex. 1133 ¶¶ 294–315, 248, 250, 175, 235, 304–305, 316–321, 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. And where 'tolerance' is used to inform changes, the disclosure simply instructs POSAs to ***not include*** inactivating substitutions in active PH20s." *Id.* at 36–37 (citing Ex. 1026, 91:30–92:20; Ex. 1133 ¶¶ 206–207, 209).

Petitioner asserts that for a number of 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 41 (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." PO Sur-reply 6. 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 "provid[es] a consistent, objective and unbiased evaluation of substitutions throughout the protein." Pet., 102-107. 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 ¶ 158; Ex. 1004 ¶ 144; Ex. 1133 ¶ 258, n.288). 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 9 (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 16–17. Patent Owner asserts that the "patent's extensive mutagenesis data transforms what would otherwise be exploratory work into routine experimentation." *Id.* at 18.

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 25 (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 27 (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 27–28 (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, regarding the breadth of claim 1, that he "calculated the number of distinct polypeptides that exist that meet the specified criteria." Ex. 1004 ¶ 154. Dr. Park's table is reproduced below:

PH20 length	*Sequence Identity %*	*# Changes*	*Pos. 312 Choices*	*Add'l Changes*	*# of Distinct Polypeptides*
430	91	38	5	37	3.83×10^{101}
430	91	38	1	37	7.66×10^{100}
430	95	21	5	20	2.20×10^{60}
430	95	21	1	20	4.40×10^{59}
433	91	38	5	37	5.01×10^{101}
433	91	38	1	37	1.00×10^{101}
433	95	21	1	20	5.08×10^{59}
447	91	40	5	39	6.98×10^{106}
447	91	40	1	39	1.40×10^{106}
447	95	22	5	21	1.88×10^{63}
465	91	41	5	40	7.06×10^{109}
465	91	41	1	40	1.41×10^{109}
474	91	42	5	41	3.16×10^{112}
474	91	42	1	41	6.32×10^{111}
474	95	23	5	22	2.59×10^{66}

Id. Dr. Park's table shows that the "number of distinct peptides is extremely large by all accounts, ranging from 10^{59} to 10^{112}." *Id.* Dr. Hecht agrees, stating the "sequence identity language causes the claims to encompass an immense number of distinct PH20 polypeptides." Ex. 1003 ¶ 120. To illustrate how large a number like 10^{59} is, Dr. Hecht states that an "aggregate weight of the smallest set containing one molecule of each of the PH20 mutants would be . . . = 3.93×10^{40} kg. The weight of the Earth is 'only' ~ 5.97×10^{24} kg." *Id.* ¶ 123. 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 ['035] patent lists a minuscule and highly biased sample of what would be within that fence, 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." *Id.* at 204:11–19.

Dr. Simpson disagrees with Dr. Hecht and Dr. Park, stating "POSAs would not evaluate the scope of the claimed genus by calculating the total number of amino acid sequences that satisfy the 91% identity limitation. POSAs would evaluate the scope of the claims by considering the variation across the set of claimed proteins. And there is little variation across this set." 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 view of the extensive structure-function guidance provided in the '035 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 sharing 91% of their sequence (including the recited change at position 312) as an extremely limited set of proteins. Those that fold are a limited set of structurally homogeneous proteins." Ex. 2070 ¶ 392. Dr. Petsko states that "[t]o further illustrate the common structural features shared by the claimed polypeptides, I generated models of several S312N and S312T variant PH20s that satisfy the sequence identity requirements of claim 1." *Id.* ¶ 413. After showing images of one set of structures with particular variant PH20s, Dr. Petsko stated that in this example, "S312N models share a common structural feature in that the amide group of the asparagine interacts with the hydroxyl group of serine 315. The S312T models share a common structural feature in that the hydroxyl group on the threonine side chain interacts with the main chain amide group of M313, the main chain amide group of lysine 314 and the hydroxyl group on the side chain of serine 315." *Id.* ¶ 418.

In deposition, despite acknowledging the accuracy of Dr. Park's calculation (*see* Ex. 1130, 90:14–16), Dr. Simpson stated "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 issue of 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, apart from position 320, 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 and Dr. Simpson, stating

> If the set of polypeptides being claimed includes any polypeptide with an amino acid sequence that meets only the above two claim requirements, 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 do not disrupt the spatial positioning of the catalytic machinery and/or substrate recognition motif. Dr. Hecht illustrated these points in his declaration.

Ex. 1133 ¶ 40 (citing Ex. 1003 ¶¶ 44–46, 55–61, 156–159). 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

"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.

Dr. Naismith states that:

> 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: "I do not agree that the 91% 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 the 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 agreed with Dr. Petsko 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. 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). Dr. Simpson acknowledged that a POSA would not expect the vast majority of the variants encompassed by claim 1 to be useful in an analysis. *See* Ex. 1130, 93:20–24.

b) Skill in the Art

The parties both addressed the skill in the art as discussed above. *See supra* Section II.A. On that record, we find that the skill in the art is high, as indicated by both parties.

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 $PH20_{1-447}$ protein that are described in the '429 Patent could be applied to produce forms of $PH20_{1-447}$ that incorporate a single amino acid substitution . . . with little effort." Ex. 1003 ¶ 203. Dr. Hecht further states that "[t]he first experimentally determined structure of a hyaluronidase was bvH, both alone and in complex with HA (published in 2007)" and that "Markovic-Housley identified the catalytic site and residues involved in catalytic activity using this structure." *Id.* ¶ 80 (citing Ex. 1033, 1028–31).

However, Dr. Hecht also states "[d]ata in the '429 Patent and a 2007 paper by Frost (EX1013) also showed that truncations of varying length at the C-terminus of PH20 caused significant variations in hyaluronidase activity." *Id.* ¶ 90. 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.* ¶ 92. Dr. Hecht states that "[n]either the scientific literature existing by 2011 nor the common disclosure provides an explanation why these PH20 truncation mutations that differ by one residue (i.e., $PH20_{1-446}$ vs. $PH20_{1-447}$ vs. $PH20_{1-448}$) exhibit variability in their activity." *Id.* ¶ 94.

Dr. Hecht states "[t]here were limits to using rational design techniques in the 2011-timeframe." *Id.* ¶ 50 (citing Ex. 1018, 378; Ex. 1059, 1225–26). "The complexity of the structure/function relationship in enzymes has proven to be the factor limiting the general application of rational design." *Id.* at n.16 (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.* ¶ 52 (citation omitted). Dr. Hecht states "changing many amino acids simultaneously risks disrupting the pattern necessary to induce formation of the original secondary structure . . . and [can] be highly destabilizing to the overall protein structure." *Id.* ¶ 55. Dr. Hecht states that in a smaller, ten amino acid substitution situation, "[t]here are approximately 6×10^{12} different scenarios of 10 substitutions." *Id.* ¶ 58.

In deposition, Dr. Hecht stated: "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 2012, 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 "[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.

Ex. 1130, 121:8–17.

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

> 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. EX1033 (Marković-Housley), 1028

Id. ¶ 140.

Dr. Cherr states that "by December 28, 2012, PH20 polypeptide vaccines had been successfully used for contraception in female guinea pigs." Ex. 2072 ¶ 35 (citing Ex. 2119; Ex. 1022; Ex. 2010; Ex. 1023). Dr. Moon states that "POSAs would have also known that 'intranasal immunization of various species, including humans, was efficient at inducing antigen-specific antibody responses in the *female* genital tract.'" Ex. 2074 ¶ 27 (quoting Ex. 2122, Abstract).

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). 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 subtly different substrate preferences and activity." Ex. 1133 ¶ 184. Dr. Naismith states 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). Exhibit 1010 (Zhang) states that "[a]nalogy to point mutations in both sperm hyaluronidase, PH-20, and bacterial *N*-acetylglucosaminidase H, further suggested Asp^{129} and Glu^{131} would be critical for catalytic activity of the enzyme. . . . Interestingly, Asp^{129} 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 the evidence shows 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 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 ¶¶ 92, 97, 113, 140–142. The evidence of record demonstrates that identifying which of the 10^{59} to 10^{112} 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. For example, this is evidenced by Zhang, which teaches that Asp^{129} 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, 9436–37.

d) Presence of Working Examples

Dr. Hecht states that the '035 patent "provides a compilation of all the mutants that apparently were produced by the inventors in Table 8. There are 6,753 entries in this table. These are all mutants generated by substituting one amino acid from $PH20_{1-447}$." Ex. 1003 ¶ 103. Dr. Hecht states that "Table 10 contains a compilation of tested 'inactive mutants' with 3,380 entries." *Id.* Dr. Hecht calculates that based on the data in the '035 patent "57.1% were inactive, and 29.4% others had activity <100%." *Id.* ¶ 105. Dr. Hecht states the '035 patent "does not identify any mutated PH20 proteins that were shown to be effective in contraceptive vaccines." *Id.* ¶ 113.

Dr. Petsko states that "[t]he '035 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 "In 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 S312G, S312K, S312L, S312N, and S312T variants in the patent. . . . the 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 '035 patent. *See generally* Ex. 2072, Ex. 2074.

Based on the evidence of record, we find that the evidence demonstrates the presence of a number of working examples. However, the evidence also shows that more than half of these working examples would not be encompassed by the claims because they were enzymatically inactive. Moreover, to the extent Patent Owner contends that inactive polypeptides are useful to provide a contraceptive effect, we note that none of the working examples in the '035 patent show modified polypeptides that provide such an effect.

e) Amount of Direction or Guidance Presented

The '035 patent states that "one or more modified PH20 polypeptides are tested for a desired activity or property, such as increased stability." Ex. 1001, 133:61–64. The '035 patent states regarding processes to make mutations in hyaluronidase enzymes such as PH20 that:

> 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 135:9–34. The '035 patent states regarding testing the resultant mutations that:

> 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 136:9–16. The '035 patent states "[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 140:61–65. The '035 patent states that "[p]roteins, such as modified PH20 polypeptides, can be purified using standard protein purification techniques known in the art." *Id.* at 150:61–63.

The ’035 patent states: “[d]ue to the role of PH20 in fertilization, PH20 can be used as an antigen for immunocontraception.” *Id.* at 71:24–26. The ’035 patent states “[i]mmunization with PH20 has been shown to be an effective contraceptive in male guinea pigs . . . . It also has been shown to be an effective contraceptive in female guinea pigs.” *Id.* at 193:24–28.

Dr. Hecht states that the ’035 patent “uses the 40% activity threshold to classify a mutant as an ‘active mutant’” and that “‘inactive mutants’ are mutants with 20% or less of the activity of unmodified PH20.” Ex. 1003 ¶¶ 100–101. Dr. Hecht states that the data in the ’035 patent shows “most of the single-replacement $PH20_{1\text{-}447}$ mutants that were tested exhibited less activity than the unmodified $PH20_{1\text{-}447}$ (*i.e.*, 57.1% were inactive, and 29.4% others had activity <100%).” *Id.* ¶ 105.

Dr. Hecht states the ’035 patent

> does not identify any mutated PH20 proteins that were shown to be effective in contraceptive vaccines. It also does not provide guidance regarding how to identify candidate inactive PH20 mutants that may be useful as contraceptive vaccines (such as by identifying common structural or functional characteristics that would be shared by such inactive mutants).

Id. ¶ 113. Dr. Hecht states “the data for testing the 409 mutants reported in Tables 11 and 12 [of the ’035 patent] does not provide any meaningful guidance to a skilled artisan about the types of mutations that would improve the stability of PH20 polypeptides generally, or for the $PH20_{1\text{-}447}$ form specifically.” *Id.* ¶ 76. Dr. Hecht states that the ’035 patent

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

Id. ¶ 172. Dr. Hecht characterizes the disclosure of the '035 patent as "best described as a research plan, as it generally outlines the types of steps one might take to carry out a mutagenesis and screening research program." *Id.* ¶ 173.

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 "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.

Neither Dr. Cherr nor Dr. Moon appear to identify any direction or teaching in the Specification of the '035 patent beyond that discussed above regarding the ability of PH20 to function as a contraceptive. *See generally* Ex. 2072, Ex. 2074. Dr. Kelsoe states that the '035 patent "references studies by the Primakoff group and states that immunization with PH20 was an 'effective' contraceptive in both male guinea pigs as well as female guinea pigs." Ex. 1134 ¶ 49.

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.

In deposition, Dr. Simpson stated

> 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 "[w]ith the '035 patent in hand, the POSA knows what positions tolerate substitution and which do not. The POSA is going to 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 a "POSA seeking to make a modified PH20 with the '035 patent in hand would not make a randomly generated combinatorial library of billions of sequences that happen to be at least 91% identical to SEQ ID NO: 3 and then screen it for activity, because it makes no sense to do so." *Id.* ¶ 347. Dr. Petsko states that the

> patent 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. ¶ 375.

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 effect -- 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 states that

> the common disclosure 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 ¶¶ 173–178; 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 ¶¶ 181–185).

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." *Id.* ¶ 210.

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 the evidence demonstrates that a POSA would have significant guidance on synthesis and expression of modified PH20 polypeptides, including single mutations within the entire PH20 structure that identify specific positions that are invariant or permissive to mutation in connection with hyaluronidase activity.

However, the evidence also shows that the '035 patent provides very limited guidance regarding effective methods to identify which members of the 10^{59} different modified PH20 polypeptides function to retain either hyaluronidase activity. To the extent Patent Owner contends the ability to provide a contraceptive effect is relevant, we find that there is essentially no guidance, either in the '035 patent or the prior art of record, demonstrating which, if any, of the possible modified polypeptides are useful for providing such an effect.

f) Quantity of Experimentation

Dr. Hecht states

> while the PH20 protein structure models Dr. Park used provided reliable insights when modeling the change of a single residue at a position where the model was, they cannot provide reliable insights when the modeled sequence incorporates many (*e.g.*, more than ~5) substitutions not found in a naturally occurring protein. That is because (i) if the modeled sequence incorporates multiple changes, it no longer has validity as a naturally occurring sequence, and (ii) the changes significantly diminish the reliability of other positions of the model used to assess the change because they are no longer based on the

> structural positioning of residues within the template structure used to generate the model. Thus, a skilled artisan would have had to discover which combinations of substitutions to the PH20 protein would result in mutants that do exhibit hyaluronidase activity by making and testing all of them, ***an impossibly large undertaking***.

Ex. 1003 ¶ 158 (emphasis added). Dr. Hecht states that "the single-replacement $PH20_{1-447}$ polypeptides reported in the common disclosure are not representative of all the types of mutated $PH20_{1-447}$ polypeptides that have a particular substitution at position 312 and sets of between 1 and 41 *additional* substitutions at any of hundreds of positions within the PH20 protein." *Id.* ¶ 159.

Dr. Hecht states that "[m]aking and identifying all of the multiple-modified PH20 polypeptides that are within the immense set of polypeptides (between 10^{59} and 10^{122} distinct mutants) defined by the claims' sequence identity parameters is not only undue experimentation, it likely is impossible." *Id.* ¶ 170. Dr. Hecht states that the directed evolution methods of the '035 patent are "the quintessential 'make and test' trial and error technique. By definition, the scientist carrying out a directed evolution protocol does not know which of the potentially trillions of possible mutants might incorporate a substitution that causes the protein to exhibit an improved characteristic." *Id.* ¶ 186.

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 "[d]id 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, ¶ 36. 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 '035 patent in hand would not make a randomly generated combinatorial

> library of billions of sequences that happen to be at least 91% identical to SEQ ID NO: 3 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 '035 patent, the POSA has a much more sensible strategy.

Id. ¶ 347. However, Dr. Petsko does not identify any teaching in the '035 patent 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 ~10^9 proteins." *Id.*

Based on the evidence of record, we find 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 time frame, the computerized techniques for making such predictions quickly became unreliable as more modifications were introduced. *See* Ex. 1004 ¶¶ 143–144. Both Dr. Simpson and Dr. Petsko acknowledge that an ordinary artisan would not even 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. And Dr. Naismith confirmed that neither computer analysis nor screening technologies would have been capable of testing the full scope of claim 1.

We find the facts here similar to those in *Idenix Pharmaceuticals LLC v. Gilead Sciences Inc.*, 941 F.3d 1149, 1156 (Fed. Cir. 2019) where, in a genus of billions, the "key enablement question is whether a person of ordinary skill in the art would know, without undue experimentation, which [species] would be effective." *Idenix* states that because of the "many thousands of [species] which need to be screened for . . . efficacy, the quantity of experimentation needed is large and weighs in favor of non-enablement." *Id.* at 1159. Here, where the number is not thousands but at least 10^{59} different polypeptides, the quantity of experimentation would be many orders of magnitude more than that needed in *Idenix*.

We find the evidence demonstrates that a very large amount of experimentation would be necessary to enable the scope of the claims of the '035 patent.

g) Predictability of the Art

Dr. Hecht states that the

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

Ex. 1003 ¶ 61. Dr. Hecht states, citing the '429 patent, that the "varying effects of changing residues in the Hyal-EGF region of PH20 show that a skilled artisan's belief that changes in this region would be unpredictable were warranted, and would be more so if multiple changes were made concurrently." *Id.* ¶ 96. Dr. Hecht states that the "effects of these myriad sets of combinations of multiple substitutions within PH20 could not have been predicted by a skilled artisan in the 2011 timeframe using the tools that were available then." *Id.* ¶ 158. Dr. Hecht notes that "[a]nother problem caused by the use in the claims of sequence identity language to define the sets of proteins is that it captures many multiply-modified PH20 polypeptides with changes that common disclosures says are deleterious or eliminate hyaluronidase activity in PH20 enzymes." *Id.* ¶ 160.

Dr. Hecht states that the "skilled artisan also could not predict whether any combinations of up to 9 or up to 2 additional (or more) substitutions could be made anywhere in the $PH20_{1-419}$ sequence or comparably truncated PH20 polypeptide that would restore hyaluronidase activity to an inactive S312T or S312N containing $PH20_{1-419}$ mutant." *Id.* ¶ 168. Dr. Hecht continues:

> In other words, the common disclosure also does not help the skilled artisan identify which of the trillions of possible PH20

> polypeptides of varying length[s] with 2 to 42 combinations have hyaluronidase activity; to practice the full scope of the claims it requires the skilled artisan to ignore what little guidance is in the specification about single-substitutions and truncations that render PH20 polypeptides inactive.

Id. ¶ 169. Dr. Hecht states that the artisan following the '035 patent's "iterative mutagenesis and screening research plan cannot know in advance of conducting multiple rounds of experiments, whether modified PH20 polypeptides will be produced that have sets of 5, 10, 15, or more substitutions and retain sufficient activity that will be selected for the next round of the process." *Id.* ¶ 184. 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.* ¶¶ 144, 151, 168–185.

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 ¶ 143. Dr. Park states "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.* ¶ 144.

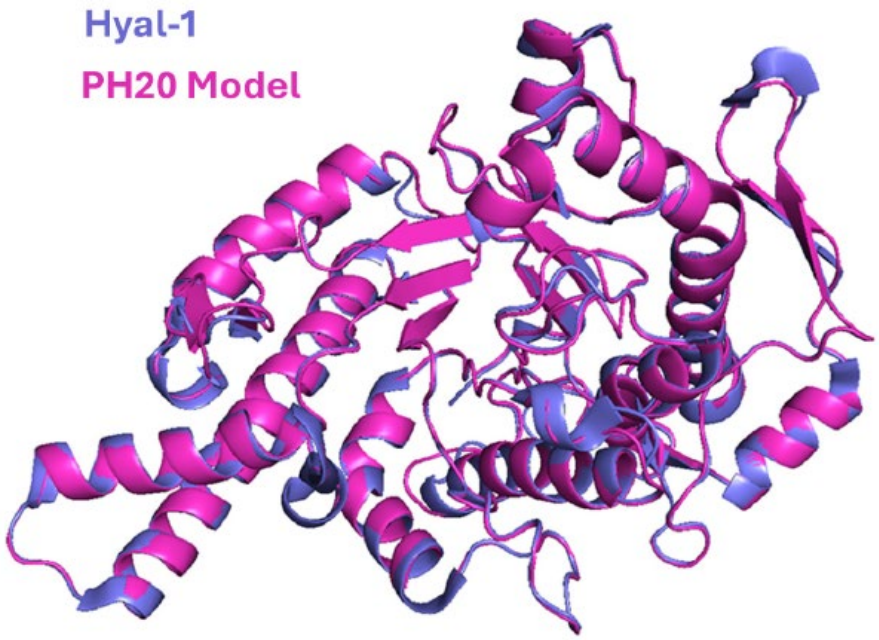
In deposition, Dr. Park, addressing single mutations, stated: "The problem is when you're looking at one substitution, there are only so many interactions that a single amino acid can make, and those are relatively straightforward to discern for an expert." Ex. 2077, 198:12–16. Dr. Park then stated that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

> 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, as shown by his analysis, that

> 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 91% 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 allow POSAs to reasonably predict what changes will maintain activity, abrogate activity, reduce activity, or improve activity." *Id.* ¶ 380 (citing Ex. 2070 ¶¶ 44, 54–56, 233–389). 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 S312N substitution. 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 S312N and S312T substitutions were 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 S312N and S312T changes in chimp, orangutan or gibbon is simply a single mutation into a sequence that has been shaped by evolution to stably fold and be active; these represent an infinitesimal portion of the patent's enclosed sequence space. There is no teaching in the patent or modelling software that would allow sets of 17 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 ¶¶ 361–366, 416–425).

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 (citing Ex. 2164, 26).

Dr. Naismith states that

> [t]he 2024 Chemistry Nobel Price Background paper 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).

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 classification." *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 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 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. 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 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.

Id. ¶ 276.

Reviewing the evidence, we find that 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.

The '035 patent itself only discusses library screening and site directed mutation approaches. *See* Ex. 1001, 135:9–34. Both Petitioner's and Patent Owner's experts made statements that the library screening or site directed mutation at all positions would not be possible over the scope of claim 1. *See, e.g.*, Ex. 1003 ¶ 158; Ex. 1131, 64:12–17; Ex. 1133 ¶ 258. However, we are more persuaded by Petitioner's experts that none of the four approaches would reasonably address the full scope of claim 1. "[T]he specification must enable the full scope of the invention as defined by its claims. The more one claims, the more one must enable." *Amgen Inc. v. Sanofi*, 598 U.S. 594, 610 (2023).

As to the use of homology modeling, we credit Dr. Hecht, Dr. Park, Dr. Naismith, and Dr. Petsko that the technology as of 2011-12 would not have been able to reliably predict the impact of mutations in the PH20 protein on the hyaluronidase or contraceptive activity, which 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."); Ex. 1131, 207:15–24; Ex. 1003 ¶¶ 55, 58; Ex. 1004 ¶ 143.

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

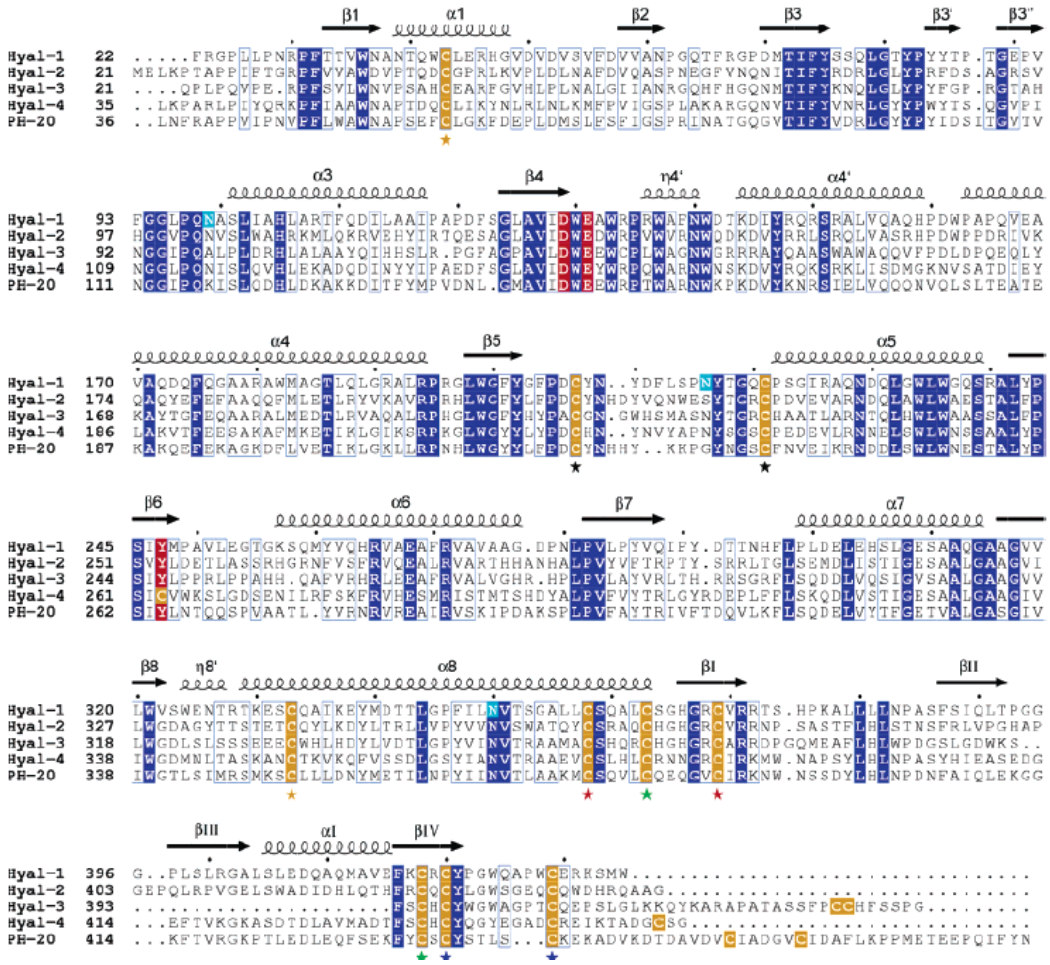


Figure 3: Structure-based sequence alignment of human hyaluronidases. Invariant residues are shown in blue except for three key catalytic residues that are colored red. Cysteine residues are colored yellow. The hHyal-1 N-glycosylated asparagines residues are colored turquoise. Residues exhibiting conservative 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 (in blue or red), cysteine (in yellow), 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 or contraceptive activity.

Therefore, based on the evidence of record, we find that the evidence shows that it is unpredictable which modified PH20 polypeptides within the scope of the claims of the '035 patent would retain hyaluronidase activity.

7. Conclusion

We find that the balance of evidence supports a finding of undue experimentation. The claims are extremely broad and the "number of distinct peptides is extremely large by all accounts, ranging from 10^{59} to 10^{112}." Ex. 1004 ¶ 154. The skill in the art is agreed as very high. While the prior art was developed in the field of hyaluronidases with alignments and projected three dimensional folding proposals (Ex. 1003 ¶ 80), there was also evidence that homology modeling was not yet reliable. *See, e.g.*, Ex. 1027, 6–7. The '035 patent 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 such multiple mutations. Ex. 1003 ¶ 103.

We find the evidence in the quantity of experimentation and predictability factors demonstrates undue experimentation, as most of the experts acknowledge that actually testing the genus would not be possible. *See, e.g.*, Ex. 1003 ¶ 186; Ex. 1133 ¶ 258; Ex. 2070 ¶ 347; Ex. 1130, 93:13–

24. Lastly, while there appears to be some agreement that modeling might allow predictability for modifications with less than five amino acid changes, experts for both parties agreed that more than five amino acid changes would be unpredictable in effect in the 2011–12 timeframe. *See, e.g.*, Ex. 1003 ¶¶ 144, 151, 168–185; Ex. 1004 ¶¶ 143–144; Ex. 1131, 102:1–9; 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.[14] Again, 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. 2010, Abstr. But in addition to the expert testimony by Dr. Kelsoe disputing Dr. Cherr and Dr. Moon's testimony, Ex. 1189 (Martin-DeLeon) cites extensive experimental evidence that PH20 polypeptide vaccines were ineffective in rabbits and mice. *See* Ex. 1189, 119. That species differences exist is not surprising, given the statement in Ex. 1189 that "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." *Id.* Exhibit 1189 further states:

> In a primate model, *Cynomolgus macaques*, combinations of adjuvant and antigens derived from synthesized and

[14] 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.5.

> recombinant proteins all produced significant immune responses in females, with circulating antibodies recognizing macaque sperm surface PH-20 (Deng et al., 2002). However, there was a lack of sterility following immunization in this model also.

Id. The failure of PH20 polypeptides as contraceptive vaccines in three of four species tested, and particularly in a primate 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. The data Patent Owner relies upon at most shows an immunocontraceptive effect for unmodified PH20 polypeptides limited to guinea pigs. It does not evidence that a POSA would have understood that the recited modified polypeptides would provide such an effect or otherwise be useful in a contraceptive vaccine.

Accordingly, even if the term "modified PH20 polypeptides" were interpreted to include inactive polypeptides that provide a contraceptive effect, the preponderance of the evidence shows that undue experimentation would also be required to make and use the full scope of modified polypeptides contemplated by the challenged claims for that purpose.

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

E. Ground III - 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;[15] 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 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

[15] *See supra* Section II.A.

> 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:

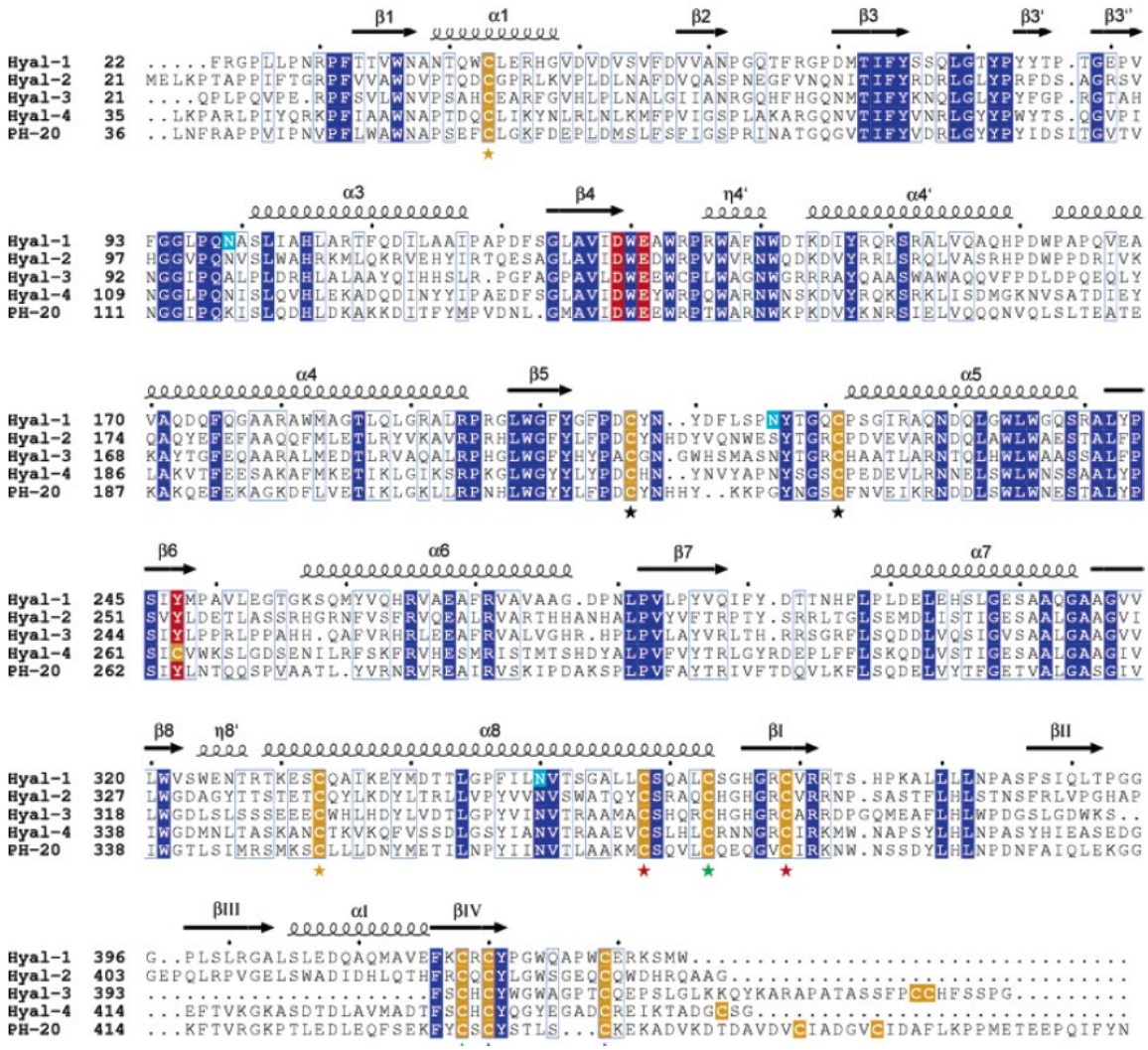


Figure 3 shows

[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) at a ***particular*** location (non-essential regions of PH20) in a ***particular*** PH20 sequence ($PH20_{1–447}$) to yield equivalents of $PH20_{1–447}$ (*i.e.*, those that do not substantially alter the activity or function of $PH20_{1-447}$)." Pet. 88 (citing Ex. 1003 ¶¶ 206–208; Ex. 1004 ¶ 32). Petitioner asserts that Chao "identifies a characteristic pattern for the Hyal-EGF domain in PH20 (at 337–409)." *Id.* at 92 (citing Ex. 1006, 6912; Ex. 1004 ¶¶ 97–98; Ex. 1003 ¶¶ 84–85).

Petitioner asserts that a "skilled artisan would first identify the essential residues in PH20 by comparing proteins homologous to PH20 that were known in 2011. . . . The multiple sequence alignment identifies the non-essential regions in PH20." *Id.* at 92 (citing Ex. 1003 ¶¶ 212–215; Ex. 1004 ¶¶ 22, 25–32, Appx. D-2, D-3; Ex. 1006, 6916). Petitioner asserts that Dr. Park performed such an analysis and that "[p]osition 312 is within a non-essential region of $PH20_{1-447}$, which is shown by Dr. Park's analysis, and also by Chao's Figure 3; both report the same bounding essential residues (*i.e.*, W304 and C316)." *Id.* at 94 (citing Ex. 1004 ¶¶ 31–32, Appx. D-2; Ex. 1003 ¶ 217; Ex. 1006, 6916).

Petitioner asserts that in Dr. Park's alignment, the "wild-type residue at position 312 in PH20 is serine (S), which occurs in ~65% of the proteins (including PH20). The second-most prevalent amino acid at position 312 is threonine (T) (~25%), which is present in 22 different hyaluronidase

proteins." *Id.* at 96 (citing Ex. 1003 ¶¶ 214, 218–232; Ex. 1004 ¶¶ 41, 41, 106).

Petitioner asserts that a "skilled artisan would have found it obvious to substitute threonine (T) or asparagine (N) for serine (S) at position 312 as a single amino acid substitution in a non-essential region of $PH20_{1-447}$." *Id.* Petitioner asserts: "First, threonine and asparagine are the second and third-most prevalent amino acids at the position corresponding to position 312 in PH20, respectively. These amino acids would have been the obvious candidates to substitute for serine at position 312 of PH20, as they are each tolerated at that position in many naturally occurring homologous hyaluronidase enzymes." *Id.* at 97 (citing Ex. 1004 ¶¶ 43, 106, 111, 121; Ex. 1003 ¶¶ 218–221). Petitioner asserts: "Second, Chao identifies residue S312 as being the first residue of the α8 α-helix in PH20, which is termed the 'N-cap' residue. Asparagine was known to be the most preferred residue for an N-cap residue at the start of an α-helix, in proteins, and threonine was known to be highly favored at that position." *Id.* at 97–98 (citing Ex. 1003 ¶¶ 219–220; Ex. 1004 ¶¶ 108–109, 120; Ex. 1076, 1650–52; Ex. 1077, 1325; Ex. 1078, 2–3). "Third, the serine at position 312 is solvent-exposed." *Id.* at 98 (citing Ex. 1003 ¶¶ 219; Ex. 1004 ¶¶ 32, 108). And fourth, "the '429 Patent identifies threonine as a conservative amino acid substitution for serine in its Table 1." *Id.* (citing Ex. 1005, 16:7-36).

Petitioner asserts that in prosecuting the '429 patent, Patent Owner relied on "affirmative statements that a skilled artisan would have expected ***any*** single amino acid substitution in ***any*** non-essential position of $PH20_{1-447}$ to not substantially affect the biological activity of the enzyme." *Id.* at 99–100. Petitioner also asserts that "a skilled artisan would have reasonably

expected the S312T and S312N substitutions to not substantially alter the biological activity (hyaluronidase activity) of $PH20_{1-447}$." *Id.* at 100.

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 312." PO Resp. 86 (citing Ex. 2068 ¶¶ 405–416). Patent Owner asserts that while Chao provides insight into human hyaluronidase structures, "[n]one of these alleged 'insights' provides a reason to modify position 312 in PH20." *Id.* at 89 (citing Ex. 2068 ¶¶ 405–416).

Patent Owner asserts that "Petitioner's expert Dr. Park's analysis confirms that nothing in the art would have motivated POSAs to modify position 312. . . . Nothing in Dr. Park's results provides a reason to elevate S312 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.

c) Petitioner's Reply

Petitioner asserts "Dr. Park identified S312T and S312N as ***two of ~750 such substitutions*** suggested by the '429 Patent before 2011. ***Each*** would have been obvious under the rationale of *KSR*." Pet. Reply 42 (citing Ex. 2176; Ex. 1133 ¶ 344). Petitioner asserts that "Dr. Park's objective and unbiased assessment found S312T and S312N tolerated, and identified an S312T:S315 interaction; Dr. Petsko repeated that assessment and reached

the same conclusion." *Id.* at 44 (citing Ex. 1004 ¶¶ 111–123; Ex. 2070 ¶ 409; Ex. 1133 ¶¶ 349–351).

d) Patent Owner's Sur-Reply

Patent Owner asserts:

> Rather than offering any explanation for why position 312 would be targeted for substitution, Petitioner abandons the motivation requirement altogether and makes the sweeping—and unsupported—claim that ***all*** ~750 amino acid residues Dr. Park identifies as available for substitution would have been obvious under *KSR*. Reply, 42–43. That is plainly wrong: "there must be some reason to select a species from the genus." ID, 53-54. Petitioner has not even attempted to identify a reason for selecting position 312 – other than attorney direction based on knowledge of the claimed invention. PO Resp., 83-85.

PO Sur-reply 28.

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 serine at position 312 of a PH20 polypeptide for modification with one of glycine, lysine, leucine, asparagine, or threonine as required by claim 1 of the '035 patent. It is undisputed that neither of the cited prior art references, the '429 patent or Chao, specifically identifies or discusses position 312 of the PH20 polypeptide. *See, e.g.*, Pet. 94; PO Resp. 86–93.

We are not persuaded by Petitioner's argument that multiple sequence alignments identify amino acids that are tolerated at particular positions (*see* Pet. 92–94), 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 PH20 with evolutionary variation, that is, where "homologous proteins have tolerated different amino acids at those positions." Ex. 1004 ¶ 31. Dr. Park distributes the twenty standard amino acids into four categories depending on their roles in forming secondary structure such as alpha helices or beta sheets, with each category having a minimum of six members. *See id.* ¶ 70. Nothing in the prior art or Dr. Park's analysis directs the ordinary artisan to position 312 itself, and Dr. Park notes that Chao did not identify position 312 of PH20 as part of the catalytic active site, unlike positions 146, 148, and 219, nor was position 312 one of the residues identified as being in the cleft where the ligand binds. *See id.* ¶ 91. Dr. Park indicates that position 312 was not identified by Chao as part of the Hyal-EGF domain, was not identified by Stern in the active site, and was not identified by Arming as impacting PH20 activity. *See id.* ¶¶ 98–101 (citing Ex. 1006, 6916; Ex. 1008, 825; Ex. 1011, 811–13).

Indeed, Dr. Hecht states that "[i]ntroducing random amino acids could disrupt that [alpha helical] pattern, which could have a range of effects in this region of the helical structure." Ex. 1003 ¶ 192. And while Dr. Hecht asserts that the '429 patent suggests conservative mutations generally, Petitioner did not point us to any specific teaching or suggestion in the prior art cited by Dr. Hecht to modify position 312 of PH20. *See, e.g.*, *id.* ¶¶ 203–205. Petitioner did not point us to anything in Dr. Hecht's Declaration that explained why position 312 was of interest in any way, versus position 311 or 313 or any other position within the PH20 polypeptide.

We also are not persuaded by Petitioner's arguments that the hydrophilic character of asparagine and threonine "would be compatible with the high solvent accessibility of position 312," and asparagine being the most common N-cap residue in α8 helix structures in proteins with threonine having "a high prevalence at N-cap positions." Pet. 106–107. These statements are not a reason, but rather statements. Dr. Park identified seven different amino acids that favor alpha helix formation. *See* Ex. 1004 ¶ 70. Figure 3 of Chao shows a number of different alpha helical regions, α1, α3, η4', α4', α4, α5, α6, α7, and α8, each composed of multiple amino acids, many of which appear to be non-conserved. *See* Ex. 1006, 6916 Fig. 3. Each of these amino acids found within alpha helices might be subject to substitution by one of the seven preferred amino acids identified by Park, but it is Petitioner's "burden to show that the 'prior art would have suggested making the *specific molecular modifications* necessary to achieve the claimed invention.'" *Amerigen Pharm. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1089 (Fed. Cir. 2019) (citing *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007)). Petitioner has not satisfied this burden of showing specific reasons to modify position 312 of the PH20 polypeptide.

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 Dr. Hecht and Dr. Park demonstrate obviousness for the claims of the '035 patent.

III. CONCLUSION

After considering the evidence and arguments presently before us in the complete trial record, we conclude that Petitioner has demonstrated, by a preponderance of the evidence, that challenged claims 1, 2, 6–14, and 16–29 are unpatentable.[16]

In summary:

Claims	35 U.S.C. §	Reference(s)/Basis	Claim(s) Shown Unpatentable	Claim(s) Not shown Unpatentable
1–4, 8–13	112(a)	Written Description	1, 2, 6–14, 16–29	
1–4, 8–13	112(a)	Enablement	1, 2, 6–14, 16–29	
1–4, 8–13	103	The ’429 patent, Chao		1, 2, 6–14, 16–29
Overall Outcome			1, 2, 6–14, 16–29	

[16] 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).

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1, 2, 6–14, and 16–29 of U.S. Patent 12,123,035 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.

For PETITIONER:

Jeffrey Kushan
SIDLEY AUSTIN LLP
jkushan@sidley.com

Mark Stewart
MERCK SHARP & DOHME LLC
mark.stewart@merck.com

Blaine Hackman
DECHERT LLP
blaine.hackman@dechert.com

Amy Mahan
SIDLEY AUSTIN LLP
amy.mahan@sidley.com

For PATENT OWNER:

Eldora Ellison
Trey Powers
Jennifer Chagnon
Tyler Liu
David Holman
STERNE, KESSLER, GOLDSTEIN & FOX PLLC
eellison-ptab@sternekessler.com
tpowers-ptab@sternekessler.com
jchagnon-ptab@sternekessler.com
tliu-ptab@sternekessler.com
dholman-ptab@sternekessler.com

Aubrey Haddach
HALOZYME THERAPEUTICS
ahaddach@halozyme.com

David Kappos
CRAVATH, SWAINE & MOORE LLP
dkappos@cravath.com

Director_PTABDecision_Review@uspto.gov
571.272.7822

Paper 142
Date: July 22, 2026

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE OFFICE OF THE UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

MERCK SHARP & DOHME LLC,

Petitioner

v.

HALOZYME, INC.,
Patent Owner.

PGR2025-00003 (Patent 11,952,600 B2)
PGR2025-00004 (Patent 12,018,298 B2)
PGR2025-00006 (Patent 12,152,262 B2)
PGR2025-00009 (Patent 12,123,035 B2)[1]

Before JOHN A. SQUIRES, *Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office*.

ORDER

[1] This order applies to each of the above-listed proceedings.

The Office received a request for Director Review of the Final Written Decision in each of the above-captioned cases and an authorized response to each request. *See* Papers 142, 144.[2]

Having considered the requests and responses, it is:

ORDERED that the requests for Director Review are denied.

[2] Citations are to the record in PGR2025-00003. The parties filed similar papers in PGR2025-00004, PGR2025-00006, PGR2025-00009.

PGR2025-00003 (Patent 11,952,600 B2)
PGR2025-00004 (Patent 12,018,298 B2)
PGR2025-00006 (Patent 12,152,262 B2)
PGR2025-00009 (Patent 12,123,035 B2)

FOR PETITIONER:

Jeffrey P. Kushan
Leif E. Peterson
Sue Wang
Amy Mahan
Christine M. Engen
Amit Bhatla
SIDLEY AUSTIN LLP
jkushan@sidley.com
leif.peterson@sidley.com
sue.wang@sidley.com
amy.mahan@sidley.com
christine.engen@sidley.com
abhatla@sidley.com

Mark Stewart
MERCK SHARP & DOHME LLC
mark.stewart@merck.com

Blaine Hackman
Brian M. Goldberg
DECHERT LLP
blaine.hackman@dechert.com
brian.goldberg@dechert.com

FOR PATENT OWNER:

Eldora L. Ellison
R. Wilson Powers III
Jennifer Meyer Chagnon
Tyler C. Liu
David Holman
Louis P. Panzica, Jr.
Pratibha Khanduri
STERNE, KESSLER, GOLDSTEIN & FOX PLLC
eellison-ptab@sternekessler.com
tpowers-ptab@sternekessler.com

PGR2025-00003 (Patent 11,952,600 B2)
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jchagnon-ptab@sternekessler.com
tliu-ptab@sternekessler.com
dholman-ptab@sternekessler.com
lpanzica-ptab@sternekessler.com
pkhanduri-ptab@sternekessler.com

Aubrey Haddach
Joshua A. Mack
Mark H. Snyder
HALOZYME, INC.
ahaddach@halozyme.com
jmack@halozyme.com
msnyder@halozyme.com

David J. Kappos
CRAVATH, SWAINE & MOORE
dkappos@cravath.com

Lauren N. Martin
QUINN EMANUEL URQUHART & SULLIVAN, LLP
laurenmartin@quinnemanuel.com