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

Paper 27
Dated: November 13, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,
Petitioner,

v.

HALOZYME, INC.,
Patent Owner.

PGR2025-00042
Patent 12,037,618 B2

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

MITCHELL, *Administrative Patent Judge*.

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

I. INTRODUCTION

Merck Sharp & Dohme LLC ("Petitioner") filed a Petition (Paper 1) requesting post-grant review of claims 1–40 of U.S. Patent No. 12,037,618 B2 (Ex. 1001, "the '618 patent"). Petitioner subsequently filed a Corrected Petition (Paper 10, "Pet.") to which we will refer in this Decision. Halozyme, Inc. ("Patent Owner") chose not to file a Patent Owner Preliminary Response, but did file exhibits including a Declaration from Barbara Triggs-Raine, Ph.D. *See* Ex. 2001.[1]

Patent Owner also filed a statutory disclaimer of claims 3, 4, 6, and 34–40 of the '618 patent, leaving claims 1, 2, 5, and 7–33 ("challenged claims") of the '618 patent at issue in the Petition. *See* Ex. 2003, 5.

We have authority to determine whether to institute a post-grant review under 35 U.S.C. § 324. Institution of a post-grant review is authorized by statute when "the information presented in the petition . . . would demonstrate that it is more likely than not that at least 1 of the claims challenged in the petition is unpatentable." 35 U.S.C. § 324(a). Applying that standard on behalf of the Director (37 C.F.R. § 42.4(a)) and in consideration of the Petition and the cited evidence of record, we determine that the information presented shows that it is more likely than not that Petitioner would prevail in establishing unpatentability of claims 3, 4, 6, and 34–40 of the '618 patent, and therefore, we grant post-grant review for the reasons articulated below.

[1] The parties also filed briefs directed to discretionary denial issues. *See* Papers 14, 18. The Director ruled on discretionary denial issues. *See* Paper 19. We do not address discretionary denial issues here.

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

II. REAL PARTIES-IN-INTEREST

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

III. RELATED PROCEEDINGS

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

U.S. Patent 11,952,600 (PGR2025-00003); U.S. Patent 12,018,298 (PGR2025-00004); U.S. Patent No. 12,152,262 (PGR2025-00006); U.S. Patent No. 12,123,035 (PGR2025-00009); U.S. Patent No. 12,110,520 (PGR2025-00017); U.S. Patent No. 12,060,590 (PGR2025-00024); U.S. Patent No. 12,054,758 (PGR2025-00030); U.S. Patent No. 12,049,652 (PGR2025-00033); U.S. Patent No. 12,104,185 (PGR2025-00039); U.S. Patent No. 12,091,692 (PGR2025-00046); U.S. Patent No. 12,077,791 (PGR2025-00050); U.S. Patent No. 12,264,345 (PGR2025-00052); U.S. Patent No. 12,195,773 (PGR2025-00053). *See* Paper 13, 1; Paper 15, 2.

The parties also identify *Halozyme, Inc. v. Merck Sharp & Dohme Corp.*, 2:25-cv-03179 (D.N.J.) as a related matter in which Patent Owner alleges infringement of the ’618 patent. Paper 13, 1; Paper 15, 1.

Patent Owner states that the ’618 patent is related to the following pending U.S. Patent Applications and patents: 18/759,577; 18/922,889;

18/069,651; 18/340,786; 19/071,005; 19/075,092; 19/071,264; 19/071,345; U.S. Patent No. 12,195,773; and U.S. Patent No. 12,264,345. Paper 15, 2.

IV. THE '618 PATENT

A. Background

The '618 patent issued July 16, 2024, from U.S. Application 17/327,586, filed May 21, 2021. Ex. 1001, codes (21), (22), (45). The '618 patent is a continuation of U.S. Application 16/512,590, filed on June 25, 2020, now U.S. Patent No. 11,066,656, which is a continuation of U.S. Application 15,226,489, filed on August 2, 2016, now U.S. Patent 10,865,400, which is a division in a lengthy set of applications that are either divisions or continuations 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 '618 patent is drawn to "[m]odified PH20 hyaluronidase polypeptides, including modified polypeptides that exhibit increased stability and/or increased activity." Ex. 1001, 2:37–40. The '618 patent teaches "[h]yaluronan (hyaluronic acid; HA) is a polypeptide that is found in the extracellular matrix of many cells, especially in soft connective tissues." *Id.* at 2:44–46. The '618 patent teaches "[c]ertain diseases are associated with expression and/or production of hyaluronan. Hyaluronan-degrading enzymes, such as hyaluronidases, are enzymes that degrade hyaluronan. By catalyzing HA degradation, hyaluronan-degrading enzymes (e.g., hyaluronidases) can be used to treat diseases or disorders associated with accumulation of HA or other glycosaminoglycans." *Id.* at 2:51–57. The

'618 patent teaches that "[v]arious hyaluronidases have been used therapeutically . . . . Many of these are ovine or bovine forms, which can be immunogenic for treatment of humans." *Id.* at 2:62–3:1.

The '618 patent states that modifications for PH20 polypeptides include amino acid replacement, deletion, and/or insertions. Ex. 1001, 3:10–12. With regard to modified PH20 hyaluronidase polypeptides, the '618 patent further teaches:

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

Id. at 3:16–36 (citation omitted).

The '618 patent teaches "modified PH20 polypeptides provided herein exhibit altered activities or properties compared to a wildtype, native or reference PH20 polypeptide." *Id.* at 73:59–61. The '618 patent further provides:

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

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

Id. at 73:61–74:5.

B. Post-Grant Review Eligibility

As a threshold issue, we must determine whether the '618 patent is eligible for post-grant review. There are two requirements that must be met for post-grant review to be available. First, post-grant review is only available if the petition is filed within nine months of the issuance of the challenged patent. 35 U.S.C. § 321(c). Petitioner certifies that the Petition, filed on April 15, 2025, is within nine months of the '618 patent's July 16, 2024, issue date. Pet. 4; Ex. 1001, code (45).

Second, post-grant review is available only for patents that issue from applications that at one point contained at least one claim with an effective filing date of March 16, 2013, or later. *See* Pub. L. No. 112-29, §§ 3(n)(1), 6(f)(2)(A). Here, the priority dates recited for the '618 patent include three filings prior to March 16, 2013. These prior filings are the '731 Application, filed December 28, 2012, U.S. Provisional Application 61/796,208, filed Nov. 1, 2012, and U.S. Provisional Application 61/631,313, filed December 30, 2011. *See* Ex. 1001, code (60).

Petitioner asserts the disclosure of the "'731 Application (including subject matter incorporated by reference) does not provide written description support for and does not enable any claim of the '618 Patent." Pet. 6.

Because the analysis of priority and PGR-eligibility in this Institution Decision relies on substantially the same analysis relevant to Petitioner's challenge based on alleged lack of written description (Ground 1), we address post grant review eligibility and written description together below. *See infra* Section IX. As discussed below, we determine that the '618 patent is eligible for post grant review. *See id.*

V. ILLUSTRATIVE CLAIM

Claim 1, the sole independent claim, is illustrative of the challenged claims in the '618 patent, and is reproduced below.

> 1. A modified PH20 polypeptide, comprising one or more amino acid modifications in an unmodified PH20 polypeptide, wherein:
>
> the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NO: 3, 7 and 32–66;
>
> amino acid modifications are selected from the group consisting of amino acid replacements(s), deletion(s), and/or insertion(s);
>
> the modified PH20 polypeptide comprises a modification at a position corresponding to position 309, with reference to amino acid positions of SEQ ID NO:3;
>
> corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the amino acid sequence of SEQ ID NO:3; and
>
> the modified PH20 polypeptide has at least 91% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7 and 32–66.

Ex. 1001, 299:37–54.

VI. ASSERTED GROUNDS

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

Ground	Reference(s)/Basis	35 U.S.C. §	Claim(s) Challenged[2]
1	Written Description	§ 112	1, 2, 5, 7–33
2	Enablement	§ 112	1, 2, 5, 7–33
3	'429 patent[3], Chao[4]	§ 103	1, 2, 5, 7–22, 24–33

See Pet. 7. Petitioner also relies on the Declarations of Michael Hecht, Ph.D. and Sheldon Park, Ph.D. *See* Exs. 1003, 1004, respectively. Patent Owner has submitted a Declaration of Barbara Triggs-Raine, Ph.D. *See* Ex. 2001.

VII. LEVEL OF ORDINARY SKILL IN THE ART

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

> have had an undergraduate degree, a Ph.D., and post-doctoral experience in scientific fields relevant to study of protein structure and function (*e.g.*, chemistry, biochemistry, biology, biophysics). From training and experience, the person would have been familiar with factors influencing protein structure,

[2] Petitioner originally challenged claims 1–40 for lack of written description and enablement, and challenged claims 1, 2, 4, 5, 7–22, and 24–40 for obviousness. *See* Pet. 7. We have adjusted the claims challenged to only those that remain in effect following Patent Owner's disclaimer. *See* Ex. 2003.

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

[4] Chao et al., *Structure of Human Hyaluronidase-1, a Hyaluronan Hydrolyzing Enzyme Involved in Tumor Growth and Angiogenesis*, 46 Biochemistry 6911–6920 (2007) (Ex. 1006).

> folding and activity, production of modified proteins using recombinant DNA techniques, and use of biological assays to characterize protein function, as well with techniques used to analyze protein structure (*i.e.*, sequence searching and alignments, protein modeling software, etc.).

Pet. 16 (citing Ex. 1003 ¶ 13).

Petitioner's proposal is sufficiently comprehensive to encompass the level of skill reflected in prior art relevant to the '618 patent. It is reasonably clear that, in indicating that a POSA would have an advanced degree (like a Ph.D.) and years of experience in analysis of protein structure, Petitioner is asserting that knowledge of proteins generally is sufficient to understand the types of problems encountered in the art and the prior art solutions to those problems, and the ordinary artisan need not have expertise specifically in hyaluronidases. *See* Pet. 15–16. Petitioner requires that the POSA would be able to apply key scientific concepts (e.g., biochemistry, recombinant biology, sequence analysis and protein modeling) to enzymes such as hyaluronidases. *See id*.

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

VIII. CLAIM CONSTRUCTION

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

meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." *Id.*

A. Petitioner's Position

Petitioner asserts the "claim [terms] are either expressly defined in the common disclosure[5] or are used with their common and ordinary meaning. Consequently, no term requires an express construction to assess the grounds in this Petition," in addition to those expressly defined in the specification. Pet. 17. Petitioner asserts "the specification describes two mutually exclusive categories of 'modified PH20 polypeptides' (*i.e.*, 'active mutants' vs. 'inactive mutants')." *Id.* at 22. Petitioner asserts the claim language reinforces that they are limited to "active mutants" for three reasons:

> First, dependent claims 5, 7, 15–16, and 25–27 require modified PH20 polypeptides to have a single substitution at 309 to one or more of the following: I309N, I309L, I309E, I309G, I309H, I309M, I309Q, I309R, I309S, I309T or I309V. The common disclosure describes $PH20_{1-447}$ polypeptides with these substitutions as "Active Mutants" with >50% activity.
>
> Second, the common disclosure identifies *no examples* of "inactive mutant" PH20 polypeptides with a substitution at position 309 . . . .
>
> Third, dependent claims 3, 6, and 23 require modified PH20 polypeptides with "increased resistance or stability" or "increased hyaluronidase activity" relative to an unmodified PH20. All require modified PH20s with hyaluronidase activity . . . .
>
> Fourth, dependent claims 30-40 require use of an "active mutant" PH20.

[5] Petitioner uses the term "common disclosure" to refer to the Specifications of both the '618 patent and the ultimate parent application, the '731 Application, filed on December 28, 2012. *See* Pet. 1 (citing Ex. 1026).

> Fifth, the specification defines a "modified PH20 polypeptide" as "a PH20 polypeptide that contains at least one amino acid modification," but explains it can "have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide *exhibits hyaluronidase activity*.

Id. at 24–27 (citing Ex. 1001, 84 (Table 3), 227 (Table 9), 2:53–3:4, 50:64–51:12, 50:25–54, 71:36–61, 96:5–17, 125:45–64, 171:56–59, 172:66–173:5, 173:66–174:11, 294:16–295:44; Ex. 1003 ¶¶ 137–140, 176–177). Petitioner also states that:

> Patentee may contend the claims encompass both "active" and "inactive" mutants, but that only compounds their § 112 problems. First, every claim (including 1) still encompasses (and must describe and enable) a subgenus of "active mutants" (*e.g.*, claim 1 contains the genus of "active mutants" defined in claim 6). Second, analogous § 112 problems exist for "inactive mutants"—those with putative utility as a contraceptive antigen—as they are a distinct subgenus within the 10^{60}+ claimed PH20 polypeptides and are neither described nor enabled.

Pet. 27 (citing Ex. 1003 ¶ 141–142).

B. Analysis

We find that on the present record, the evidence supports a broaddefinition of "modified PH20 polypeptide" that includes active molecules.

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

Southwall Tech., Inc. v. Cardinal IG Co., 54 F.3d 1570, 1578 (Fed. Cir. 1995). "[T]he specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise

possess. In such cases, the inventor's lexicography governs." *Phillips*, 415 F.3d at 1316.

Here, the '618 patent defines "PH20" as a type of hyaluronidase enzyme and "includes those of any origin including, but not limited to, human, chimpanzee, Cynomolgus monkey, Rhesus monkey, murine, bovine, ovine, guinea pig, rabbit and rat origin." Ex. 1001, 44:16–19. The '618 patent further explains that "[r]eference to PH20 includes precursor PH20 polypeptides and mature PH20 polypeptides (such as those in which a signal sequence has been removed), truncated forms thereof that have activity, and includes allelic variants and species variants, variants encoded by splice variants, and other variants." *Id.* at 44:30–35. The '618 patent states that "PH20 polypeptides also include those that contain chemical or posttranslational modifications and those that do not contain chemical or posttranslational modifications." *Id.* at 44:39–42. The '618 patent provides an express definition of the term "modified PH20 polypeptide" which

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

Id. at 46:63–47:11 (emphasis added).

Based on this express definition, the current record does not support the interpretation of Dr. Triggs-Raine that the "term 'modified PH20 polypeptide,' therefore, has a purely structural meaning in the context of the specification." Ex. 2001 ¶ 68. Indeed, when reproducing the definition from this column of the '618 patent, Dr. Triggs-Raine does not include any text after the first period, stating that "is not part of the express definition of 'modified PH20 polypeptide'" and "merely describes an *upper limit* for the number of modifications possibly allowing a modified PH20 polypeptide to exhibit enzymatic activity." Ex. 2001 ¶¶ 67, 77–78.

On this record, however, we find that the entire text quoted above is part of the definition of "modified PH20 polypeptide" because it continues to detail specific elements required including a requirement that replacements in the PH20 polypeptide are permitted "so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity." Ex. 1001, 47:2–4; *see* Ex. 2001 ¶¶ 48, 67 (stating a "patent's definition controls"). Indeed, while some of the language in the definitional paragraph is permissive in nature, i.e.., describing the number of amino acid replacements a modified PH20 polypeptide "can have" or "[t]ypically . . . contains" or the other modifications the polypeptide "can include," the phrase "so long as" is not. *See* Ex. 1001, 47:1–11. This distinction demonstrates that hyaluronidase activity is not an optional feature of a non-limiting example as Patent Owner posits, but a requirement of the "modified PH20 polypeptide" defined and claimed in the '618 patent. See *Alynylam Pharms., Inc. v. Moderna, Inc*., 138 F.4th 1326, 1333 (Fed. Cir. 2025) (explaining that the "contrast" between "non-limiting terms" and more definitive statements may indicate that the latter is definitional). Moreover, Dr. Triggs-Raine recognizes the

"therapeutic use of hyaluronidases" and notes that "different hyaluronidases were known to have different functions and substrates." Ex. 2001 ¶¶ 29, 113.[6] That is, Dr. Triggs-Raine recognizes hyaluronidase activity as the primary utility for the modified PH20 polypeptides recited in claim 1.

Thus, the evidence of record shows the '618 patent recognizes a broad understanding of a "modified PH20 polypeptide" as encompassing PH20 sequences from a variety of different mammalian species, with or without precursor or signal sequences, with or without post-translational modifications, and with up to 150 amino acid replacements.

The express definition of "modified PH20 polypeptide" in the '618 patent permits up to 150 amino acid replacements but ***only*** "so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity." Ex. 1001, 47:2–4. That is, the provided definition of "modified PH20 polypeptide" in the '618 patent expressly requires some hyaluronidase activity. Neither Patent Owner's disclaimer of claims 3, 4, 6, and 34–40 nor the additional limitations required by dependent claim 17 and 18 impacts the claim differentiation argument. The original issuance of these claims indicates that claim 1 encompasses modified PH20 polypeptides with hyaluronidase activity, and there is no limitation in claim 1 that includes inactive PH20 polypeptides with no hyaluronidase activity. *See id* at 299:37–54. On the current record, we therefore adopt the definition for "modified

[6] We recognize Dr. Triggs-Raine also cites "the role of PH20 in contraception," but on this record, provides no evidence that a single modified PH20, as opposed to the naturally occurring PH20, functions as a contraceptive in any species. *See* Ex. 2001 ¶ 40.

PH20 polypeptide" as recited in the '618 patent to encompass polypeptides with some hyaluronidase activity.[7]

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

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

IX. GROUND I - WRITTEN DESCRIPTION

A. Principles of Law

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

[7] As to Dr. Triggs-Rainee's statement that the term "modified PH20 polypeptide" encompasses enzymatically inactive polypeptides (Ex. 2001 ¶ 75), we note the '618 patent imposes functional requirements on inactive polypeptides as well, stating that "[a]lso provided are modified PH20 polypeptides that are inactive, and that can be used, for example, as antigens in contraception vaccines." Ex. 1001, 74:3–5. We address this concept further in the written description analysis.

Owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015).

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

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

B. Petitioner's Position

Petitioner asserts the "claim parameters capture between 10^{60} and 10^{113} distinct PH20 polypeptides. . . . Relative to that broad scope, the '618 Patent and the '731 Application provide only a meager disclosure: ***singly***-modified PH20 polypeptides and a prophetic, make-and-test research plan to discover multiply-modified ones." Pet. 28 (emphasis in original). Petitioner asserts:

> Claims 1-2, 6-15, and 25-27 encompass modified PH20 polypeptides that are not only immense in number but are structurally and functionally diverse. They include mutants with between 2-21 substitutions for the narrowest claims (*e.g.* claims 24 and 25) to 2-42 for the broadest (claim1). The optional sets of substitutions can be anywhere in the sequence (*i.e.*, clustered in a narrow region, spaced apart in groups, or spread randomly throughout the sequence), to any of 19 other amino acids, and arranged in any manner. The claims thus capture a mutant with

> 5 substituted hydrophobic residues clustered in a small region, as well as one with up to 42 substitutions that mix polar, charged, aliphatic and aromatic amino acids together in any manner.

Id. at 34 (citing Ex. 1003 ¶¶ 130–131; Ex. 1001, 59:7–14, 46:1–5, 46:14–16, 40:25–31).

Petitioner asserts the '618 patent "simply instructs the skilled artisan 'to generate a modified PH20 polypeptide containing any one or more of the described mutation[s], and test each for a property or activity as described herein.'" *Id.* at 35 (citing Ex. 1001, 76:47–52; Ex. 1003 ¶ 206). Petitioner acknowledges that the '618 patent identifies inactive amino acid substitutions and "identifies these changes as: (i) any substitution at 96 different positions in the PH20 sequence, and (ii) 313 specific amino acid substitutions listed in Tables 5 and 10." *Id.* at 36 (citing Ex. 1001, 78:27–79:2). But, Petitioner notes, the "claim language however captures active mutants that include one or more of the substitutions in Tables 5 and 10." *Id.* at 37.

Petitioner asserts that based on the prior art and the common disclosure, it is reported "that wild-type PH20 polypeptides terminating at or below position 442 have ***significantly reduced or no*** hyaluronidase activity," and that "PH20 mutants terminating below position 432 lacked hyaluronidase activity, while those terminating between positions 432 and 448 had widely varying activities." Pet. 37–38. Petitioner also asserts that the '618 patent provides no examples or guidance for "enzymatically active multiply-substituted PH20 mutants truncated to positions 419 and 447." *Id.* at 40 (citing Ex. 1003 ¶¶ 96–98, 100, 102, 171–174).

Petitioner asserts that of approximately 5,917 tested single amino acid changes, "~87% of the 5,917 single-replacement $PH20_{1-447}$ polypeptides that

were made and tested [have] ***less*** activity than unmodified $PH20_{1-447}$." *Id.* at 42 (citing Ex. 1003 ¶¶ 110, 116–117). Petitioner asserts the data shows the unpredictability of mutation where introducing "different substitutions at the same position in $PH20_{1-447}$ yielded active and inactive mutants, with >800 unclassified mutants." *Id.* at 43 (citing Ex. 1001, Tables 8, 9, 10). Petitioner asserts that:

> The common disclosure reports results from testing a portion of a library of ~6,743 single-replacement $PH20_{1-447}$ polypeptide sequences. These mutants were produced using a library of CHO cells transfected with a plasmid encoding mutagenized $PH20_{1-447}$ sequences where one of 447 positions in the sequence "was changed to one of about 15 amino acid residues, such that each member contained a single amino change." Results for ~5,917 of the mutants are reported.
>
> The common disclosure classifies more than half (~57%) of the tested mutants as "inactive mutants" and ~30% as having less activity than unmodified $PH20_{1-447}$ (20%-100%). In other words, it portrays ~87% of the 5,917 single-replacement $PH20_{1-447}$ polypeptides that were made and tested as having ***less*** activity than unmodified $PH20_{1-447}$.

Id. at 41–42 (citing Ex. 1001, 125:65–126:9, 194:1–3, 192:51–60; Ex. 1003 ¶¶ 110, 113–114, 116–117). Petitioner concludes the '618 patent's "empirical test results for single substitution mutants do not identify to a skilled artisan which of the 10^{60}+ PH20 mutants with a 309 substitution and 1–41 additional substitutions are enzymatically active." *Id.* at 44 (citing Ex. 1003 ¶¶ 149, 151, 206). Petitioner also asserts that the '618 patent "does not identify any—let alone ***which***—combinations of substitutions in a multiply-modified PH20 improve stability." *Id.* at 46–47 (citing Ex. 1003 ¶¶ 69, 76).

Petitioner asserts that the '618 patent "does not describe any multiply-modified PH20 polypeptides that are 'active mutants.' Instead, it simply presents ***the idea*** of multiply-modified PH20 polypeptides." *Id.* at 47 (citing Ex. 1001, 47:1–11). Petitioner asserts that the '618 patent outlines a "prophetic research plan requiring 'iterative' make-and-test experiments that ***might discover*** such PH20 polypeptides," but that the research plan does not "identify ***which*** multiply-modified PH20 polypeptides can be made or *are* active mutants." *Id.* at 48 (citing Ex. 1003 ¶¶ 185–189, 196–197, 200); *see also* Ex. 1001, 41:3–10, 42:23–25, 125:65–126:43, 126:52–128:28, 128:55–133:41.

Petitioner asserts the '618 patent does not identify

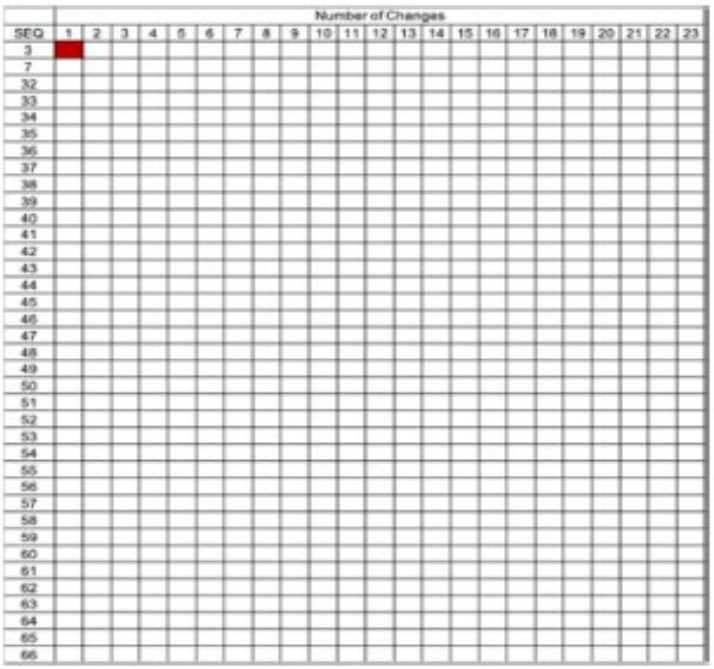
> the structural significance of any of the ~2,500 mutations that yielded single residue "active mutant" $PH20_{1-447}$ polypeptides (or the ~3,400 inactive mutants or ~830 mutants that were uncharacterized). For example, it does not identify the effect of any replacement on any domain structure, any structural motif(s) or even the local secondary structure at the site of the substitution in the PH20 polypeptide, nor does it identify how any such (possible) structural change(s) is/are responsible for the measured change in hyaluronidase activity.

Pet. 50–51 (citing Ex. 1003 ¶¶ 148–149, 158).

Petitioner asserts the "[s]ingle-replacement $PH20_{1-447}$ examples are not representative of the 10^{60}+ $PH20_{1-447}$ polypeptides having ***2 to 42 additional substitutions*** at any of 19 other amino acids at any of hundreds of positions within the protein." *Id.* at 53 (emphasis in original) (citing Ex. 1003 ¶¶ 61, 152, 166). Petitioner asserts the "single-replacement active mutant PH20 polypeptides in the disclosure thus are not representative of the unidentified number of undisclosed enzymatically active multiply-substituted PH20 mutants within the claims' scope, which comprise myriad combinations of

substitutions that each can uniquely impact the structures and properties of the mutated protein." *Id.* at 54 (citing Ex. 1003 ¶¶ 152, 156).

Petitioner asserts that the figure below illustrates how non-representative the single-replacement $PH20_{1-447}$ mutants are:



Pet. 56. 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*. Petitioner concludes that "a skilled artisan would not have viewed the examples of single amino acid replacements in $PH20_{1-447}$ in the common disclosure to e ***representative*** of the diversity of 'active mutant' modified PH20 polypeptides encompassed by the claims." *Id*. at 57 (citing Ex. 1003 ¶ 152).

Petitioner asserts that the other claims in the '618 patent lack written description support for the same or substantially similar reasons. *See id*. at 58–64.

C. Analysis

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

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

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

Id. at 1349. *Ariad* explains "that an adequate written description requires a precise definition, such as by structure, formula, chemical name, physical properties, or other properties, of species falling within the genus sufficient to distinguish the genus from other materials." *Id.* at 1350. *Ariad*

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

Id.

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

polypeptide as a contraceptive antigen serves to satisfy the utility requirement for the instant claims, there is a similar concern as to whether modified PH20 polypeptides with significant differences from the native protein as encompassed by claim 1 would maintain the antigenic determinants necessary to function as contraceptives. *See* Ex. 1003 ¶ 124.

That the modified PH20 polypeptides would be homogenous in function is contradicted both by evidence in the '618 patent itself and by Dr. Hecht and Dr. Parker. The '618 patent discloses synthesis of 6,753 single amino acid mutations in residues 1–447 of SEQ ID NO: 3. *See* Ex. 1001, 192:20–194:3. The '618 patent teaches that just under 10% of these mutations, i.e. over 600, "exhibit activity that is increased compared to wildtype." *Id.* at 226:27–28. Appendix A of Dr. Hecht's Declaration shows 3,380 of these mutations were inactive, or 57.13%. *See* Ex. 1003, Appendix A-1, 171.

Thus, the '618 patent evidences that even when only a single mutation is made in the PH20 polypeptide, that single mutation is more likely than not to alter the structure in such a way as to inactivate the hyaluronidase activity found in the native PH20 polypeptide.

On this record, Dr. Hecht persuasively demonstrates that when the full scope of claim 1 is addressed, which includes not just single mutations in the PH20 polypeptide, but also multiple mutations, there is no expectation of structural homogeneity, stating that "[i]ntroducing multiple amino acid changes simultaneously . . . could prevent the folding of sequences into secondary structures and structural motifs and can destabilize those structures if they do form." Ex. 1003 ¶ 59. Dr. Hecht notes that claim 1 allows "21-42 changes, with each additional change (except at position 309)

being to and of 19 alternative amino acids. But the up to 21-42 changes also can be at any of between 430 and 465 different positions (or, in the case of the broadest claims, 474) depending on which unmodified PH20 sequence is referenced." *Id.* ¶ 131. Dr. Park calculates that "95% sequence identity [i.e., the higher percentage identity recited by the narrowest of the challenged claims] to $PH20_{1\text{-}465}$ means that the protein can have 23 total changes," and that where one of those changes is at position 309 as required by claim 1, the number of possible PH20 polypeptides with twenty-two additional changes is "extremely large by all accounts, ranging from 2.64×10^{60} to 1.20×10^{113}." *See* Ex. 1004 ¶¶ 162–163. Dr. Hecht characterizes the number of possible mutations as "astronomical in size." Ex. 1003 ¶ 136.

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; *see* Ex. 1004 ¶¶ 94–99. Dr. Park notes that Zhang found "a mutation at Asn350 in the 'c-terminal EGF-like domain' abolished hyaluronidase activity but one at Asn216 did not." Ex. 1004 ¶ 96 (citing Ex. 1010, 9438–9439). Dr. Park also cites Ex. 1011 (Arming), which states:

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

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

Dr. Hecht also addressed the use of PH20 polypeptides as antigens for contraceptives, a use contemplated by the '618 patent. *See* Ex. 1001, 75:57–59, 186:26–45; Ex. 1003 ¶ 120. Dr. Hecht stated "subsequently published papers . . . reported negative results in experiments to cause contraception by immunizing mammals (rats, mice) with PH20." Ex. 1003 ¶ 121 (citing Ex. 1019, 325; Ex. 1020, 181; Ex. 1021, 30310). Dr. Hecht cites to Rosengren (Ex. 1061), which states "several attempts were made to immunize males with PH20 as an immunocontraceptive approach in animal models. These studies involved rabbits (45,46), mice, (47), and guinea pigs (48), and only the latter experienced infertility following PH20 immunization." *Id*. ¶ 122 (quoting Ex. 1061, 1154).

Dr. Hecht states that these published reports

> all suggest that the wild-type human PH201-447 protein as well as PH20 polypeptides from other species do induce formation of antibodies, just not those that affect fertility in humans or many rodents. The brief suggestion in the common disclosure about possibly using inactive mutant forms of PH20 as the immunogen of a contraceptive vaccine does not seem credible given these other experimental results.
>
> I note that the common disclosure does not identify any ***mutated*** PH20 polypeptides that were effective when used in a contraceptive vaccine. In addition, as I noted in ¶ 122, published reports showed that antibodies that do not impair fertility can form in humans naturally or in response to administration of recombinantly produced PH201-447. This suggests that there are structures on the wild-type human PH20 that can be recognized by antibodies that do not cause contraception in humans. But there is nothing in the common disclosure that distinguishes

> those structures on PH20 from structures that might induce antibodies that do confer a contraceptive effect, or whether the latter structures are preserved in any particular modified PH20 polypeptide. The common disclosure does not provide any guidance that would allow a skilled artisan to determine whether any active or inactive mutants are useful as contraceptive vaccines (such as by identifying common structural or functional characteristics shared by those inactive mutants), without making and testing all ~1060 (or more) modified PH20 polypeptides within the parameters of each claim.

Ex. 1003 ¶ 123– 124 (emphasis in original). This shows that even the native PH20 polypeptide does not necessarily function as a contraceptive. These facts are analogous to those in *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc*., 759 F.3d 1285, 1300 (Fed. Cir. 2014), where the claims contained structurally diverse antibodies, but the patent at issue only described structurally similar antibodies.

Therefore, the only evidence of any contraceptive activity is for the native protein without any mutations. The evidence demonstrates that not all native PH20 molecules necessarily function as contraceptives, much less mutated forms that might differ in structure and binding affinities as antigens. Rather, even for the single mutations tested, the ’618 patent employed a trial-and-error approach for hyaluronidase activity and did no testing to determine if any of the mutations had contraceptive function. *See* Ex. 1001, 194:1–3; *see also In re Alonso*, 545 F.3d 1015, 1020 (Fed. Cir. 2008) (“We have previously held in a similar context that ‘a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those

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

On the current record, the evidence shows it is more likely than not that the claims of the '618 patent fail to satisfy the written description requirement because they "recite a description of the problem to be solved while claiming all solutions to it and . . . cover any compound later actually invented and determined to fall within the claim's functional boundaries—leaving it to the pharmaceutical industry to complete an unfinished invention." *Ariad*, 598 F.3d at 1353.

Accordingly, on the current record, we find that Petitioner has demonstrated that it is more likely than not that the challenged claims of the '618 patent do 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 '618 patent in the '731 Application or any of the subsequent divisional or continuation applications leading to the '618 patent that claim priority to the '731 Application (which appear to all have similar specifications) for the reasons given above. Therefore, the '618 patent might not receive the benefit of priority to the earlier filed applications, and based on this preliminary determination, is eligible for post-grant review because the effective filing date is no earlier than the '618 patent's filing date of May 21, 2021. *See* Ex. 1001, code (22).

X. GROUND II - ENABLEMENT

A. Principles of Law

"[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *Trustees of Boston Univ. v. Everlight*

Elecs. Co., 896 F.3d 1357, 1362 (Fed. Cir. 2018) (bracketing in original; internal quotations omitted). That is, "there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill [in the art] how to make and how to use the invention as broadly as it is claimed." *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991).

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

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

B. Petitioner's Position

Petitioner asserts

> the common disclosure utterly fails to enable the immense genus of modified PH20 polypeptides claimed. Using that disclosure and knowledge in the prior art, the skilled artisan would have to perform undue experimentation to identify which of the 10^{60}+ PH20 polypeptides having multiple amino acid replacements and/or truncations within the scope of the claims that are useful because they are "active mutants," those "inactive mutants" that the disclosure contends are useful as a contraceptive antigen, and those which have no utility.

Pet. 66–67 (citing Ex. 1003 ¶¶ 182–184, 203). Petitioner asserts the "the claims capture massive number of multiply-modified PH20 polypeptides that have *unknowable* properties absent the skilled artisan producing and testing 10^{60} and 10^{113} distinct mutants pursuant to the common disclosure's prophetic 'make and test' methodology." *Id.* at 69 (citing Ex. 1003 ¶¶ 163–165, 175).

Petitioner asserts the '618 patent

> provides an extremely narrow set of working examples: ~5,916 randomly generated single-replacement $PH20_{1-447}$ polypeptides, of which ~2500 were "active mutants," ~3380 were "inactive mutants" and ~830 mutants that are only characterized by their desired sequence—they are not classified as either "active" or "inactive" mutants. Combined, those examples are a tiny fraction of the 10^{60} to 10^{113} modified PH20 polypeptides covered by the claims. They also provide no guidance that would help a skilled artisan navigate the "trial-and-error" methodology the common disclosure describes using to make multiply-modified PH20 polypeptides; indeed, none incorporate more than one substitution and none truncate the PH20 polypeptide before position 447.

Id. at 70–71 (citing Ex. 1003 ¶¶ 113, 114, 162–166, 173).

Petitioner asserts the "common disclosure provides no credible guidance on practicing the full scope of the claims" because "it describes an explicitly prophetic and 'iterative' 'make and test' process for ***discovering*** active mutant PH20 polypeptides" involving "manually performing iterative rounds of ***randomized*** mutations (up to 41 rounds per starting molecule under the broadest claims) to ***discover*** which of the 10^{60}+ possible modified PH20 polypeptides the claims encompass might possess hyaluronidase activity." *Id.* at 71 (emphasis in original) (citing Ex. 1003 ¶¶ 143, 149, 191–193). Petitioner asserts the "'***iterative, trial-and-error process[es]***' the common disclosure specifies here are thus indistinguishable from those consistently found to not enable broad genus claims to modified proteins or other useful compounds." *Id.* at 73 (emphasis and bracketing in original) (citing *Idenix Pharm. LLC v. Gilead Sci. Inc*., 941 F.3d 1149, 1161–63 (Fed. Cir. 2019)).

Petitioner asserts "skilled artisans around this time period could ***not*** have predicted the effects of making more than a few concurrent amino acid

replacements within a PH20 polypeptide." *Id.* at 74 (citing Ex. 1003 ¶¶ 165, 243). Petitioner asserts the "cumulative effects of multiple changes would also have rapidly exceeded the capacity of computer-based, rational design protein engineering techniques to reliably predict the effects of each change on the protein's structure." *Id.* at 75 (citing Ex. 1003 ¶¶ 165, 203, 243; Ex. 1004 ¶¶ 142–144).

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 the range of multiply-changed PH20 polypeptides being claimed. Likewise, while there was significant public knowledge about hyaluronidases, there was no solved structure of the PH20 protein. Also, the public literature generally reported on ***loss of activity*** from mutations in hyaluronidases, and did not predictably teach how to introduce changes that ***enhanced*** stability or activity.

Id. at 76–77 (emphasis in original) (citing Ex. 1003 ¶¶ 165, 243; Ex. 1011, 812–814; Ex. 1010, 9437–9439).

C. Analysis

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

1. Breadth of Claims and Nature of the Invention

Petitioner's declarant Dr. Park states, regarding the breadth of claim 1, that he "calculated the number of distinct polypeptides that exist that meet the specified criteria." Ex. 1004 ¶ 163. Dr. Park's table is reproduced below:

PH20 length	*Sequence Identity %*	*# Changes*	*Pos. 309 Choices*	*Add'l Changes*	*# of Distinct Polypeptides*
474	91	42	19	41	1.20×10^{113}
474	95	23	19	22	9.85×10^{66}
474	91	42	6	41	3.79×10^{112}
474	91	42	1	41	6.32×10^{111}
465	91	41	19	40	2.68×10^{110}
465	95	23	19	22	6.39×10^{66}
465	91	41	1	40	1.41×10^{109}
433	91	41	19	40	1.35×10^{109}
430	91	41	19	40	1.01×10^{109}
433	91	41	1	40	7.10×10^{107}
430	91	41	1	40	5.30×10^{107}
465	91	41	11	40	1.55×10^{110}
447	91	40	1	39	1.40×10^{106}
430	95	21	6	20	2.64×10^{60}
433	95	21	6	20	3.05×10^{60}

Id. Dr. Park's table shows that the "number of distinct polypeptides is extremely large by all accounts, ranging from 2.64×10^{60} to 1.20×10^{113} distinct polypeptides." *Id.* Petitioner's declarant Dr. Hecht agrees, stating that there are "an immense number of mutants that fall within the sequence identity parameters of the claims." Ex. 1003 ¶ 115. To illustrate how large a number like 1.20×10^{113} is, Dr. Hecht states that an "aggregate weight of the smallest set containing one molecule of each of the PH20 mutants would be $2.64 \times 10^{60} \times 8.94 \times 10^{-20} = 2.36 \times 10^{38}$ kg. The weight of the Earth is 'only' ~ 5.97×10^{24} kg." *Id.* ¶ 134.

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

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

2. Skill in the Art

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

3. State of the Prior Art

Dr. Hecht acknowledges protein expression is routine, stating the "conventional procedures relating to production of the wild-type $PH20_{1-447}$ 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 ¶ 216 (citing Ex. 1005, 39:54–40:21 ('429 patent)). Dr. Hecht further states that "[t]he first experimentally determined structure of a hyaluronidase was of bvH, both alone and in complex with HA (published in 2007)," and that "Markovic-Housley identified the catalytic site and residues involved in catalytic activity using this structure." *Id*. ¶ 80 (citing Ex. 1033, 1028–1031).

Dr. Hecht, however, 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.* ¶ 94 (citing Ex. 1005, 87:52–88:24; Ex. 1013, 430–432, Fig. 2). Dr. Hecht states the "Zhang paper reported that a truncation just upstream of the start of the Hyal-EGF domain in HYAL1 reduced its activity to ~6%." *Id.* ¶ 96. Dr. Hecht states that "[n]either the scientific literature existing by

2011 nor the common disclosure provides an explanation why these PH20 truncation mutations that differ by one residue (i.e., $PH20_{1-446}$ vs. $PH20_{1-447}$ vs. $PH20_{1-448}$) exhibit variability in their activity." *Id.* ¶ 99.

Dr. Hecht states "[t]here were limits to using rational design techniques in the 2011-timeframe." *Id.* ¶ 50 (citing Ex. 1018, 378; Ex. 1059, 1225–1226). "The complexity of the structure/function relationship in enzymes has proven to be the factor limiting the general application of rational design." *Id*. at n.17 (citing Ex. 1018, 378). Dr. Hecht states regarding another approach to protein modification, termed directed evolution, that the "challenge with directed evolution is scale. One has to identify the successful mutant out of an immense number of possibilities, which presents different kinds of challenges." *Id.* ¶ 52 (internal footnote omitted). Dr. Hecht states "changing many amino acids simultaneously risks disrupting the pattern necessary to induce formation of the original secondary structure . . . and [can] be highly destabilizing to the overall protein structure." *Id*. ¶ 55 (citing Ex. 1046, 2034; Ex. 1047, 6349, 6352). Dr. Hecht states that even in a smaller, ten amino acid substitution example, "[t]here are approximately 6 x 10^{12} different scenarios of 10 substitutions." *Id.* ¶ 58.

On the current record, we find the evidence shows that simply making and expressing modified PH20 polypeptides was well within the state of the prior art. The evidence of record, however, also demonstrates that the prior art was aware that mutations, whether conservative or non-conservative, may impact protein function and physical shape. The evidence of record demonstrates that identifying which of the 10^{60} and 10^{113} members of the PH20 polypeptide genus would either retain functional hyaluronidase

activity or contraceptive activity was not established as known in the prior art.

4. Presence of Working Examples

Dr. Hecht agrees that the '618 patent lists 6,753 $PH20_{1-447}$ mutants listed in Table 8 that were generated by encoding "variant proteins wherein each of residues . . . 1–447 of SEQ ID NO:3 . . . was changed to one of about 15 amino acids, such that each member contained a single amino acid change.'" Ex. 1003 ¶ 108. Dr. Hecht states "the number of 'inactive mutants' listed in Table 5 does not match the number of tested inactive mutants listed in Table 10 (*i.e.*, 3,368 vs. 3,380)." *Id.* ¶ 113. Dr. Hecht calculates that based on the data in Table 10 of the '618 patent that 57.1% of the tested mutants were inactive, and 29.4% others had activity <100%. *Id.* ¶ 116.

Dr. Hecht states the '618 patent "does not identify any ***mutated*** PH20 polypeptides that were shown to be effective when used in a contraceptive vaccine." *Id.* ¶ 124 (emphasis in original).

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

5. Amount of Direction or Guidance Presented

The '618 patent states "[p]roteins, such as modified PH20 polypeptides, can be purified using standard protein purification techniques known in the art." Ex. 1001, 143:56–58.

Dr. Hecht states the '618 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 ¶¶ 105–106. Dr. Hecht states that the data in the '618 patent show "most of the single-replacement $PH20_{1-447}$ mutants exhibited less activity than the unmodified $PH20_{1-447}$ (*i.e.*, 57.1% were inactive, and 29.4% others had activity <100%)." *Id.* ¶ 116.

Dr. Hecht states the '618 patent

> does not provide any guidance that would allow a skilled artisan to determine whether any active or inactive mutants are useful as contraceptive vaccines (such as by identifying common structural or functional characteristics that would be shared by those inactive mutants).

Id. ¶ 124. Dr. Hecht states "the data for testing the 409 mutants reported in Tables 11 and 12 [of the '618 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 $PH20_{1-447}$ form specifically." *Id.* ¶ 76. Dr. Hecht states the '618 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. ¶ 184. Dr. Hecht characterizes the disclosure of the '618 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.* ¶ 185.

On the current record, we find the evidence demonstrates significant guidance on synthesis and expression of modified PH20 polypeptides. The evidence also shows, however, that the '618 patent provides minimal guidance regarding effective methods to identify which members of the immense modified PH20 polypeptide genus function to retain either hyaluronidase activity or exhibit contraceptive activity.

6. Quantity of Experimentation

Dr. Hecht states

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

Ex. 1003 ¶ 165 (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 309 and sets of between 1 and 41 *additional* substitutions at any of hundreds of positions within the PH20 protein." *Id.* ¶ 166 (emphasis in original).

Dr. Hecht states "[m]aking and identifying all of the multiple-modified PH20 polypeptides that are within the immense set of polypeptides (between 10^{59} and 10^{113} distinct mutants) defined by the claims' sequence identity parameters and that are enzymatically active would require not only an undue amount of experimentation, it likely is impossible." *Id.* ¶ 182. Dr. Hecht states the directed evolution methods of the '618 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.* ¶ 199.

We find the facts here similar to those in *Idenix*, 941 F.3d at 1156, where, in a genus of billions, the "key enablement question is whether a person of ordinary skill in the art would know, without undue experimentation, which [species] would be effective." *Idenix* states because of the "many thousands of [species] which need to be screened for . . . efficacy, the quantity of experimentation needed is large and weighs in favor of non-enablement." *Id.* at 1159.

On the current record, we find the evidence demonstrates that a very large amount of experimentation would be necessary to enable the scope of the claims of the '618 patent.

7. Predictability of the Art

Dr. Hecht states that the

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

Ex. 1003 ¶ 61. Dr. Hecht states, citing the '429 patent, that the "varying effects of changing residues in the Hyal-EGF region of PH20 show that a skilled artisan's belief that changes in this region would be unpredictable were warranted and would be more so if multiple changes were made concurrently." *Id.* ¶ 101. Dr. Hecht states the "effects of these myriad sets of combinations of multiple substitutions within PH20 could not have been predicted by a skilled artisan in the 2011 timeframe using the tools that were available then." *Id.* ¶ 165. Dr. Hecht notes that "[a]nother problem caused by the use in the claims of sequence identity language to define the sets of proteins is that it captures many multiply-modified PH20 polypeptides with changes that common disclosure says are deleterious or eliminate hyaluronidase activity in PH20 enzymes." *Id.* ¶ 167.

Dr. Hecht states the "skilled artisan also could not predict whether any combinations of up to 9 or up to 2 additional (or more) substitutions could be made anywhere in the $PH20_{1-419}$ sequence or comparably truncated PH20 polypeptide that would restore hyaluronidase activity to an inactive I309N containing $PH20_{1-419}$ mutant." *Id*. ¶ 174. Dr. Hecht continues:

> In other words, the common disclosure not only does not help the skilled artisan identify which of the 10^{60}+ of possible PH20 polypeptides of varying length with 2 to 42 substitutions have

> hyaluronidase activity; to make and use all such enzymatically active PH20 polypeptides within the full scope of the claims requires the skilled artisan to ignore what little guidance is in the specification about single-substitutions and truncations that render PH20 polypeptides inactive.

Id. ¶ 175. Dr. Hecht states that the artisan following the '618 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.* ¶ 196. On the record before us, we credit Dr. Hecht's testimony as showing it is highly unpredictable which modified polypeptides would have hyaluronidase or contraceptive activity. *See id.* ¶¶ 61, 101, 165, 167, 174, 175, 196.

On the current record, we find the evidence shows that it is highly unpredictable which modified PH20 polypeptides within the scope of the claims of the '618 patent would have any functional utility.

D. Conclusion

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

XI. GROUND III - OBVIOUSNESS

A. Principles of Law

The Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007) reaffirmed the framework for determining obviousness set forth in *Graham v. John Deere Co*., 383 U.S. 1 (1966). In *KSR*, the Court summarized the four factual inquiries set forth in *Graham* (383 U.S. at 17–18) that are applied in determining whether a claim is unpatentable as obvious under 35 U.S.C. § 103 as follows: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the art;[8] and (4) considering objective evidence indicating obviousness or non-obviousness. *KSR*, 550 U.S. at 406.

B. Overview of the Asserted Prior Art

1. The '429 Patent (Ex. 1005)

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

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

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

[8] *See supra* Section VII.

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

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

2. Chao (Ex. 1006)

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

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

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

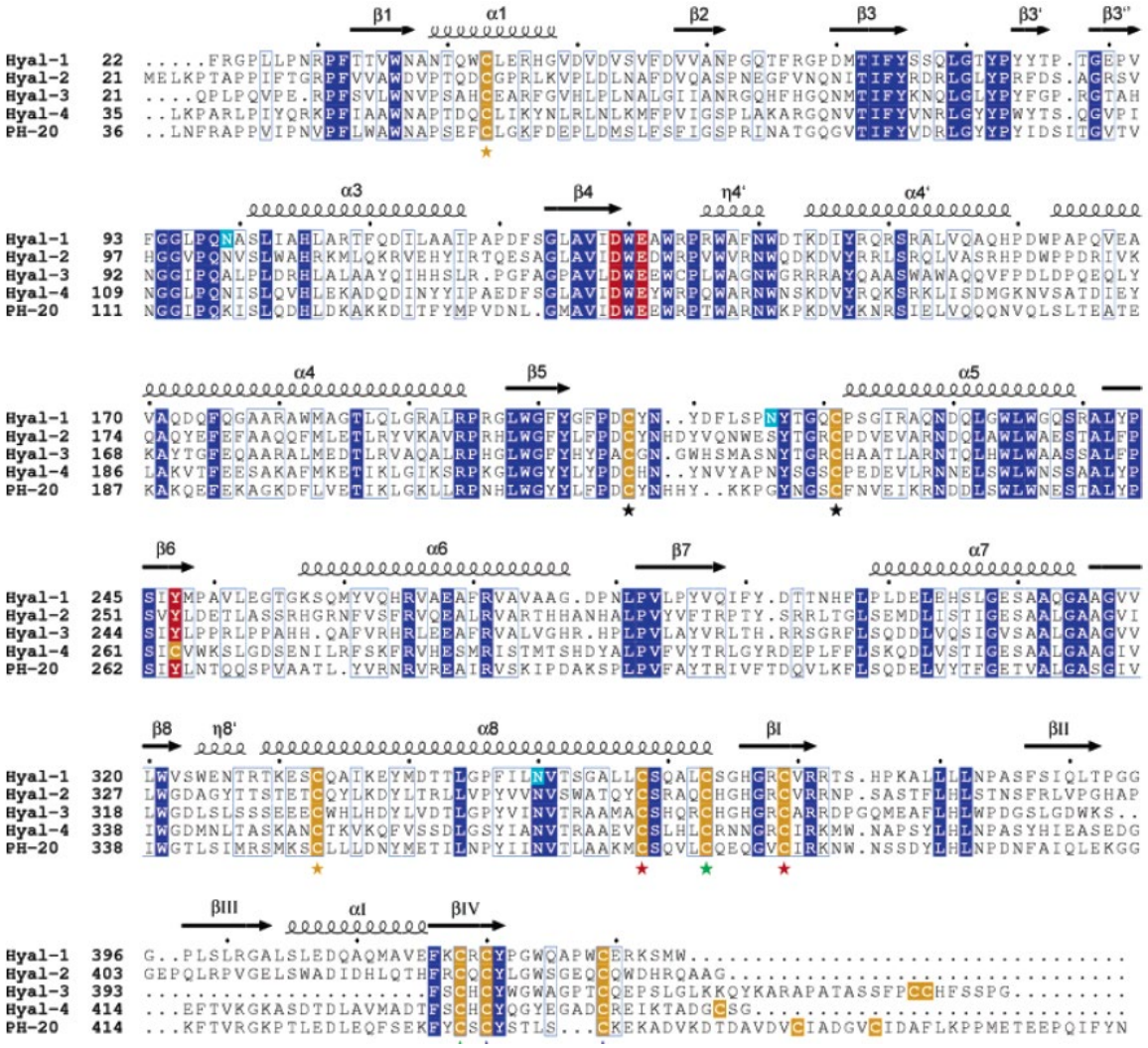


Figure 3 shows:

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

Id. at 6916.

C. Asserted Obviousness over the '429 Patent and Chao

1. Petitioner's Position

Petitioner asserts that the '429 patent "teaches making a ***particular*** type of modification (a single amino acid substitution) in ***particular*** locations (non-essential regions of PH20) in a ***particular*** PH20 sequence ($PH20_{1–447)}$ to yield equivalents that do not substantially alter the activity or function of $PH20_{1–447}$." Pet. 91 (citing Ex. 1003 ¶¶ 219–220; Ex. 1004 ¶ 32). Petitioner asserts "Chao showed that human and non-human hyaluronidases share a highly conserved active site and identified residues that interact with HA, *inter alia*, by superimposing HYAL1 and bee venom hyaluronidase structures." *Id.* at 93 (citing Ex. 1006, 6917 (Figure 4A), 6914–6916, Figure 2C; Ex. 1004 ¶¶ 89–91; Ex. 1003 ¶¶ 81–82).

Petitioner asserts that a "skilled artisan would first identify the essential residues in PH20 by comparing proteins homologous to PH20 that were known in 2011," in particular by using a multi-sequence alignment of those proteins. *Id.* at 96 (citing Ex. 1003 ¶¶ 226–228; Ex. 1004 ¶¶ 22, 25–30, Appendix D-3; Ex. 1017, 224–226). Petitioner asserts that Dr. Park performed such an analysis and that "Position 309 is within a non-essential region of $PH20_{1–447}$—Dr. Park's analysis and Chao's Figure 3 both report the same bounding essential residues (*i.e.*, W304 and C316)." *Id.* at 97 (citing Ex. 1003 ¶ 231; Ex. 1004 ¶¶ 31–32, Appendix D-2; Ex. 1006, 6916).

Petitioner asserts that in Dr. Park's alignment, the "wild-type residue at position 309 in PH20 is isoleucine (I), which occurs at positions corresponding to position 309 in ~4.5% of homologous proteins, while leucine is the most prevalent amino acid found at those positions (~33%) (*i.e.*, leucine occurs in 29 different hyaluronidase proteins), and asparagine

occurs at that position in ~9% of the proteins." *Id.* at 99–100 (citing Ex. 1003 ¶ 232; Ex. 1004 ¶ 114).

Petitioner asserts that a

> skilled artisan would have selected asparagine (N) as one of the obvious choices for such a single substitution at position 309 in $PH20_{1–447}$. Asparagine occurs at positions corresponding to 309 in 9% of homologous, naturally occurring hyaluronidase sequences known by 2011, including in human HYAL1 (as shown in Chao Figure 3). This high frequency of occurrence suggests to a skilled artisan that asparagine will not be tolerated in PH20 at position 309, and makes it an obvious amino acid to substitute into position 309 of $PH20_{1-447}$ under the rationale of the '429 Patent. Consequently, a skilled artisan would have found asparagine to be an obvious substitution for isoleucine at position 309 in $PH20_{1-447}$ pursuant to the guidance in the '429 Patent, Chao, and publicly available information.

Id. at 100–101 (citing Ex 1003 ¶¶ 232–235; Ex. 1004 ¶¶ 43, 106, 114).

Petitioner asserts that in securing its '429 patent to modified $PH20_{1-447}$ proteins, Patent Owner "relied on its statements that a skilled artisan would have expected ***any*** single amino acid substitution in ***any*** non-essential position of $PH20_{1–447}$ to not substantially affect the activity of the enzyme." *Id.* at 101. Petitioner also asserts "[p]atentee should not be permitted to now contend a skilled artisan would not have reasonably expected that the I209N substitution in $PH20_{1-447}$ would yield an enzyme with substantially the same activity as unmodified $PH20_{1-447}$." *Id.* at 101–102.

2. Analysis

On the current record, we agree with Patent Owner that Petitioner has not provided any persuasive reason to particularly target position 309 of a PH20 polypeptide for modification as required by claim 1 of the '618 patent.

Neither the '429 patent nor Chao specifically identifies or discusses position 309 of the PH20 polypeptide. *See, e.g.*, Pet. 96.

We are not persuaded by Petitioner's argument that multiple sequence alignments identify amino acids that are tolerated at particular positions (*see* Pet. 95–97), because tolerance is not a positive reason to make a substitution. "It is not enough, even after *KSR*, to support a determination of obviousness that a reference includes a broad generic disclosure and a common utility to that in the claims and other prior art references—there must be some reason to select a species from the genus." *Knauf Insulation, Inc. v. Rockwool Int'l A/S*, 788 Fed. Appx. 728, 733 (Fed. Cir. 2019).

Dr. Park identified 379 positions in PH20 with evolutionary variation, that is, where "homologous proteins have tolerated different amino acids at those positions." Ex. 1004 ¶ 31. According to Petitioner, the amino acids at these 379 positions "would be considered 'non-essential' residues" and therefore it would have been obvious to make modifications at any of these positions. *See id.*; *see also* Pet. 91–92 (characterizing "non-essential regions of PH20" as "particular locations" that would be obvious to modify).

Nothing in the prior art or Dr. Park's analysis directs the ordinary artisan to position 309 itself, and Dr. Park notes that Chao did not identify position 309 of PH20 as part of the catalytic active site, unlike positions 146, 148, and 219, nor was position 309 one of the residues identified as being in the cleft where ligand binds. *See* Ex. 1004 ¶ 91. Dr. Park indicates that position 309 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, 811–813).

Moreover, while Dr. Hecht asserts that the '429 patent suggests making "single amino acid substitutions in non-essential regions of polypeptides," Petitioner does not sufficiently demonstrate why this would have led a POSA to modify position 309 of PH20. *See, e.g.*, Ex. 1003 ¶¶ 215–217. Petitioner does not point us to anything in Dr. Hecht's Declaration that explains why position 309 was of interest in any way, as compared to any of the other 379 positions within the PH20 polypeptide Dr. Park identifies as "non-essential." *See* Ex. 1004 ¶ 31, Appendix D-2.

We also are not persuaded by Petitioner's argument that Chao "identified a characteristic pattern for the Hyal-EGF domain, which in PH20 is at positions 337–409." Pet. 95 (citing Ex. 1006, 6911; Ex. 1004 ¶¶ 97–98; Ex. 1003 ¶¶ 84–85). Dr. Park identified 10 different amino acids that occur in homologous proteins at positions corresponding to position 309 in PH20, and states that the "types of amino acids that appear at position 309 vary significantly, and include amino acids that are polar and non-polar, have high and low helix propensities, and have large or small side chains." Ex. 1004 ¶ 106. Dr. Park concludes that position 309 "is not well conserved, suggesting that substitutions of many different amino acids will likely be tolerated at position 309 in the human PH20 protein." *Id*. Dr. Park also identifies a "lack of a strict secondary structure" in the region of position 309, which Dr. Park determines "is consistent with this position tolerating many different kinds of amino acids in homologous hyaluronidase proteins." *Id*. ¶ 108. Identifying a tolerance for substitution, however, does not appear on the record before us to satisfy Petitioner's "burden to show that the 'prior art would have suggested making the *specific molecular modifications* necessary to achieve the claimed invention.'" *Amerigen Pharm. Ltd. v. UCB*

Pharma GmbH, 913 F.3d 1076, 1089 (Fed. Cir. 2019) (citing *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd*., 492 F.3d 1350, 1356 (Fed. Cir. 2007)). On this record, Petitioner has not satisfied this burden of showing specific reasons to modify position 309 of the PH20 polypeptide.

Accordingly, on the current record, we find that Petitioner has not shown that it is more likely than not to establish that the combination of the '429 patent and Chao with the knowledge and teaching described by Dr. Hecht and Dr. Park demonstrates that the challenged claims of the '618 patent would have been obvious.

XII. CONCLUSION

Petitioner has, at this stage of the proceedings, established that it will more likely than not prevail in showing that at least one of the challenged claims is unpatentable. This determination is, however, based on a preliminary record and is not final on any issues of patentability. We will make a final determination on the patentability of the challenged claims, as necessary and applying the preponderance of the evidence standard, based on a fully developed record through trial.

XIII. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 324(a) post grant review of claims 1, 2, 5, and 7–33 of the '618 patent is hereby *granted* on the grounds set forth in the Petition, commencing on the entry date of this Order, and

pursuant to 35 U.S.C. § 324(d) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial; and

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

For PETITIONER:

Jeffrey Kushan
Mark Stewart
SIDLEY AUSTIN LLP
jkushan@sidley.com
mark.stewart@merck.com

For PATENT OWNER:

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

Aubrey Haddach
Joshua Mack
HALOZYME, INC.
ahaddach@halozyme.com
jmack@halozyme.com

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