

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyme Inc.,
Patent Owner.

Case No. PGR2025-00053
U.S. Patent No. 12,195,773

PETITION FOR POST GRANT REVIEW

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35 U.S.C. § 1205

I. Introduction

Petitioner Merck Sharp & Dohme LLC (“Merck”) requests post grant review of U.S. Patent No. 12,195,773 (“’773 Patent”).

Claims 1-15 of the ’773 Patent claims are unpatentable for at least three independent reasons. The first two are linked to their extreme breadth. By claiming any human PH20 polypeptide that (i) *must have* one amino acid substitution at position 320, and (ii) *may have* up to 19 additional modifications at *any* of 446 other positions, they capture $\sim 10^{57}$ distinct polypeptides. The scale of these genera is unfathomable. The collective weight of one of each polypeptide in the smallest genus exceeds the weight of the Earth, and practicing its full scope requires many lifetimes of “making and testing” using the patent’s methodology.

These immensely broad claims, measured against the common disclosure of the ’773 Patent and its ultimate parent ’731 Application,¹ utterly fail the written description and enablement requirements of § 112(a), rendering each unpatentable. It also precludes the claims from a valid § 120 benefit to the ’731 Application, the only non-provisional application filed before March 16, 2013, thus making the ’773 Patent PGR eligible.

¹ 13/694,731 (’731 Application) (EX1026).

Regarding written description, the common disclosure makes no effort to identify (and never contends there is) a common structure shared by the $\sim 10^{57}$ **soluble**, multiply-modified human PH20 polypeptides being claimed, much less those that also are “active” or “inactive” mutants. The disclosed examples also are not representative. Each has only **one** amino acid substitution within **one** PH20₁₋₄₄₇ sequence, and none were tested for solubility, while the patent claims soluble human PH20 proteins with myriad **undescribed** combinations of 5, 10, 15, or 20 substitutions—one at position 320 and the rest anywhere in the PH20 sequence. The disclosure is nothing more than a research plan, lacking any blaze marks, and does not describe the claimed genera.

Regarding enablement, equally fatal problems exist: the disclosure identifies **no** soluble multiply-modified human PH20 polypeptides, much less affirmatively guides the selection of **which** combinations of 2 to 20 modifications yield soluble PH20 enzymes. As the common disclosure admits, determining if a modified PH20 polypeptide is soluble requires testing it. The only methods it describes for making multiply-modified PH20 polypeptides are prophetic, requiring iterative rounds of “trial-and-error discovery,” a methodology the Supreme Court found incapable of enabling much smaller genera of polypeptides.² Practicing the full

² *Amgen Inc. v. Sanofi*, 598 U.S. 594, 614 (2023).

scope of the claims requires skilled artisans to make and test $\sim 10^{57}$ distinct polypeptides. That is far more than undue experimentation—it is impossible.

Patentee's recent conduct with other members of '773 Patent family reflects even its recognition that the challenged claims are fatally defective. Each time Petitioner challenged comparable Halozyme patent claims requiring soluble modified PH20 polypeptides (or those with increased activity) on written description and non-enablement grounds, Patentee *statutorily disclaimed* those claims, rather than defended them.³

Claims 1-2 and 5-15 are also unpatentable because each captures at least one obvious single-substitution PH20₁₋₄₄₇ mutant—where aspartic acid (D) at position 320 is changed to lysine (K). Patentee's '429 Patent (EX1005) directed artisans to make single amino acid substitutions in the non-essential regions of PH20₁₋₄₄₇ (and expressly claimed them). Skilled artisans implementing that guidance in 2011 would have considered Chao (EX1006)—not considered during examination—and from those collective teachings and their knowledge, would have (i) identified position 320 as being in a non-essential region of PH20, (ii) found it obvious to make the D to K change at position 320, and (iii) reasonably expected this mutant

³ PGR2025-00003 (claims 5-7), PGR2025-00004 (claims 5-6), PGR2025-00006 (claims 5-7), PGR2025-00009 (claims 4-5, 15).

to be soluble and retain enzymatic activity. As Patentee stated in its '429 Patent: “[t]hose of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity”.⁴ As the claims capture this obvious mutant and compositions and methods of administering and manufacturing it, they are unpatentable.

The '773 Patent claims are unpatentable. The Board should institute trial.

II. Compliance with PGR Requirements

A. Certification of Standing

Petitioner certifies this Petition is filed within 9 months of the '773 Patent's issuance. Petitioner certifies it is not barred or estopped from requesting this PGR. Petitioner and its privies have not filed a civil action challenging the '773 Patent, while litigation involving it was commenced by Patentee less than one year from this date.

The '773 Patent is eligible for post-grant review because at least one of its claims is not entitled to an effective filing date prior to March 16, 2013.

A patent is PGR eligible if it issued from an application filed after March 16, 2013 “if the patent contains ... at least one claim that was not disclosed in compliance with the written description and enablement requirements of § 112(a)

⁴ EX1005, 16:17-22.

in the earlier application for which the benefit of an earlier filing date prior to March 16, 2013 was sought.” *Inguran, LLC v. Premium Genetics (UK) Ltd.*, PGR2015-00017, Paper 8, 16-17 (P.T.A.B. Dec. 22, 2015); *US Endodontics, LLC v. Gold Standard Instruments, LLC*, PGR2015-00019, Paper 17, 8 (P.T.A.B. Jan. 29, 2016); *Collegium Pharm., Inc. v. Purdue Pharma L.P.*, 2021 WL 6340198, *14-18 (P.T.A.B. Nov. 19, 2021); *Intex Recreation Corp. v. Team Worldwide Corp.*, 2020 WL 2071543, *26 (P.T.A.B. Apr. 29, 2020).

Only one of the applications to which the ’773 Patent claims benefit under 35 U.S.C. § 120 and/or § 121—U.S. Application No. 13/694,731 (the ’731 Application)—was filed before March 16, 2013. That application, issued as U.S. Patent No. 9,447,401 (EX1025), claims priority to two provisional applications (61/631,313, filed November 1, 2012 and 61/796,208, filed December 30, 2011) and WO 01/3087 (“WO087”). Relative to the provisional applications, the ’731 Application alters several passages, adds new examples and tested mutants and makes other changes.⁵

The ’731 Application (including subject matter incorporated by reference) does not provide written description support for and does not enable any claim of the ’773 Patent (§§ V.A, V.B). The same is true for the ’773 Patent, whose

⁵ EX1026, 153:15-163:26, 324-34, 19:25-26, 28; EX1051; EX1052.

disclosure relative to the claims is generally the same as the '731 Application.⁶

The '773 Patent is PGR eligible as at least one of its claims does not comply with § 112(a) based on the '731 Application filed before March 16, 2013.

B. Mandatory Notices

1. Real Party-in-Interest

Merck Sharp & Dohme LLC is the real party-in-interest for this Petition.

2. Related Proceedings

PGR2025-00003, PGR2025-00004, PGR2025-00006, PGR2025-00009, PGR2025-00017, PGR2025-00024, PGR2025-00030, PGR2025-00033, PGR2025-00039, PGR2025-00042, PGR2025-00046, and PGR2025-00050 are related proceedings.

On April 24, 2025, Patent Owner filed a complaint in *Halozyme, Inc. v. Merck Sharp & Dohme Corp.*, Case No. 2-25-cv-03179 (D.N.J.), alleging infringement of, *inter alia*, the '773 Patent.

⁶ The “common disclosure” refers to the shared disclosure of the '773 Patent and the '731 Application (EX1026). Citations are to the '773 Patent; EX1015 correlates citations to the '731 Application. The disclosures are highly similar but not identical. *See* EX1068, ¶ 6; *generally* EX1045.

3. Counsel and Service Information

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Petitioner consents to service via e-mail at the email addresses listed above.

III. Grounds

The grounds advanced in this Petition are:

- (a) Claims 1-15 are unpatentable under 35 U.S.C. § 112 as lacking adequate written description.
- (b) Claims 1-15 are unpatentable under 35 U.S.C. § 112 as not being enabled.
- (c) Claims 1-2 and 5-15 are unpatentable as obvious under 35 U.S.C. § 103 based on the '429 Patent (EX1005), Chao (EX1006), and knowledge held by a person of ordinary skill in the art.

Petitioner's grounds are supported by the evidence submitted with this Petition, including testimony from Dr. Michael Hecht (EX1003) and Dr. Sheldon Park (EX1004).

The full-length PH20 protein (SEQ ID NO: 6) includes a 35 amino acid signal sequence, yielding position numbers in mature forms of PH20 that differ

from SEQ ID NO: 6 by 35 residues.⁷ The annotation “PH20_{1-n}” refers to a sequence of 1-n residues in PH20 (*e.g.*, PH20₁₋₄₄₇ is SEQ ID NO: 3), and “AxxxB” is used to identify the position of a substitution (*e.g.*, “D320K”).

IV. Background on the '773 Patent

A. Field of the Patent

The '773 Patent concerns the human PH20 hyaluronidase enzyme and structurally altered, soluble forms of that protein that retain enzymatic activity.⁸

1. Protein Structures

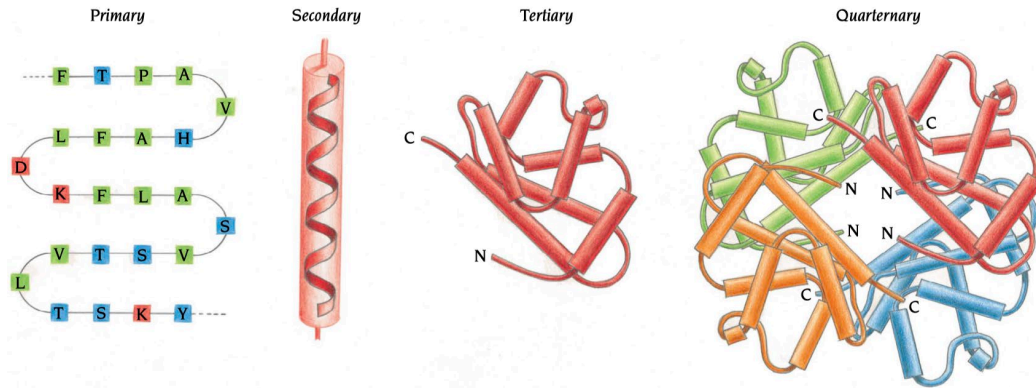
Proteins are comprised of sequences of amino acids. A protein's activity, however, derives from its unique, three-dimensional shape—its structure.⁹ That is dictated by specific and often characteristic patterns of amino acids in its sequence, which induce formation and maintenance of various secondary structures and structural motifs, which are packed into compact domains that define the protein's overall structure (tertiary structure).¹⁰

⁷ EX1003, ¶ 15, Appendix A-11.

⁸ EX1001, 2:50-53.

⁹ EX1003, ¶ 36.

¹⁰ EX1014, 3-4, 24-32, Figure 1.1; EX1039, 136-37 (Figure 3-11); EX1003, ¶¶ 36-40.



Secondary structures, such as α -helices or β -strands, are formed and stabilized by different but characteristic patterns of amino acids (below).¹¹

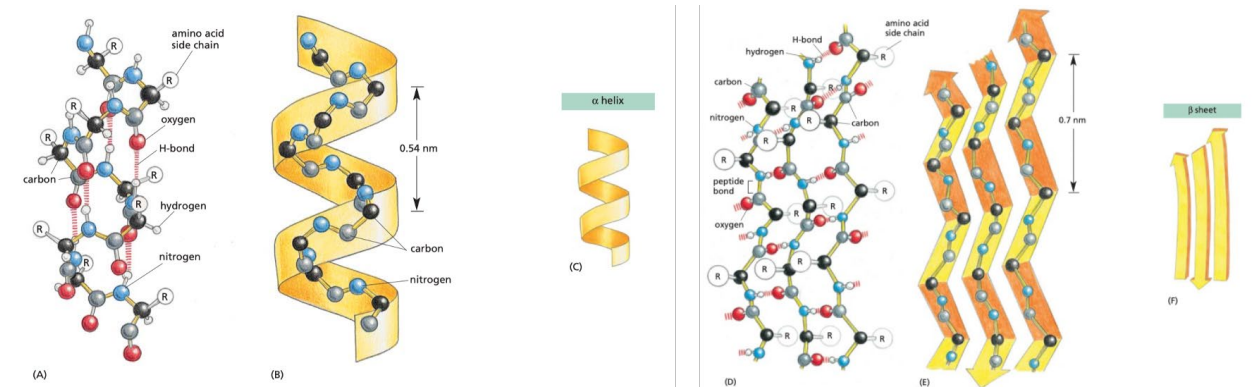


Figure 3-7 The regular conformation of the polypeptide backbone in the α helix and the β sheet. <GTAG> <TGCT> (A, B, and C) The α helix. The N-H of every peptide bond is hydrogen-bonded to the C=O of a neighboring peptide bond located four peptide bonds away in the same chain. Note that all of the N-H groups point up in this diagram and that all of the C=O groups point down (toward the C-terminus); this gives a polarity to the helix, with the C-terminus having a partial negative and the N-terminus a partial positive charge. (D, E, and F) The β sheet. In this example, adjacent peptide chains run in opposite (antiparallel) directions. Hydrogen-bonding between peptide bonds in different strands holds the individual polypeptide chains (strands) together in a β sheet, and the amino acid side chains in each strand alternately project above and below the plane of the sheet. (A) and (D) show all the atoms in the polypeptide backbone, but the amino acid side chains are truncated and denoted by R. In contrast, (B) and (E) show the backbone atoms only, while (C) and (F) display the shorthand symbols that are used to represent the α helix and the β sheet in ribbon drawings of proteins (see Panel 3-2B).

¹¹ EX1039, 134; EX1014, 14-22, Figures 2.2, 2.5, Table 2.1; EX1047, 2031-32; EX1003, ¶¶ 40-43.

Intervening sequences between those characteristic sequences are important too; they direct and facilitate positioning and arrangement of the various secondary structures into structural motifs and the protein's tertiary structure.¹²

Changes to a protein's amino acid sequence can affect the folding, formation and stability of these various structures that define the protein's overall shape. For example, changing even a single residue known to be critical to the protein's structure or activity can render a protein inactive.¹³

Making many concurrent changes to a protein's sequence can cause myriad effects on the protein's structure, especially when they are in or affect the same region(s) of the protein.¹⁴ For example, they can disrupt the characteristic patterns, spacing and/or types of amino acids required to induce formation and stability of secondary structures, and disrupt folding and positioning of the secondary structures and structural motifs into the protein's tertiary structure.¹⁵ Multiple changes in different regions of the amino acid sequence also cause unfavorable

¹² EX1003, ¶¶ 44-46; EX1014, 21-22.

¹³ EX1003, ¶¶ 54, 170; EX1004, ¶¶ 20, 25.

¹⁴ EX1003, ¶ 178.

¹⁵ EX1003, ¶¶ 55-56, 164; EX1047, 6349; EX1046, 2034; *see also* EX1040, 14412-13; EX1041, 21149-50; EX1042, 1-3.

spatial interactions that destabilize or impair folding.¹⁶ Consequently, predicting the effects of the myriad interactions that may be disrupted by multiple concurrent substitutions was beyond the capacity of skilled artisans and available computational tools.¹⁷

2. Hyaluronidase Enzymes

PH20 enzymes are structurally similar and evolutionarily related to a class of enzymes (hyaluronidases) found in many species.¹⁸ PH20 breaks down hyaluronan (“HA”) by selectively hydrolyzing glycosidic linkages.¹⁹ In humans, PH20 exists naturally as a GPI anchored protein; deletion of its GPI-anchoring sequence yields a soluble, neutral active enzyme.²⁰

¹⁶ EX1003, ¶¶ 57-59.

¹⁷ EX1003, ¶¶ 50, 178, 213, 253; EX1004, ¶¶ 155-157.

¹⁸ EX1007, 10:18-30; EX1006, 6911, 6916 (Figure 3); EX1003, ¶¶ 33, 78.

¹⁹ EX1003, ¶ 78; EX1008, 819.

²⁰ EX1005, 2:40-61, 87:52-88:24; EX1013, 430-32, Figure 2; EX1003, ¶¶ 93, 221; EX1029, 546, Figure 1.

Many essential residues in PH20 and similar hyaluronidases had been identified before 2011. Several are in the shared catalytic site of the protein;²¹ mutating individual residues in or near that site can abolish enzymatic activity.²² Conserved cysteine residues that stabilize the protein structure are also essential,²³ as are certain conserved asparagine residues involved in glycosylation.²⁴

In 2007, Chao reported an experimentally determined structure of the human HYAL1 hyaluronidase, and used an alignment of the five human hyaluronidases to illustrate shared secondary structures and conserved residues in these proteins.²⁵ Among its findings was that human hyaluronidases contain a unique structure—the Hyal-EGF domain—which prior modeling studies had incorrectly characterized.²⁶

²¹ EX1006, 6914-16, Figure 3; EX1007, 35:28-36:10; EX1011, 810-14; EX1008, 824-25; EX1009, 6912-17.

²² EX1011, 812-14; EX1010, 9435-39, Table 1.

²³ EX1006, 6914-16, Figure 3; EX1011, 810-11; EX1005, 88:21-22.

²⁴ EX1005, 7:9-27; EX1007, 36:12-20; EX1010, 9433, 9435-40.

²⁵ EX1006, 6914-18.

²⁶ EX1006, 6912-13 (“The HyalEGF-like fold does not resemble the Hyal-1 C-terminal domain fold predicted by *ab initio* approaches”), 6916-18; EX1010, 9439-40; EX1003, ¶¶ 85-89; EX1004, ¶¶ 97-99.

Chao also identified essential residues, including those in the catalytic site that interact with HA, using its experimentally-determined structure, its sequence analysis and an earlier structure of the bee venom hyaluronidase.²⁷

3. Protein Engineering

There are two general approaches used to engineer changes into proteins.²⁸ In “rational design,” skilled artisans employed computational tools—sequence alignments and protein structure models—to study the protein and then select where and what changes to introduce.²⁹ For example, a “multiple-sequence alignment” (“MSA”)³⁰ produced by aligning known sequences of homologous, naturally occurring proteins identifies positions with no or little amino acid variation (“conserved” / “essential” residues) and positions where different amino

²⁷ EX1006, 6912-13, 6916-18, Figures 2C, 4A; EX1033, 1028-29, 1035; EX1010, 9434, 9436, Figure 1.

²⁸ EX1003, ¶ 47.

²⁹ EX1016, 181-82; EX1017, 223, 236; EX1003, ¶¶ 48-50.

³⁰ EX1017, 224-27; EX1016, 181-86 (Figure 1); EX1003, ¶¶ 49-50; EX1004, ¶¶ 22-23, 29.

acids occur (“non-conserved” / “non-essential” residues).³¹ A structural model using the protein’s sequence but based on experimentally determined structures of homologous proteins enabled assessment of interactions between amino acids at a particular positions.³²

Using rational design techniques, a skilled artisan could assess, with varying effort, effects of changing one or a few amino acids, but could not use those techniques to predict the effects of many concurrent changes, given the escalating complexity of numerous, interrelated interactions (which exponentially increase with the number of changes) and the limits of protein modeling tools.³³ Accurate computational prediction of a protein’s structure from its amino acid sequence was not possible until around 2020 (below).³⁴

³¹ EX1003, ¶¶ 238-39; EX1004, ¶¶ 21-22, 25, 30-31; EX1016, 181-84; EX1017, 224-25; EX1014, 351.

³² EX1017, 228-30; EX1031, 461, 463, 469-71; EX1014, 351-52; EX1032, 265-66; EX1004, ¶ 37; *also id.* 33-36; EX1003, ¶¶ 249-51.

³³ EX1003, ¶¶ 50, 180; EX1004, ¶¶ 155-157.

³⁴ EX1024, 6-10; EX1003, ¶ 178.

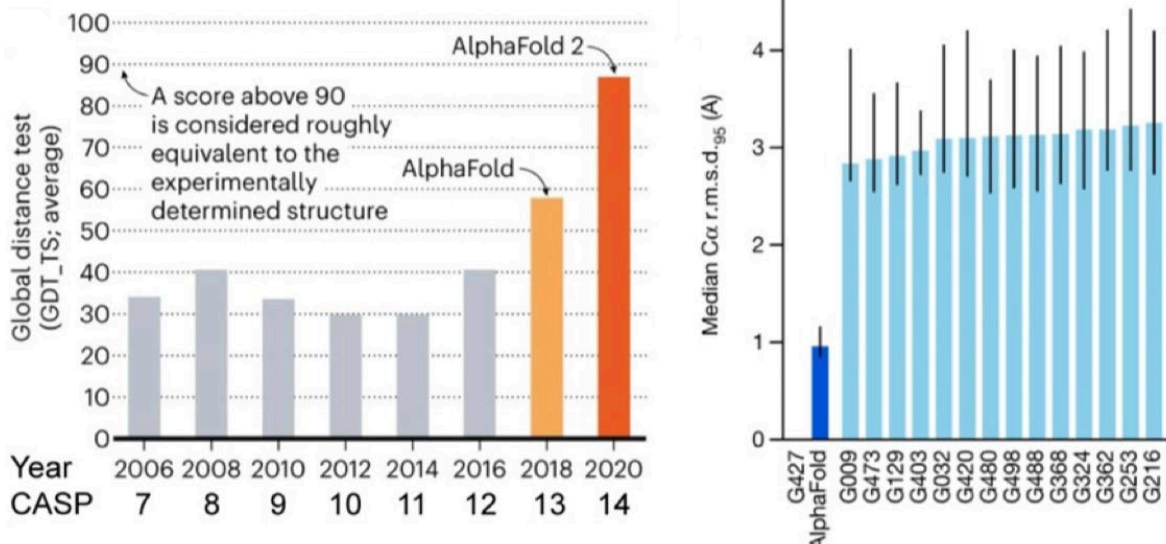


Figure 6. Left: progress of the CASP performance over the years for the best models and the most difficult targets.³⁸ Right: performance of AlphaFold2 relative to the top 15 entries by other groups in CASP14. Data are the median coordinate error and the 95% confidence interval of the median, estimated from 10 000 bootstrap samples.⁴¹

“Directed evolution” techniques arose due to the limits of rational design.³⁵ They use “trial-and-error” experiments to find mutants with randomly distributed changes that exhibit desired properties, but require creation and screening of large libraries of mutants, each with one amino acid randomly changed at one position in its sequence.³⁶ Importantly, until a desired mutant is made, found, and tested, whether it exists and its sequence and properties are unknown.³⁷ Sophisticated assays that rapidly and precisely identify mutants with desired properties are

³⁵ EX1003, ¶ 51; EX1059, 1225-26; EX1018, 378.

³⁶ EX1003, ¶ 51; EX1059, 1225-26; EX1018, 378.

³⁷ EX1003, ¶ 206.

critical, given the scale of experimentation this approach requires.³⁸ The '773 Patent embodies this approach.³⁹

B. Person of Ordinary Skill in the Art

While the '773 Patent claims priority to provisional applications dating to December 30, 2011 and benefit to the '731 Application (filed December 28, 2012), they are not supported as § 112(a) requires by those earlier-filed applications. *See* §§ II.A, V.A, V.B. Regardless, the obviousness grounds rely on prior art published before and knowledge/perspectives of a skilled artisan before December 2011.

In 2011, a person 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

³⁸ EX1003, ¶¶ 52-53.

³⁹ EX1003, ¶¶ 165, 195, 205, 211.

protein structure (*i.e.*, sequence searching and alignments, protein modeling software, etc.).⁴⁰

C. Prosecution History

During examination of the '773 Patent, rejections for ineligible subject matter, anticipation, double patenting, improper dependency were imposed not relevant to the grounds, which were overcome by claim amendments, cancellation of claims, and terminal disclaimers.⁴¹ Indefiniteness and written description rejections also were imposed—because those implicate construction of the claims, they are addressed in § IV.D.2,

D. The Challenged Claims

The claim terms are either expressly defined in the common disclosure or are used with their common and ordinary meaning. However, a clear understanding of the requirements imposed by those definitions and of the claim breadth is necessary, as it shows that each captures massive genera of structurally distinct soluble human PH20 polypeptides neither adequately described in nor enabled by the common disclosure of the '731 Application and the '773 Patent.

⁴⁰ EX1003, ¶ 13.

⁴¹ EX1002, 528-543, 550-553, 556-557, 651-655, 664-665.

1. “Soluble Human PH20 Polypeptide”

Claim 1 requires a “soluble human PH20 polypeptide,” which the common disclosure defines as follows:

As used herein, soluble human PH20 (sHuPH20) includes human PH20 polypeptides that lack a contiguous sequence of amino acids from the C-terminus of human PH20 that includes all or a portion of the glycosylphosphatidylinositol (GPI) anchor sequence (C-terminally truncated PH2 polypeptides) such that upon expression, the polypeptides are soluble under physiological conditions.⁴²

As defined, there are three attributes of “sHuPH20” polypeptides.

First, they have a human PH20 sequence (*e.g.*, SEQ ID NO: 7).

Second, it “lacks a contiguous sequence of amino acids that includes all or a portion of the [GPI] anchor sequence,” which the common disclosure identifies as “ATMFIVSILFLIISVAS” (positions 456 to 474 of SEQ ID NO:7), and a GPI

⁴² EX1001, 45:24-35 (emphasis added).

anchor residue at 455.⁴³ A soluble wild-type human PH20 may—but does not necessarily—result if it terminates between positions 455 and 473.⁴⁴

Third, “a soluble PH20 refers to a polypeptide characterized by its solubility under physiological conditions.”⁴⁵ “Solubility” with reference to proteins is expressly defined:

As used herein, “solubility” with reference to a protein refers to a protein that *is homogenous in an aqueous solution*, whereby protein molecules diffuse and do not sediment spontaneously. Hence a soluble protein solution is one in which there is an absence of a visible or discrete particle in a solution containing the protein, such that the particles cannot be easily filtered. Generally, a protein is soluble if there are no visible or discrete particles in the solution.⁴⁶

⁴³ EX1001, 70:55-62 (“...a GPI-anchor attachment signal sequence of human PH20 is located at amino acid positions 491-509 of the precursor polypeptide set forth in SEQ ID NO:6, and the ω -site is amino acid position 490.”);

EX1003, ¶¶ 130-131.

⁴⁴ EX1003, ¶ 132.

⁴⁵ EX1001, 44:62-64.

⁴⁶ EX1001, 49:23-30.

Particles are insoluble aggregates of a protein that form when the normal structure of the protein is disrupted (*e.g.*, by mutations, environmental conditions, etc.), thereby causing hydrophobic patches within the protein to become exposed to the aqueous environment that induce strong but non-specific interactions with other hydrophobic patches in the same or other proteins.⁴⁷

Thus, per the common disclosure's definitions, a "soluble human PH20 polypeptide" is "a human PH20 polypeptide that (i) omits all or part of the C-terminal sequence 456-474 of SEQ ID NO:7, and (ii) is homogenous in an aqueous solution at physiological conditions."⁴⁸

2. The Claims Encompass Soluble Human PH20 Polypeptides with Up to 20 Changes in SEQ ID NO:3

The claims define an incredibly broad and diverse genus of modified "soluble human PH20 polypeptides."

Claim 1 defines the genus as containing "soluble human PH20 polypeptides" that:

⁴⁷ EX1001, 49:33-40 ("aggregation ... refers to the presence of visible or discrete particles in solution containing the protein"), 180:27-29; EX1003, ¶¶ 39, 152; EX1014, 99, 117 ("Unfolded proteins with exposed hydrophobic patches aggregate easily by non-specific hydrophobic interactions.").

⁴⁸ EX1003, ¶ 135.

- **must** contain **one** amino acid replacement at position 320 (*i.e.*, from D to any of H, K, and R); and
- **may** contain up to 19 **additional** modifications after alignment with SEQ ID NO: 3 to maximize the number of identical residues.

Certain dependent claims restrict these parameters:

- (i) claim 2 requires the position 320 substitution to be K, and
- (ii) claims 3-4 require the soluble human PH20 polypeptide to exhibit increased hyaluronidase activity.

Claims 5-7 specify a nucleic acid encoding the soluble human PH20 polypeptides of claim 1, a recombinant expression vector for expressing that nucleic acid, or a host cell comprising the recombinant expression vector, while claims 8-15 define pharmaceutical compositions or methods of administering or manufacturing the soluble human PH20 polypeptides of claim 1.

The common disclosure explains that “modifications” are “deletions, insertions and replacements of amino acids.”⁴⁹ They are identified as differences between sequences that have been aligned using standard alignment programs. An alignment identifies positions in the sequences where there are non-identical amino acids, are gaps or added amino acids, with the total number of differences

⁴⁹ EX1001, 46:12-16, 59:15-23.

determining the overall degree of sequence identity.⁵⁰ Further, “differences can be represented as point mutations randomly distributed over the entire length of an amino acid sequence” and that “[d]ifferences are defined as [] amino acid substitutions, insertions or deletions.”⁵¹ Also, “amino acids selected to replace the target positions on the particular protein being optimized can be either all of the remaining 19 amino acids, or a more restricted group containing only selected amino acids.”⁵² Except for position 320, no language in the claims restricts what *type* of modification is made (replacement, addition or deletion), *where* they can occur within the modified PH20 sequence, or *which* of 19 other amino acids can be substituted or added at those positions.

A skilled artisan would have understood from the claim language, the common disclosure and the prosecution history that the phrase “19 or less additional amino acid modifications, after alignment with SEQ ID NO:3” in claim 1 limits the soluble human PH20 polypeptides being claimed to those with up to 20 total modifications relative to SEQ ID NO:3.⁵³ Indeed, the phrase “19 or less

⁵⁰ EX1001, 57:45-67, 58:37-39, 59:3-14; *see also id.* at 57:48-58:28.

⁵¹ EX1001, 59:15-23; *see also id.* at 3:36-37, 46:12-16, 25-27.

⁵² EX1001, 136:41-48; *see also id.* at 141:66-142:1.

⁵³ EX1003, ¶¶ 128-129.

additional amino acid modifications” would become meaningless if the claim was read as allowing 19 modifications in *any* PH20 sequence. That is because differences in length relative to an aligned sequence are “modifications” (insertions or deletions), and not defining which reference sequences the “19 or less modifications” language is applied to would make it impossible to know whether any particular modified PH20 polypeptide meets the claim requirements.

The prosecution history supports this reading. Patentee introduced the phrase “19 or less additional amino acid modifications, after alignment with SEQ ID NO:3” language to overcome an indefiniteness rejection, arguing that it meant “[t]he claim, thus, is limited to no more than 19 modifications.”⁵⁴ The Examiner then rejected pending dependent claims reciting other sequence identifiers for PH20s of different lengths (e.g., “a C-terminally truncated polypeptide of SEQ ID NO: 7, 10, ...”), stating those were “inconsistent with” requiring “19 or less amino acid modifications, after alignment with SEQ ID NO: 3” because each of the other sequences “may have more than 19 additional modifications relative to SEQ ID NO: 3.”⁵⁵ Patentee cancelled those dependent claims to secure allowance.⁵⁶

⁵⁴ EX1002, 520-523, 554.

⁵⁵ EX1002, 654-55; *also id.* at 551-553, 653-657.

⁵⁶ EX1002, 663-665, 773.

The claim parameters capture an immense number of distinct modified PH20 polypeptides having up to 20 total changes relative to SEQ ID NO:3 including one substitution at position 320 to 1 or 3 alternatives (below):⁵⁷

Claims	Length of PH20 Polypeptide	# of Total Changes	Pos. 320 Choices	# of Distinct Polypeptides
1, 3-15	447	20	3	7.2×10^{57}
2	447	20	1	2.4×10^{57}

Claims 1-15 also claim one specific soluble human PH20₁₋₄₄₇ polypeptide that replaces one amino acid (D320) in SEQ ID NO: 3 with lysine (K) (“D320K”).⁵⁸

3. Modified “Soluble Human PH20 Polypeptides” That Are “Active Mutants” Are Being Claimed

The specification describes two mutually exclusive categories of “modified PH20 polypeptides” with (alleged) utility: “active mutants” vs. “inactive mutants.”

- “*Active mutants*” are modified PH20 polypeptides that “exhibit at least 40% of the hyaluronidase activity of the corresponding PH20

⁵⁷ EX1003, ¶¶ 140, 142; EX1004, ¶¶ 163-164.

⁵⁸ EX1003, ¶ 159.

polypeptide not containing the amino acid modification (e.g., amino acid replacement).”⁵⁹

- “*Inactive mutants*” are modified PH20 polypeptides that “generally exhibit less than 20% ... of the hyaluronidase activity of a wildtype or reference PH20 polypeptide, such as the polypeptide set forth in SEQ ID NO: 3 or 7.”⁶⁰

Mutants are classified into tables of “active” or “inactive” mutants using the >40% (Tables 3 and 9) or <20% (Tables 5 and 10) thresholds.⁶¹

The claimed “soluble human PH20 polypeptides” are “modified PH20 polypeptides” because each is “a PH20 polypeptide that contains at least one amino acid modification, such as at least one amino acid replacement ... in its

⁵⁹ EX1001, 74:1-6; *see also id.* at 77:54-58 (“active mutants” “can exhibit 40% to 5000% of the hyaluronidase activity of a wildtype or reference PH20 polypeptide ...”); *id.* at 77:50-54.

⁶⁰ EX1001, 118:30-40. *See also id.* at 255:52-57 (mutants with <20% activity “were rescreened to confirm that the dead mutants are inactive” in Table 10).

⁶¹ EX1001, 79:18-80:22, 233:22-24, 118:49-120:3, 256:64-67 (“reconfirmed inactive mutants are set forth in Table 10.”); EX1003 ¶¶ 102, 104-105, 118.

sequence of amino acids compared to a reference unmodified PH20 polypeptide” (*i.e.*, at least a position 320 substitution).⁶²

The common disclosure reports no examples of an “active mutant” modified PH20 with two or more replacements.⁶³ It also reports no examples of an enzymatically active PH20₁₋₄₄₇ that combines within it: (i) a mutation that preserved activity in Tables 3 and 9 (“active mutants”) *plus* (ii) a second mutation that eliminated activity in Tables 5 and 10 (“inactive mutants”).

The specification portrays “active” and “inactive” mutants as having distinct utilities requiring mutually exclusive properties. “Active mutants” are portrayed as being therapeutically useful *because they possess hyaluronidase activity*.⁶⁴ The only identified utility alleged for “inactive mutants” (which lack hyaluronidase activity) is “as antigens in contraception vaccines,” which, is implausible.⁶⁵ *See*

⁶² EX1001, 47:7-12.

⁶³ *E.g.*, EX1003, ¶¶ 160-161, 163, 166.

⁶⁴ EX1001, 181:14-20; *see also id.* at 2:57-3:3, 71:53-67, 181:14-194:49; EX1003, ¶ 119.

⁶⁵ EX1001, 71:13-15; *see also id.* at 70:64-71:67, 74:10-12, 194:49-195:6 (for “contraception” “the modified PH20 polypeptides can be inactive enzymes, such as any described in Sections C.2.”); EX1003, ¶ 120-123.

§ V.B.2. “Active mutants” also are not portrayed as having contraceptive utility; they are used *in combination* with contraceptive agents.⁶⁶

The claim language reinforces that each claims soluble human PH20 polypeptides that are “active mutants” and meet the claim parameters.

First, each claim requires soluble human PH20 polypeptides having one of three replacements at position 320 that yielded an “active mutant” as a single-replacement PH20₁₋₄₄₇ polypeptide (*i.e.*, D320H, D320K, or D320R) (below).⁶⁷

TABLE 9-continued

ACTIVE MUTANTS		
mutant	SEQ ID NO	AvgNorm Act.
D320E		0.78
D320G		0.83
→ D320H	618	1.75
D320I		1.00
→ D320K	619	6.42
D320M		0.79
D320N		0.52
→ D320R	620	3.19
D320S		1.19
D320W		0.40
D320V		0.35
D320Y		0.86
D320L		0.37

EX1001, 237-238

Second, claims 3-4 restrict the genus of soluble human PH20 polypeptides being claimed in claim 1 to those that with *increased* hyaluronidase activity or at

⁶⁶ EX1001, 157:10-23; EX1060, 1711.

⁶⁷ EX1001, 85 (Table 3), 237-238 (Table 9), 100:19-31; EX1003, ¶¶ 146-148.

least 120% of hyaluronidase activity of the SEQ ID NO: 3 unmodified PH20, thus narrowing the genus of “active mutants” of claim 1.

Third, claims 9-14 define pharmaceutical compositions and methods of administration that require use of PH20 polypeptides with hyaluronidase activity: each claim specifies compositions “further comprising a therapeutically active agent.” The common disclosure explains such combinations enhance delivery of the other agent, which requires use of an *active* PH20 polypeptide.⁶⁸

The specification reinforces that the claims are limited to (or at least encompass) “active mutants.”

First, the specification defines a “PH20” as a “type of hyaluronidase that occurs in sperm and is neutral-active,”⁶⁹ which means it has “the ability to ... enzymatically catalyze the cleavage of hyaluronic acid at neutral pH” (i.e., 6.0-7.8).⁷⁰ Then, it explains that such starting “neutral-active” PH20 polypeptides are modified to “contain[] at least one amino acid modification” and can “have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide

⁶⁸ EX1001, 181:14-30, 182:18-41, 32:14-15, 37:62-65, 3:8-14.

⁶⁹ EX1001, 44:25-26; *see also id.* at 44:28-54.

⁷⁰ EX1001, 49:8-11.

exhibits hyaluronidase activity.”⁷¹ This aligns with the specification’s prophetic methodology for discovering multiply-modified PH20 polypeptides by selecting “active mutants” with one substitution, randomly introducing another, and screening to find “double mutants” that *retained* hyaluronidase activity.⁷²

Likewise, the claims require one substitution that yields an “active mutant” and permit others. By specifying the soluble human PH20 has a first substitution that retains activity, and then permits up to 19 additional modifications to that “active” single substitution mutant, the claims and common disclosure convey to the skilled artisan that the claimed soluble human PH20 polypeptides include those that are enzymatically active.⁷³

Second, the common disclosure explains that when producing *soluble* human PH20 polypeptides, modifications are made to *preserve* their enzymatic activity:

Exemplary soluble PH20 polypeptides are C-terminal truncated human PH20 polypeptides that are mature (lacking a signal sequence), soluble and *exhibit neutral activity*, ... For example,

⁷¹ EX1001, 47:7-22; *see also id.* at 3:30-50, 4:1-12, 46:30-34, 72:60-73:30, 74:27-30, 75:23-30, 80:4-22; EX1003, ¶ 149.

⁷² EX1001, 141:33-44; *see also id.* at 41:17-24.

⁷³ EX1003, ¶¶ 148-149.

soluble PH20 polypeptides ... includes a sequence of amino acids that has at least 85%, ... sequence identity to a contiguous sequence of amino acids that has a C-terminal amino acid residue after amino acid 464 of SEQ ID NO:6 and *retains hyaluronidase activity*.⁷⁴

By contrast, it neither describes nor contemplates producing “soluble” PH20 polypeptides that are modified to make them inactive.

Patentee may contend claims 1-2 and 5-15 should be read as encompassing soluble forms of both “active” and “inactive” mutants. Reading the claims in that manner only exacerbates the § 112 problems, as the common disclosure would not only have to describe and enable the full sub-genus of “active mutants” in claim 1 (including increased activity mutants per claims 3-4) but the *additional* sub-genus of “inactive” mutants (and demonstrate credible utility for the latter), for which no procedures of production are described.

V. All Challenged Claims Are Unpatentable Under § 112 and None Are Entitled to Benefit to Any Pre-March 13, 2013 Application

Claims 1-15 are unpatentable because each lacks written description in and was not enabled by the common disclosure of the '773 Patent and the '731 Application in 2011.

⁷⁴ EX1001, 72:60-73:8 (emphases added); *also id.* at 45:12-16, 72:30-46; EX1003, ¶ 150.

Per § IV.D.2, the claim language defines enormous genera: approximately 10^{57} distinct polypeptides. Their real-world scope is absurd—simply producing one molecule of each mutant (required to know if each is soluble, and is an active or inactive mutant) would consume an aggregate mass ($\sim 2 \times 10^{35}$ kg) that exceeds the mass of Earth ($\sim 6 \times 10^{24}$ kg).⁷⁵ Testing each is impossible—literally.

Relative to that broad scope, the '773 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. It nowhere demonstrates possession of the vast majority of the claimed soluble PH20 polypeptides (*i.e.*, the multiply-modified ones) nor does it enable a skilled artisan to practice that full-scope without undue experimentation. And instead of defending comparable “soluble” and “increased activity” claims in related patents Merck challenged, Patentee *statutorily disclaimed* them.⁷⁶

Finally, should Patentee contend the claims include in their scope modified PH20 polypeptides that incorporate more than 20 modifications relative to SEQ ID

⁷⁵ EX1003, ¶¶ 143, 213; *see also, e.g.*, EX1039, 136-37 (10^{390} forms of a polypeptide possible from 300 residue sequence).

⁷⁶ PGR2025-00003 (claims 5-7), PGR2025-00004 (claims 5-6), PGR2025-00006 (claims 5-7), PGR2025-00009 (claims 3-5, 15).

NO:3, that would render the claims indefinite and unpatentable under § 112(b), as it would vitiate the “19 or less modifications” language added to define the boundaries of the claims.

A. All Claims Lack Written Description

The written description analysis focuses on the four corners of the patent disclosure.⁷⁷ “To fulfill the written description requirement, a patent owner must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and demonstrate that by disclosure in the specification of the patent.”⁷⁸

If the claims define a genus, the written description must “show that one has truly invented a genus . . .,” “[o]therwise, one has only a research plan, leaving it to others to explore the unknown contours of the claimed genus.”⁷⁹ “[A] genus can be sufficiently disclosed by either a representative number of species falling within

⁷⁷ *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*).

⁷⁸ *Idenix Pharm., LLC v. Gilead Scis., Inc.*, 941 F.3d 1149, 1163 (Fed. Cir. 2019) (internal quotation marks omitted).

⁷⁹ *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300 (Fed. Cir. 2014).

the scope of the genus or structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus.”⁸⁰ Also, the species in the claimed genus must share a common quality or attribute.⁸¹

Claims to genera of chemical compounds require “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.”⁸² “[M]erely drawing a fence around the outer limits of a purported genus” does not “demonstrate[] that the applicant has an invented species sufficient to support a claim to a genus...”⁸³ As the Federal Circuit has explained:

... just because a moiety is listed as one possible choice for one position does not mean there is *ipsis verbis* support for every species or sub-genus that chooses that moiety. Were this the case, a “laundry list” disclosure of every possible moiety for every possible position would constitute a written description of every species in the genus. This cannot be because such a disclosure

⁸⁰ *Idenix*, 941 F.3d at 1164.

⁸¹ *Corona Cord Tire Co., v. Dovan Chemical Corp.*, 276 U.S. 358, 385 (1928), citing *Incalescent Lamp Patent*, 159 U.S. 465, 475 (1895).

⁸² *Ariad*, 598 F.3d at 1350.

⁸³ *Ariad*, 598 F.3d at 1349-1350.

would not “reasonably lead” those skilled in the art to any particular species.⁸⁴

This is true for any genus of chemical compounds, although broad genus claims defined with “functional language” create an “especially acute” problem.⁸⁵

“One factor in considering [written description] is how large a genus is involved and what species of the genus are described in the patent ... [I]f the disclosed species only abide in a corner of the genus, one has not described the genus sufficiently to show that the inventor invented, or had possession, of the genus.”⁸⁶ A disclosure that fails to “provide sufficient blaze marks to direct a POSA to the specific subset” of a genus with the claimed function or characteristic does not satisfy § 112(a).⁸⁷

⁸⁴ *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571 (Fed. Cir. 1996); *accord Regents of Univ. of Minn. v. Gilead Sciences., Inc.*, 61 F. 4th 1350, 1357 (Fed. Cir. 2023).

⁸⁵ *Ariad*, 598 F.3d at 1349.

⁸⁶ *AbbVie*, 759 F.3d at 1299-1300.

⁸⁷ *Idenix*, 941 F.3d at 1164.

Claims defining immense numbers of compounds using sequence identity or comparable parameters are routinely found to lack sufficient written description by disclosures that exemplify only a tiny fraction of the claimed genera.

- In *AbbVie*, 300 examples of IL-12 antibodies were found insufficient because “[a]lthough the number of the described species appears high quantitatively, the described species are all of the similar type and do not qualitatively represent other types of antibodies encompassed by the genus.”⁸⁸
- In *Idenix*, method of treatment claims using broad genera of compounds that captured “more than 7,000 unique configurations” were found unpatentable because the disclosure did not indicate which of the thousands of compounds would be effective.⁸⁹
- In *Boehringer*, claims employing “90% sequence homology” were found to capture a “broad genus of amino acid sequence homologues” but imposed no restrictions where particular replacements could be made, thereby causing the claim “to cover, at minimum, thousands of

⁸⁸ *AbbVie*, 59 F.3d at 1300-1301.

⁸⁹ *Idenix*, 941 F.3d at 1158-64.

amino acid sequences.”⁹⁰ The specification’s failure to “explain what, if any, structural features exist (*e.g.*, remain) in sequences that vary by as much as 10% that allow them to retain the antigenic characteristics referenced in the Specification” rendered them unpatentable (*i.e.*, the same property that would be required of “inactive mutant” modified PH20 polypeptides to function as antigens in the contraceptive vaccines contemplated by the disclosure).⁹¹

The deficiencies shared by these disclosures was the absence of legitimate descriptions of chemical compounds (species) demonstrating possession of the diverse genera being claimed.

Novozymes also rejects the proposition that written description is established if one can perform experiments that might discover additional species:

Novozymes nonetheless maintains that one of ordinary skill in the art directed to position 239 would have known how to test every possible variant at that position and thus would have found the claimed variants as a matter of course. That argument misses the point, however. The question before us is not whether one of ordinary skill in the art presented with the 2000 application would have been enabled to take those final steps, but whether the 2000

⁹⁰ *Boehringer*, at 16. The claims included methods of using proteins. *Id.* at 6.

⁹¹ *Boehringer*, at 35; EX1001, 71:13-15, 194:51-195:2.

application “discloses the [variants] to him, specifically, as something appellants actually invented.”⁹²

As the Court concluded:

In this case, to actually possess the variant enzymes claimed in the '23 patent would have required Novozymes to confirm its predictions by actually making and testing individual variants or at least identifying subclasses of variants that could be expected to possess the claimed properties, which it did not do before filing the 2000 application. At best, the 2000 application describes a roadmap for producing candidate alpha-amylase variants and then determining which might exhibit enhanced thermostability. A patent, however, “is not a reward for the search, but compensation for its successful conclusion.” *Ariad*, 598 F.3d at 1353 (quoting *University of Rochester*, 358 F.3d at 930 n. 10). For that reason, the written description requirement prohibits a patentee from “leaving it to the ... industry to complete an unfinished invention.”⁹³

Finally, written description deficiencies cannot be remedied by contending that subject matter not described would have been obvious from the disclosure.⁹⁴

⁹² *Novozymes*, 723 F.3d at 1350 (citation omitted).

⁹³ *Novozymes*, 723 F.3d at 1350 (quoting *Ariad*, 598 F.3d at 1353).

⁹⁴ *Lockwood v. Am. Airlines, Inc.*, 107 F. 3d 1565, 1571-72 (Fed. Cir. 1997).

1. Claims 1-2 Lack Written Description

The deficiencies of the present claims dwarf those in the cases discussed above—they capture much larger, much less predictable, and much more diverse genera, and the common disclosure is far more limited. Because the common disclosure neither discloses a representative number of species, nor identifies sufficient structural features common to the members of each claimed genus, it fails to demonstrate possession of the genera of soluble human PH20 polypeptides being claimed in the '773 Patent.

(a) The Claims Capture Massive and Diverse Genera of Soluble Human PH20 Polypeptides

As explained in § IV.D.2, the species of modified soluble human PH20 polypeptides being claimed are not only immense in number, but structurally and functionally diverse. They include mutants with myriad combinations of optional modifications be anywhere in the sequence (*i.e.*, clustered in a narrow region, spaced apart in groups, or spread randomly throughout the sequence), with replacements being to any of 19 other amino acids.⁹⁵ They capture mutants with 5 substituted hydrophobic or charged residues clustered in a small region or ones

⁹⁵ EX1003, ¶¶ 127-129; EX1001, 59:15-22, 46:12-16, 46:25-27, 40:39-45.

with 20 substitutions randomly mixing polar, charged, aliphatic, and aromatic residues any order.⁹⁶

These myriad changes can induce significant changes to protein structure: altering secondary structures, structural motifs, and higher order structures, and disrupting folding, which can eliminate structures necessary for catalytic activity, ligand binding, domain structures (*e.g.*, HyalEGF), or the overall structure of the protein.⁹⁷ Any of these structural disruptions in the modified PH20 polypeptide can expose hydrophobic patches in to the aqueous environment, causing aggregation and rendering the protein insoluble.⁹⁸

⁹⁶ EX1003, ¶ 127.

⁹⁷ EX1003, ¶¶ 55-60, 161, 164, 176.

⁹⁸ EX1003, ¶¶ 39, 115, 152; EX1001, 108:43-46 (human PH20 “rapidly loses activity... due to unfolding of the protein and subsequent aggregate formation”), 108:62-109:5 (human PH20 may unfold in the presence of hydrophobic compounds, which “perturb[] the structural integrity” of the protein and “translates to a significant loss of rHuPH20 enzymatic activity”), 141:53-63 (“residues that are associated with activity and/or stability of the molecule generally are critical residues that are involved in the structural

(b) *Soluble Human PH20 Polypeptides within the Immense Genera Being Claimed Are Not Described*

Within the vast genera of $\sim 10^{57}$ human PH20 polypeptides being claimed are an unknown number that are soluble. Solubility is not a characteristic that can be predicted for human PH20 polypeptides incorporating numerous (e.g., 5, 10, 15 or 20) modifications as the claims permit.⁹⁹ Instead, as the common disclosure explains, “a soluble PH20 refers to a polypeptide characterized by its solubility under physiological conditions,”¹⁰⁰ and solubility is determined by making and testing each mutated PH20 polypeptide (“[s]olubility can be assessed by any suitable method that demonstrates solubility under physiologic conditions”).¹⁰¹

The failure to describe the claimed genera of human PH20 that are soluble is fatal to the '773 Patent. Compounding these problems, the common disclosure also does not describe which of the $\sim 10^{57}$ human PH20 polypeptides being claimed possess one of the two alternative utilities identified in the disclosure: (i) those that are useful because they possess $\geq 40\%$ of the hyaluronidase activity of an

folding or other activities of the molecule” and “when mutated, a normal activity of the protein is ablated or reduced”).

⁹⁹ EX1003, ¶¶ 62, 151, 178, 207-208.

¹⁰⁰ EX1001, 45:24-30.

¹⁰¹ EX1001, 45:35-37, 72:6-14, 179:47-61; EX1003, ¶¶ 136-137.

unmodified PH20₁₋₄₄₇ (“active mutants”),¹⁰² or (ii) those that lack hyaluronidase activity, and for which the disclosure identifies only an implausible contraceptive utility.¹⁰³

The common disclosure, thus, does not describe those modified PH20 polypeptides within the $\sim 10^{57}$ human PH20 polypeptides being claimed that *are* soluble and *do* possess one of the two alternative utilities. That is certainly true for the disclosed “inactive mutants” in Tables 5 and 10—the experiments used to classify these single-substitution PH20 mutants as “inactive mutants” did not prove any inactive mutants were actually made, much less proved they were and that each was soluble. *See* § V.A.1(b)(i). By contrast, while many “active mutants” with increased hyaluronidase activity are likely soluble, many others with some hyaluronidase activity may prove to be mostly insoluble when tested.¹⁰⁴ And

¹⁰² EX1001, 181:11-20 (PH20 polypeptides with hyaluronidase activity can degrade hyaluronan (HA), which makes them useful as “spreading agents” that enhance diffusion of injected drugs and treating HA-implicated diseases); EX1080, 230-31.

¹⁰³ EX1001, 74:10-12, 194:49-195:2; EX1003, ¶¶ 120-123.

¹⁰⁴ EX1003, ¶ 151.

despite repeatedly citing an assay to test if a mutated human PH20 is soluble,¹⁰⁵ no data from testing any mutant for solubility is reported in the common disclosure.

A skilled artisan also would not consider the *singly*-modified human PH20₁₋₄₄₇ polypeptides—the only ones described in the common disclosure—to be representative of *multiply-modified* soluble human PH20 polypeptides. The latter incorporate *combinations* of 2-20 substitutions, deletions, and insertions that together can cause far more disruptive structural changes to the proteins, which can impair both the solubility and activity of the PH20 polypeptides.¹⁰⁶ The common disclosure describes *no multiply-modified* human PH20 polypeptides (which make up the vast majority of claimed PH20 polypeptides), much less those that are soluble, and within those have practical utility.

What the common disclosure instead provides are “research plans” that instruct the skilled artisan “to generate a modified PH20 polypeptide containing any one or more of the described mutations, and test each for a property [e.g.,

¹⁰⁵ EX1001, 45:35-37, 72:6-14, 179:47-61; EX1028 (describing Triton X-114 detergent assay to separate soluble from insoluble proteins); EX1003, ¶ 136.

¹⁰⁶ EX1003, ¶¶ 59, 61-62, 153, 161, 176.

solubility]¹⁰⁷ or activity as described herein.”¹⁰⁸ The first of these—to find mutants that are soluble—simply points the skilled artisan to prior art methods to determine which of the $\sim 10^{57}$ human PH20 polypeptides being claimed are soluble by making and testing each one.¹⁰⁹ The research plan for finding “active mutant” human PH20 polypeptides with multiple modifications is prophetic and involves iterative rounds of random mutagenesis followed by screening for mutants that retain hyaluronidase activity.¹¹⁰ And no research plan is described for producing inactive mutants that possess contraceptive utility—what might make a mutant human PH20 useful for that utility is not just undescribed, it is unknown.¹¹¹

The common disclosure provides no guidance that navigates this confusing landscape and does not describe the vast majority of multiply-modified human

¹⁰⁷ EX1001, 48:40-44 (“As used herein, property refers to a physical or structural property, such as... solubility, aggregation or crystallization of a protein.”).

¹⁰⁸ EX1001, 76:56-61; EX1003, ¶ 218.

¹⁰⁹ EX1001, 45:35-37, 72:6-14, 179:47-61; EX1028; EX1003, ¶¶ 178, 184, 191, 194.

¹¹⁰ EX1001, 141:31-142:3; *also id.* at 77:31-39, 100:19-31, 107:7-12, 133:59-64; EX1003, ¶¶ 195-198, 204-205.

¹¹¹ EX1003, ¶ 124.

PH20 polypeptides being claimed, much less the unknown numbers of them that are soluble and additionally are useful.

(i) Empirical Test Results of Single-Replacement Modified PH20 Polypeptides Do Not Identify Multiply-Modified Soluble or Enzymatically Active PH20 Polypeptides

The empirical results in the common disclosure do not identify or provide any predictive guidance to a skilled artisan about the structural features of multiply-modified human PH20 polypeptides within the claimed genera that are enzymatically active or inactive, much less those that are also soluble.

The common disclosure reports results from testing a portion of a library of ~6,743 single-replacement PH20₁₋₄₄₇ polypeptides.¹¹² The mutants were generated via a mutagenesis process which randomly substituted one of ~15 amino acids into positions at every position in PH20₁₋₄₄₇ “such that each member contained a single amino change.”¹¹³ Approximately 5,917 were tested, while ~846 were uncharacterized.¹¹⁴ More than half (~57%) of these mutants were classified as

¹¹² EX1001, 133:59-134:3, 202:16-18, 201:14-202:2.

¹¹³ EX1001, 201:14-202:5.

¹¹⁴ EX1003, ¶ 114. Inconsistent numbers and classifications of mutants are not explained: (i) Table 3 lists 2,516 single-replacement PH20₁₋₄₄₇ mutants as “active mutants,” but Table 9 identifies only 2,376 mutants that exhibit >40%

“inactive mutants,” while ~30% (1335) exhibited less activity than unmodified PH20₁₋₄₄₇ (20%-100%).¹¹⁵ In other words, ~87% of the single-replacement PH20₁₋₄₄₇ polypeptides had *less* activity than unmodified PH20₁₋₄₄₇.¹¹⁶

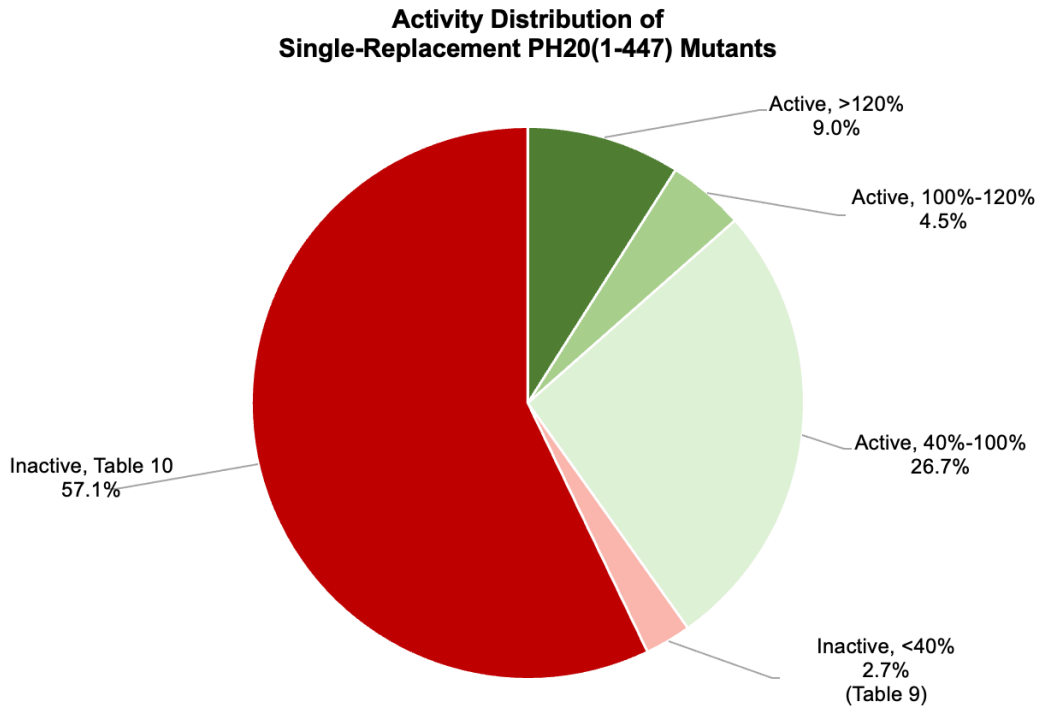
Activity vs. Unmodified PH20	Number	% of Tested (5916)
Active Mutants (Table 9)		
>120%	532	9.0%
100%-120%	267	4.5%
40%-100%	1577	26.7%
Inactive Mutants (Table 9)		
<40%	160	2.7%
Inactive Mutants (Table 10)		
Table 10 ‘inactive mutants’	3,380	57.1%

hyaluronidase activity; (ii) Tables 5 and 10 list 3,368 and 3,380 PH20₁₋₄₄₇

“inactive mutants,” respectively. *Id.* at ¶ 113.

¹¹⁵ EX1003, ¶ 116.

¹¹⁶ *Id.*



Notably, the data is not analyzed in the common disclosure—it is simply presented. No attempt is made to assess the impact of any single substitution on the protein’s structure, much less extrapolate these results to PH20 polypeptides with multiple substitutions.¹¹⁷

The data’s quality is also questionable: no control values or statistical assessments are provided for activity measurements. The unmodified PH20₁₋₄₄₇ control exhibited activity ranges spanning most of the range of values for activities observed for tested mutants in so-called “stability” tests (*i.e.*, unmodified PH20₁₋₄₄₇ showed hyaluronidase activity ranges of 97% and 87% across two rounds of

¹¹⁷ EX1003, ¶ 160-161, 165.

testing).¹¹⁸ As Dr. Hecht observes, this “significant variation raises serious doubts about how probative or instructive the values of individual tested mutants that fall within the range of variability observed for the control can possibly be.”¹¹⁹

The common disclosure does not report the measured hyaluronidase activity of the ~3,380 “inactive mutants” or ~830 (12%) mutants it does not classify, even though they were screened in the same experiment that yielded values that are reported for “active mutants” (Table 9).¹²⁰ Nor did it demonstrate these ~3,380 “inactive mutants” were actually produced, properly folded, and were soluble.¹²¹ Instead, the experimental protocol equated the *absence* of hyaluronidase activity in supernatants of cells as evidence that a mutant was an “inactive mutant.”¹²² But the *absence* of hyaluronidase activity is not proof that a properly folded and soluble inactive mutant *was* produced. A lack of activity would be observed if a

¹¹⁸ EX1003, ¶¶ 71-73, Appendix A-7, A-8; EX1001, 287:44-53, Table 12.

¹¹⁹ EX1003, ¶ 73; *see also* EX1001, 287:44-53 (positive control also varied).

¹²⁰ EX1003, ¶¶ 109, 114; EX1001, 234:26-255:51 (Table 9), 257:1-267:32 (Table 10).

¹²¹ EX1003, ¶¶ 110-111.

¹²² EX1003, ¶¶ 109-111; EX1001, 230:60-233:9.

mutant was not successfully produced within the cell,¹²³ was not secreted or was secreted but did not properly fold or misfolds.¹²⁴ The latter scenarios are more likely to result in insoluble proteins.¹²⁵ Skilled artisans thus cannot determine from the common disclosure *which* of ~4,180 “inactive” or unclassified mutants are soluble human PH20 polypeptides, much less which were (i) properly folded and enzymatically inactive, (ii) not successfully produced by or secreted from the transfected cells (iii) secreted but did not correctly fold, or (iv) were properly folded but were catalytically inactive.¹²⁶

The unexplained data by itself reveals no trends or correlations even for single-replacement PH20₁₋₄₄₇ polypeptides.¹²⁷ For example, different substitutions at the same position in PH20₁₋₄₄₇ yielded both active and inactive mutants, along with unreported effects for >800 mutants.¹²⁸

¹²³ EX1003, ¶114; EX1087, 944.

¹²⁴ EX1003, ¶ 114.

¹²⁵ EX1003, ¶¶ 114-115.

¹²⁶ EX1003, ¶¶ 110-112, 114.

¹²⁷ EX1003, ¶¶ 117, 160-161.

¹²⁸ EX1001, Tables 8, 9, 10.

Position	Active	Inactive	Unclassified
45	I, K	A, D, F, G, P, W	H, M, Q, S, T, V, Y
110	V	F, K, L, M, P, W	A, C, D, G, H, N, R, S
124	H, L, R	C, D, E, F, N	A, G, I, P, S, T, V, W
290	I, M	D, Q, Y	A, C, G, H, K, L, R, S, T, V
343	T, V	C, D, F, I, P, W	E, G, L, M, R, S, Y

Making multiple substitutions in a PH20 polypeptide can cause unpredictable interactions within the protein's structure (with resulting effects on solubility and/or function) that do not occur in single-substitution mutants.¹²⁹ The empirical test results for singly-substituted mutants thus cannot identify to a skilled artisan which of the $\sim 10^{57}$ PH20 mutants being claimed are soluble human PH20 polypeptides, or those that also are “active mutants” or “inactive mutants.”¹³⁰ All the data shows is that *most* of the tested single-substitution mutants impaired or eliminated PH20's activity.¹³¹

Finally, the results reported in Tables 11 and 12 from two runs of putative “stability” testing of ~ 409 single-replacement PH20₁₋₄₄₇ polypeptides provide no meaningful insights into which singly- or multiply-modified human PH20

¹²⁹ EX1003, ¶¶ 54-59, 61-62, 151, 163.

¹³⁰ EX1003, ¶¶ 160-161, 165, 184.

¹³¹ EX1003, ¶ 116.

polypeptides are soluble.¹³² The experiments also did not measure protein stability—they simply report activity.¹³³ Unsurprisingly, single-replacement PH20₁₋₄₄₇ polypeptides showed higher activity at 37° C than at 4° C, given that PH20 exists at the former temperature in humans,¹³⁴ while testing with m-cresol showed only a few mutants resisted its denaturing effects, with no explanation why.¹³⁵ And none of the mutants incorporated *combinations* of substitutions. The so-called “stability” results provide no probative insights into which multiply-modified PH20 polypeptides might be active,¹³⁶ and provides no information on solubility.

(ii) The Common Disclosure’s Research Plan Does Not Identify Multiply-Mutated Soluble Human PH20 Polypeptides that Are Useful

Instead of describing *any* multiply-modified human PH20 polypeptides with specific structures and associated properties, such as solubility or activity, the

¹³² EX1001, 267:37-269:54, 269:56-276:29 (Table 11), 276:30-287:36 (Table 12).

¹³³ EX1001, 269:38-55; EX1003, ¶¶ 68-70.

¹³⁴ EX1003, ¶ 74; EX1001, 177:48-57.

¹³⁵ EX1003, ¶ 70.

¹³⁶ EX1003, ¶¶ 76-77.

common disclosure simply presents *the idea* of making multiply-modified PH20 polypeptides and determining what their utilities may be (if any).

Much of the disclosure simply identifies hoped for but unrealized results. For example, “modified PH20 polypeptides”¹³⁷ are PH20 polypeptides (“a type of hyaluronidase that occurs on in sperm and is neutral-active”)¹³⁸ that “*can have* up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity,” “[*typically*” contains between 1 and 50 amino acid replacements and “*can include* any one or more other modifications, in addition to at least one amino acid replacement ...”¹³⁹ Likewise, it contends modified PH20 polypeptides “*can* exhibit altered, such as improved or increased, properties or activities compared to the corresponding PH20 polypeptide not containing the amino acid modification (*e.g.*, amino acid replacement).”¹⁴⁰

¹³⁷ EX1001, 47:7-12, 23-31; § IV.D.3.

¹³⁸ EX1001, 44:25-26 (“PH20 refers to), 49:8-11 (“neutral active refers to the ability of a PH20 polypeptide to enzymatically catalyze the cleavage of hyaluronic acid at neutral pH...”).

¹³⁹ EX1001, 47:12-22 (emphasis added).

¹⁴⁰ EX1001, 99:46-52 (emphasis added).

None of these statements identify any *actual* multiply-modified PH20 polypeptides that *are* soluble and *are* enzymatically active (*i.e.*, specific PH20 polypeptides with particular combinations of modifications), much less provide results from testing any. They simply draw boundaries around a theoretical and immense genus of multiply-modified PH20 polypeptides, leaving it to the skilled artisan to discover which are soluble, and are enzymatically active or inactive.

The common disclosure also describes no methods that produce any *specific* multiply-modified, soluble human PH20 polypeptides.¹⁴¹ Instead, it provides a prophetic research plan requiring “iterative” make-and-test experiments that *might discover* such PH20 polypeptides:

The method provided herein [] is *iterative*. In one example, after the method is performed, any modified hyaluronan-degrading enzymes identified as exhibiting stability ... *can be modified or further modified* to increase or optimize the stability. A secondary library *can be* created by introducing additional modifications in a first identified modified hyaluronan-degrading enzyme. ... The secondary library *can be* tested using the assays and methods described herein.¹⁴²

¹⁴¹ EX1003, ¶¶ 192-193.

¹⁴² EX1001, 141:31-44 (emphases added); *see also id.* at 41:17-24, 134:38-43, 139:27-40; EX1003, ¶¶ 194-199.

This prophetic research plan is effectively meaningless—it does not indicate that any particular soluble, enzymatically-active multiply-modified PH20 polypeptides will be found, much less identify *which* ones are.¹⁴³

An alternative plan suggests that mutations can be “targeted near” “critical residues” which supposedly “can be identified because, when mutated, a normal activity of the protein is ablated or reduced.”¹⁴⁴ But Tables 5 and 10 show that at least one substitution at each of 405 positions between positions 1 and 444 of PH20₁₋₄₄₇ resulted in an inactive mutant.¹⁴⁵ The common disclosure’s guidance thus is to target locations “near” ~90% of the amino acids in PH20₁₋₄₄₇, which is no different than targeting *every* residue.¹⁴⁶ It is, like the first proposed “iterative” process, meaningless.

The common disclosure provides even less guidance regarding production of *soluble*, multiply-modified PH20 polypeptides. It simply points to what is desired: modified human PH20 polypeptides that “can be secreted upon expression from

¹⁴³ EX1003, ¶¶ 200-202, 205-206, 208; EX1001, 42:36-38; *see generally id.*, 133:59-134:37, 134:47-136:23, 136:53-141:29.

¹⁴⁴ EX1001, 141:45-142:3; EX1003, ¶ 199.

¹⁴⁵ EX1003, ¶ 201, Appendix A-3.

¹⁴⁶ EX1003, ¶ 201.

cells and are soluble in the supernatant...”¹⁴⁷ with soluble ones being (logically) “characterized by [their] solubility under physiological conditions.”¹⁴⁸ To find which of the $\sim 10^{57}$ possible mutants being claimed are those “soluble” ones, the common disclosure simply says to test them: “[t]he solubility of a PH20 polypeptide can be determined by any method known to one of the skill in the art,”¹⁴⁹ and cites (three times) a 1981 test for determining solubility of any protein.¹⁵⁰

This guidance also assumes *incorrectly* that all multiply-mutated human PH20 polypeptides will be secreted by the cell. Multiple mutations introduced into the human PH20 can cause the protein to misfold, slow folding or create new structures within the protein, which can occur inside (or outside) the cell.¹⁵¹ When

¹⁴⁷ EX1001, 30:14-18, 11:29-36.

¹⁴⁸ EX1001, 44:63-65.

¹⁴⁹ EX1001, 179:47-48.

¹⁵⁰ EX1001, 45:4-8, 72:3-17, 179:48-53.

¹⁵¹ EX1003, ¶¶ 115, 151-152.

they occur inside the cells, it can trigger quality control mechanisms in the cell that degrade the mutant.¹⁵²

These prophetic research plans, based entirely on unfocused, iterative “make-and-test” experiments, provide no direction to the skilled artisan about which of the $\sim 10^{57}$ multiply-modified human PH20 polypeptides being claimed are in fact soluble or enzymatically active.¹⁵³ Instead, they require the skilled artisan to endlessly repeat cycles of making and testing until the unknown number of soluble human multiply-modified PH20 polypeptides are produced and identified.¹⁵⁴ That in no way demonstrates possession of the claimed genus.

¹⁵² EX1003, ¶¶ 114, 115; EX1001, 69:19-23; EX1087, 944 (“If folding is delayed or an illegitimate conformation arises, the substrate is either subjected to additional folding cycles or is selected for a process termed ER-associated degradation (ERAD).”).

¹⁵³ EX1003, ¶¶ 205-206, 208, 214.

¹⁵⁴ EX1003, ¶¶ 211-213; EX1001, 136:31-36, 136:24-48, 139:47-51, 139:62-67, 140:17-31.

(c) *The Common Disclosure Does Not Identify a Structure-Function Relationship for Multiply-Modified, Enzymatically Active Soluble Human PH20 Polypeptides*

The common disclosure does not identify which of the 6,753 singly-substituted human PH20 polypeptides that were supposedly made are soluble.¹⁵⁵ And it identifies no multiply-modified ones that were even made. The only guidance it does provide concerns *unclaimed* human PH20 polypeptides: *unmodified* full-length human PH20 (1-474) can be made “soluble” by removing “all or a portion of the [GPI] anchor sequence” (*i.e.*, 456 to 474 of SEQ ID NO47:7).¹⁵⁶ It plainly does not identify a “structure-function” relationship for all soluble multiply-modified human PH20 polypeptides.¹⁵⁷

The common disclosure also does not identify the *structural* significance of any of the ~2,500 mutations that yielded single residue “active mutant” PH20₁₋₄₄₇ polypeptides (or that ~3,400 “inactive mutants” were even produced).¹⁵⁸ 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

¹⁵⁵ EX1001, 201:14-202:5.

¹⁵⁶ EX1001, 44:64-45:3, 45:24-30, 69:62-67.

¹⁵⁷ EX1003, ¶ 101.

¹⁵⁸ EX1003, ¶¶ 165, 177; § V.A.1.b)(i).

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.¹⁵⁹ Instead, it simply lists single replacements to random amino acids at random positions classified based on results of a hyaluronidase activity assay (including negative results)—and no solubility test results are reported.¹⁶⁰

The common disclosure also does not identify any *sets* of specific amino acid replacements that correlate to structural domains or motifs that positively or negatively influence solubility or hyaluronidase activity, much less *predictably* increase activity to defined thresholds.¹⁶¹ Again, it simply reports activity data from testing randomly generated *single*-replacement PH20₁₋₄₄₇ mutants.

The common disclosure's empirically identified examples of “active mutant” single-replacement PH20₁₋₄₄₇ mutants also do not *by themselves* identify any “structure-function” relationship linking them generally to all soluble and/or enzymatically active forms of modified PH20 polypeptides.¹⁶² They certainly do

¹⁵⁹ EX1003, ¶¶ 160-161, 165.

¹⁶⁰ EX1001, 233:22-234:25; EX1003, ¶¶ 160-61.

¹⁶¹ EX1003, ¶¶ 55, 164-65.

¹⁶² EX1003, ¶¶ 61, 165, 177, 179.

not do so for the much larger genus of modified human PH20 polypeptides having a position 320 substitution and up to 19 additional modifications—none were made, and no information is provided about which might be soluble, active or inactive.¹⁶³

Critically, the common disclosure *does not even contend* that an amino acid replacement at a particular position (*e.g.*, 320) that made a PH20₁₋₄₄₇ an “active mutant” will make any other modified PH20 polypeptide with that same amino acid replacement (plus between 1 and 19 additional replacements, insertions or deletions) an “active mutant.”¹⁶⁴ It also says nothing about whether all such modified human PH20 polypeptides would be soluble. Such an assertion would have no scientific credibility—whether a protein such as PH20 remains soluble or soluble after incorporating multiple modifications is dictated by its overall structure, which can be influenced unpredictably by different combinations of changes to its amino acid sequence.¹⁶⁵

The common disclosure, thus, does not identify to a skilled artisan *any* structural features shared by the many, diverse multiply-modified human PH20

¹⁶³ EX1003, ¶¶ 166, 177.

¹⁶⁴ EX1003, ¶¶ 215-16.

¹⁶⁵ EX1003, ¶¶ 56-57, 59, 62.

polypeptides being claimed that are soluble, and are either enzymatically active or inactive.¹⁶⁶ It cannot satisfy the written description requirement of § 112(a) as a disclosure that links a functional property to a particular structure *shared* by the members of the genus.

(d) *The Common Disclosure Does Not Describe a Representative Number of Multiply-Modified Enzymatically Active Soluble Human PH20 Polypeptides*

The ~2,500 active mutant *single*-replacement PH20₁₋₄₄₇ polypeptides in the disclosure are not representative of the ~10⁵⁷ multiply-modified soluble human PH20 polypeptides being claimed—those with between *2 and 20 modifications* at any of hundreds of positions within the protein.¹⁶⁷ The latter proteins are structurally distinct from single replacement PH20 polypeptides, both as to their sequences and as to the various secondary structures and structural motifs within them that result when multiple amino acid modifications are incorporated. Those distinct structures result from the distinct interactions the modified sequences can have with their neighboring residues relative to wild-type sequences.¹⁶⁸ For example, introducing a first amino acid substitution often affects the neighbors of

¹⁶⁶ EX1003, ¶¶ 177-78.

¹⁶⁷ See § IV.D.1; EX1003, ¶¶ 61, 165, 175-176, 179.

¹⁶⁸ EX1003, ¶¶ 55-56, 58-61, 163, 176.

that original/replaced amino acid by, for example, (i) introducing a stabilizing interaction, (ii) removing a stabilizing interaction, and/or (iii) introducing a conflicting interaction (*e.g.*, adverse charge or hydrophobicity interactions).¹⁶⁹

Introducing a second substitution in that region may reverse those interactions (or not) with each neighboring residue, and a third substitution may do the same, with up to 20 rounds permitted by the claims, each potentially impacting each interaction.¹⁷⁰

Internal insertions or deletions of varying lengths, or replacements of many residues in one region of the protein also can materially disrupt the secondary structure(s) in a domain or of the entire protein.¹⁷¹ Such changes may alter patterns of amino acids necessary for formation of secondary structures, prevent interactions between residues that influence folding (and folding rates), and shift spatial positioning of residues that must interact to create or stabilize the protein's structure (*e.g.*, cysteines that ordinarily form disulfide bonds).¹⁷²

¹⁶⁹ EX1003, ¶¶ 56-58.

¹⁷⁰ EX1003, ¶¶ 58-61, 163.

¹⁷¹ EX1003, ¶¶ 55-60, 161, 164, 176.

¹⁷² EX1003, ¶¶ 55-60, 176.

The properties of singly-substituted PH20 polypeptides thus are not representative of multiply-modified ones, as the latter will contain distinct structures influenced by the myriad effects caused by making multiple modifications in the PH20 polypeptide. And no information is provided that links these myriad, different structures to required properties (*e.g.*, solubility, activity) of the claimed modified PH20 polypeptides.¹⁷³

The enzymatically inactive single-replacement PH20₁₋₄₄₇ polypeptides listed in Tables 5 and 10 also are not representative of multiply-modified PH20 polypeptides that soluble and *either* active or inactive. None were characterized and it is unclear if any were actually produced. Regardless, the lack of information about *why* those mutants exhibited no enzymatic activity precludes finding them to representative of the untold unknown number of multiply-modified human PH20 polypeptides that are soluble, active and meet the claims' parameters. Such "inactive mutant" proteins necessarily contain distinct structures not present in single-substitution "active mutants." And a skilled artisan could not have predicted from these single-replacement PH20₁₋₄₄₇ "inactive mutant" examples whether human PH20 mutants that incorporate numerous additional modifications

¹⁷³ EX1003, ¶¶ 160, 165.

could yield soluble and active forms of the protein, much less the precise additional changes necessary to do so.¹⁷⁴

The common disclosure thus provides a very narrow set of working examples relative to the tremendous diversity of modified soluble human PH20 polypeptides being claimed.¹⁷⁵ The examples are restricted to *one type of change* (a single amino acid replacement) in *one type of PH20 polypeptide* (SEQ ID NO: 3).¹⁷⁶ By contrast, the claims encompass PH20 sequences with one identified replacement at position 320, and up to 19 additional changes.¹⁷⁷ Consequently, a skilled artisan would not have viewed the common disclosure's examples of individual single amino acid replacements in PH20₁₋₄₄₇ as being *representative* of the diversity of modified soluble human PH20 polypeptides being claimed.¹⁷⁸

¹⁷⁴ EX1003, ¶ 171.

¹⁷⁵ EX1003, ¶¶ 165, 175-176, 179.

¹⁷⁶ EX1003, ¶¶ 107, 166.

¹⁷⁷ EX1003, ¶¶ 127-129.

¹⁷⁸ EX1003, ¶ 165.

(e) *The Claims Capture Multiply-Modified Soluble Human PH20 Polypeptides the Disclosure Excludes from the Class of Enzymatically Active PH20 Proteins*

By their literal language, the claims capture modified PH20 polypeptides with changes the common disclosure says rendered the PH20₁₋₄₄₇ mutants inactive. But the common disclosure instructs that “active mutants” should ***not*** incorporate amino acid substitutions that as single substitutions rendered PH20₁₋₄₄₇ inactive, stating:

To retain hyaluronidase activity, modifications typically ***are not made*** at those positions that are less tolerant to change or required for hyaluronidase activity.¹⁷⁹

It 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 that are made at other positions.¹⁸⁰ This observation plainly is not limited to single-replacement PH20₁₋₄₄₇ mutants—those that yielded single-substitution “inactive mutants” are already identified (Tables 5 and 10). Instead, by stating that the listed substitutions should not be included in enzymatically active multiply-modified PH20 polypeptides, it clearly conveys to the skilled artisan that the

¹⁷⁹ EX1001, 78:38-40 (emphases added).

¹⁸⁰ EX1001, 78:40-79:13.

claimed multiply-modified human PH20 polypeptides that are enzymatically active do not and should not contain them.¹⁸¹

The common disclosure provides no examples of multiply-modified human PH20 polypeptides that disregard these restrictions.¹⁸² There are no descriptions of modifications that might be made that will restore activity and render soluble enzymatically *inactive* PH20 polypeptides or which the specification teaches to *not* make.¹⁸³ And the common disclosure provides no examples of any single human PH20 polypeptide having any combinations of substitutions listed in Tables 3 and 9 with and substitutions listed in Tables 5 and 10, much less show that such multiply-mutated human PH20 polypeptides are soluble and enzymatically active.

The claims thus independently violate the written description requirement for the reasons articulated by the Federal Circuit in *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479-80 (Fed. Cir. 1998)—if a disclosure “unambiguously limited” the invention, but the claims circumvent that limitation, those claims are “broader than the supporting disclosure” and are unpatentable.

¹⁸¹ EX1003, ¶¶ 168-171, 180-182; EX1001, 78:38-79:13, 69:1-11.

¹⁸² EX1003, ¶ 171, 181-183.

¹⁸³ EX1003, ¶ 184.

2. Dependent Claims 3-15 Lack Written Description

(a) Claims 3-4

Claims 3 and 4 require the modified soluble human PH20 polypeptides of claim 1 to exhibit (i) increased hyaluronidase activity (claim 3) or (ii) at least 120% of hyaluronidase activity (claim 4) relative to unmodified PH20₁₋₄₄₇.

The reasons provided in § V.A.1 explaining why the claims generally lack written description apply with full force to claims 3 and 4.

In addition, the common disclosure's recitation of a *desired* level of hyaluronidase activity in claims 3 and 4 does not identify *which* of the $\sim 10^{57}$ human PH20 polypeptides meeting the claim parameters *are* (i) soluble, and (ii) *do* exhibit such increased hyaluronidase activity.¹⁸⁴

The three single-substitution position 320 PH20₁₋₄₄₇ mutants that exhibited increased activity compared to unmodified PH20₁₋₄₄₇ are not representative of each claim's immense genus of human PH20.¹⁸⁵ The common disclosure does not describe any multiply-modified soluble human PH20 polypeptides with any level of hyaluronidase activity."¹⁸⁶

¹⁸⁴ EX1003, ¶¶ 156-158, 184, 206-207.

¹⁸⁵ EX1001, 237-238 (Table 9); EX1003, ¶¶ 165, 215-216.

¹⁸⁶ EX1003, ¶¶ 154, 193.

Second, the common disclosure identifies no common structural feature shared by all soluble human PH20 polypeptides being claimed that exhibit increased hyaluronidase activity.¹⁸⁷ The presence of a *single* substitution at position 320 in a modified PH20 certainly does not demonstrate possession of every *multiply*-modified soluble human PH20 polypeptide with increased activity also having that position 320 substitution, and the common disclosure does not contend otherwise.¹⁸⁸

Again, when Petitioner challenged comparable claims in related patents, Patentee consistently disclaimed rather than defended those claims.¹⁸⁹

Claims 3 and 4 lack written description in the common disclosure.

(b) Claims 5-15

Claims 5-15 claim nucleic acids, recombinant expression vectors, host cells, pharmaceutical compositions, methods of administering such compositions, and methods of manufacture, all utilizing the immense genus of modified soluble

¹⁸⁷ EX1003, ¶¶ 177, 206, 214.

¹⁸⁸ EX1003, ¶¶ 165-166, 206.

¹⁸⁹ *E.g.*, PGR2025-00003 (claims 5-6), PGR2025-00004 (claims 5-6), PGR2025-00006 (claims 5-6), PGR2025-00009 (claim 4).

human PH20 polypeptides defined by claim 1. They lack written description for the same reasons explained in § V.A.1.¹⁹⁰

B. All Challenged Claims Are Not Enabled

All challenged claims are also unpatentable as non-enabled.

“If a patent claims an entire class of ... compositions of matter, the patent’s specification must enable a person skilled in the art to make and use the *entire* class,” *i.e.*, “the *full scope* of the invention,” and so the “more one claims, the more one must enable.”¹⁹¹ “It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.”¹⁹² “Claims are not enabled when, at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation.”¹⁹³

¹⁹⁰ *Idenix*, 941 F.3d at 1155, 1165; *Boehringer*, PGR2020-00076, Paper 42, at 40-41.

¹⁹¹ *Amgen*, 598 U.S. at 610 (emphases added).

¹⁹² *Idenix*, 941 F.3d at 1159.

¹⁹³ *Wyeth & Cordis Corp. v. Abbott. Labs*, 720 F.3d 1380, 1383-84 (Fed. Cir. 2013).

Although not required, enablement may be assessed using the *Wands* factors, which consider: “(1) the quantity of experimentation necessary; (2) how routine any necessary experimentation is in the relevant field; (3) whether the patent discloses specific working examples of the claimed invention; (4) the amount of guidance presented in the patent; (5) the nature and predictability of the field; (6) the level of ordinary skill; and (7) the scope of the claimed invention.”¹⁹⁴

Where the scope of the claims is large, few working examples are disclosed, and the only guidance to practice “the full scope of the invention [is] to use trial and error to narrow down the potential candidates to those satisfying the claims’ functional limitations—the asserted claims are not enabled.”¹⁹⁵

“It is well established that the enablement requirement of § 112 incorporates the utility requirement of § 101.”¹⁹⁶ A claimed invention also must be ***presently useful***—stating a hypothesis and proposing testing to determine its accuracy is

¹⁹⁴ *Idenix*, 941 F.3d at 1156 (citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)).

¹⁹⁵ *Baxalta Inc. v. Genentech, Inc.*, 579 F. Supp. 3d 595, 615-16 (D. Del. 2022) (Dyk, T., sitting by designation) *aff’d* 81 F.4th 1362 (Fed. Cir. 2023).

¹⁹⁶ *In re Fisher*, 421 F.3d 1365, 1379 (Fed. Cir. 2005).

insufficient.¹⁹⁷ Further, if a claim encompasses significant numbers of inoperative embodiments, and a skilled artisan must engage in undue experimentation to identify the operative ones, that renders the claims non-enabled.¹⁹⁸

Here, enabling the full scope of the claims requires at least enabling the subgenus of soluble multiply-modified PH20 polypeptides that satisfy the claim parameters—if that subgenus is not enabled, the full scope of the claims cannot be. The same is true for soluble multiply-modified PH20 polypeptides that are also enzymatically active (and useful) or inactive (only implausible utility). But to do so here, a skilled artisan would have to perform an impossible amount of iterative experimentation using the disclosure’s prophetic, iterative “make and test” methodology for making multiply-modified PH20 polypeptides and knowledge in the prior art, to discover which of the $\sim 10^{57}$ modified PH20 polypeptides claimed are (i) soluble and (ii) enzymatically active. The same experimentation is necessary to also identify soluble “inactive mutants” (if any) with (implausible)

¹⁹⁷ *In re '318 Patent Infringement Litigation*, 583 F.3d 1317, 1327 (Fed. Cir. 2009); *In re Kirk*, 376 F.2d, 936, 942 (C.C.P.A. 1967) (emphasis added).

¹⁹⁸ *Crown Operations Intern. Ltd v. Solutia Inc.*, 389 F.3d 1367, 1380, FN8 (Fed. Cir. 2002); *Atlas Powder Co. v. E.I. Dupont De Nemours*, 750 F.2d 1569, 1577 (Fed. Cir. 1984).

contraceptive utility, as well as to identify mutants that cannot be made or are insoluble, and have no utility.¹⁹⁹

1. Claims 1-2 Are Not Enabled

Assessing enablement pursuant to *Amgen* or using the factors in *In re Wands* yields the same conclusion—the claims are not enabled by the common disclosure.

(a) *Extreme Scope of the Claims*

Claims 1-2 define an immense and diverse genus of $\sim 10^{57}$ distinct modified soluble human PH20 polypeptides. *Supra* §§ IV.D.1., V.A.1. Within the immense genera of PH20 polypeptides being claimed are an unknown and undisclosed number of soluble, “active mutant” multiply-modified human PH20 polypeptides. Practicing the full scope of just this subgenus pursuant to the guidance in the common disclosure requires making and testing $\sim 10^{57}$ distinct PH20 polypeptides.²⁰⁰ The common disclosure provides no other way to determine *which* of the myriad combinations of modifications (in addition to position 320) yield soluble, enzymatically active human PH20 polypeptides within the claims’ scope.²⁰¹

¹⁹⁹ EX1003, ¶¶ 124-125, 136-138, 110-112, 115.

²⁰⁰ EX1003, ¶¶ 138, 205-208, 213-214; EX1001, 76:56-61.

²⁰¹ EX1003, ¶¶ 136, 160-161, 163.

Practicing that full genus, however, raises substantial scientific questions left unanswered by the common disclosure. Among the PH20 polypeptides being claimed are active mutants the common disclosure says to not make. For example, it instructs that single substitutions that rendered PH20₁₋₄₄₇ inactive should not be included in human PH20 polypeptides that are enzymatically active, explaining that “[t]o retain hyaluronidase activity, modifications typically are not made at those positions that are less tolerant to change or required for hyaluronidase activity.”²⁰² It likewise instructs that enzymatically active human PH20 polypeptides should exclude substitutions or deletions that change or remove highly conserved residues in hyaluronidases, stating that the “results herein confirm *the requirement* of PH20 amino acid residues ... [at numerous conserved positions]...*for hyaluronidase activity*, since mutagenesis of these residues results in an enzyme that is not active (e.g., *it is not expressed* or is inactive when expressed, see e.g., Tables 5 and 10).”²⁰³

A skilled artisan could not have predicted whether a human PH20 polypeptide would be soluble and enzymatically active if it (i) included a claimed position 320 substitution and (ii) incorporated 1 to 19 additional substitutions or

²⁰² EX1001, 76:1-13; EX1003, ¶ 168. See § V.A.1(e).

²⁰³ EX1001, 68:33-69:11; EX1003, ¶ 169.

deletions the common disclosure instructs to not include in “active mutants.”

Certainly, the common disclosure is no help—it says to *not make* such combinations in “active mutants.”

More generally, whether there are any (or how many) soluble and “active mutant” forms of human PH20 polypeptides within the scope of the claims is unknown. The common disclosure identifies none, and answering this question, again, requires making and testing 10^{57+} different multiply-modified human PH20 polypeptides.²⁰⁴ The claims thus capture massive genera of multiply-modified soluble human PH20 polypeptides, most of which would have *unknowable* properties absent individual production and testing for solubility and activity.

Comparable claims have routinely been found non-enabled. For example, the claims in *Amgen* covered “millions” of different, untested antibodies,²⁰⁵ while in *Idenix*, a skilled artisan would “understand that ‘billions and billions’ of compounds literally meet the structural limitations of the claim.”²⁰⁶ In both cases (as here), the enormous claim scope was contrasted to limited working examples in the patent, the field found unpredictable, and an immense quantity of

²⁰⁴ EX1003, ¶¶ 138, 205-208, 213-214.

²⁰⁵ 598 U.S. at 603.

²⁰⁶ 941 F.3d at 1157; *also id.*, 1159.

experimentation was needed to practice the claims' full scope (*Wands* Factors 1, 3, 4, and 7).

(b) *Limited Working Examples and Only a Research Plan for Discovering Active Mutant Soluble Human PH20 Polypeptides*

The number of “working examples” meeting the claim requirements and are “active mutants” is tiny—13 of the 16 position 320 singly-substituted PH20₁₋₄₄₇ mutants were reported as “active mutants.”²⁰⁷ None were shown to be soluble. These examples are a microscopic fraction of the 10⁵⁷+ modified soluble human PH20 polypeptides being claimed, and provide no guidance that would help a skilled artisan avoid the “trial-and-error” methodology the common disclosure specifies for making multiply-modified human PH20 polypeptides. None incorporate more than one substitution or multiple types of modifications.²⁰⁸

The remaining tested PH20 mutants outside position 320 provide no meaningful insights into making multiply-modified PH20 polypeptides meeting the claims' parameters. None illustrate the effects of making modifications at *multiple* positions needed for secondary structures, structural motifs, or for stabilizing the

²⁰⁷ EX1001, 221 (Table 8), 237-238 (Table 9).

²⁰⁸ EX1003, ¶ 169.

PH20 protein structure.²⁰⁹ The common disclosure also does not use its examples to suggest any particular combinations of substitutions that together alter any aspect of the PH20 protein structure in a predictable way. Instead, it simply provides lists of possible substitutions with no indication as to the effect(s) of their combination.²¹⁰ The examples thus do not help a skilled artisan discover multiply-modified soluble human PH20 polypeptides that are enzymatically active.

Whether a multiply-modified human PH20 will be soluble depends on the structure of each mutant—if the modifications (individually or collectively) cause structural changes that expose hydrophobic patches or structures to the aqueous environment, that increases the likelihood the mutant will be insoluble.²¹¹ But nothing in the common disclosure enables a skilled artisan to predict the effect of modifications on solubility—it instead instructs *testing* each one.²¹²

²⁰⁹ EX1003, ¶¶ 163, 176-177.

²¹⁰ EX1001, 17:24-28:4.

²¹¹ EX1003, ¶¶ 39, 62, 115, 151-152; EX1014, 99, 117; EX1081, 897.

²¹² EX1001, 45:35-39, 179:48-53, 72:6-9; EX1003, ¶¶ 136-138.

The working examples in the common disclosure thus provide no credible guidance on practicing the full scope of the genus of enzymatically active soluble human PH20 polypeptides being claimed.²¹³

The alternative is an explicitly prophetic and “iterative” process for *discovering* active mutant multiply-modified PH20 polypeptides. *See* § V.A.1.d. This prospective research plan requires a skilled artisan to engage in undue experimentation to practice the full scope of the claims. First, it requires manually performing iterative rounds of *randomized* mutations (up to 19 rounds per starting molecule under the claims) to *discover* which of the $\sim 10^{57}$ possible modified human PH20 polypeptides within the claims might possess hyaluronidase activity.²¹⁴ This methodology requires the skilled artisan to iteratively repeat this

²¹³ EX1003, ¶ 184.

²¹⁴ EX1003, ¶¶ 194-196; *see also* EX1018, 382 (“combinatorial randomization of only five residues generates a library of 205 possibilities (3.2×10^6 mutants), too large a number for manual screening”). Chica credited a “ground-breaking” predictive molecular modeling technique that was later shown to be false. EX1018, 384, 382; EX1030, 569; EX1034, 258; EX1036, 275, 277; EX1048, 859.

research plan until $\sim 10^{57}$ multiply-modified PH20 polypeptides have been made and tested.

That testing does not identify which modified PH20 polypeptide are soluble, which requires a different experiment.²¹⁵ For solubility, the common disclosure identifies one exemplary test for identifying soluble mutant PH20 polypeptides.²¹⁶ It also recognizes skilled artisans know of other tests, such as centrifugation in aqueous solution) to determine if each PH20 polypeptides is soluble.²¹⁷ Regardless which test is used, the skilled artisan has to make and test each of $\sim 10^{57}$ mutant human PH20 polypeptides being claimed to know *which* are “soluble.”²¹⁸

The common disclosure also provides no meaningful guidance or information that a skilled artisan could use to direct the outcome of the prophetic procedures to yield soluble *or* enzymatically active (or both) human PH20 polypeptides with the range of multiple modifications specified by the claims:

²¹⁵ EX1003, ¶¶ 136-138.

²¹⁶ EX1001, 45:5-8, 179:48-53, 72:6-9.

²¹⁷ EX1001, 72:6-9.

²¹⁸ EX1003, ¶ 137.

- (i) it identifies *no* specific combination of two or more replacements, additions or deletions within any human PH20 polypeptide that yielded a soluble and/or “active mutants”;
- (ii) it provides no data from testing *any* human PH20 polypeptide with two or more substitutions for either solubility or activity; and
- (iii) it does not identify any regions or residues that are “associated with the activity and/or stability of the molecule” or “critical residues involved in structural folding or other activities’ of the molecule” when two or more concurrent replacements have been made, nor does it provide predictive guidance about such changes on solubility or activity.²¹⁹

Regardless whether performing individual rounds of the common disclosure’s “iterative” methodology and general experimental assays might be considered “routine,” the aggregate scale of experimentation required to practice the *full scope* of the claims goes far beyond undue—it is impossible.²²⁰ A skilled artisan could not predict whether a particular multiply-modified human PH20 polypeptide will be soluble and enzymatically active without making and testing

²¹⁹ EX1003, ¶¶ 160-161, 165-166, 175-176, 179.

²²⁰ EX1003, ¶¶ 138-139, 191, 213; EX1001, 177:45-179:61.

it.²²¹ The “*iterative, trial-and-error process[es]*” the common disclosure specifies are indistinguishable from those consistently found insufficient to enable comparable genus claims to modified proteins and compounds.²²²

(c) *Making Multiple Changes to PH20 Polypeptides Was Unpredictable*

Like any protein, the solubility and activity of PH20 can be unpredictably influenced by changes to its amino acid sequence.²²³ Introducing changes (replacements, insertions, or deletions) can alter the local structure of the protein where the change is made, which may disrupt secondary structures or structural motifs within the protein that are important to its biological activity (e.g., catalysis, ligand binding, etc.), its stability and whether it will be soluble.²²⁴

As explained in § VI below, by 2011, skilled artisans could have assessed whether certain *single* amino acid substitutions at certain positions would be

²²¹ EX1003, ¶¶ 138, 205-208, 213-214.

²²² *Idenix*, 941 F.3d at 1161-63 (emphasis added); *see also Amgen*, 598 U.S. at 612-15; *Wyeth*, 720 F.3d at 1384-86; *Baxalta*, 597 F. Supp. 3d at 616-19.

²²³ EX1003, ¶¶ 61-62.

²²⁴ EX1003, ¶¶ 115, 153, 176.

tolerated within the PH20 protein structure with a reasonable (though not absolute) expectation of success.²²⁵

By contrast, introducing *multiple* concurrent changes in a particular region of a protein greatly increases the likelihood of disrupting secondary structures and structural motifs essential to the protein's activity and/or stability, and can even introduce new ones into the protein.²²⁶ Replacing multiple amino acids thus can introduce an immense number of simultaneous influences on a protein's structure that cannot be predicted.²²⁷

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.²²⁸ Indeed, it was not until 2020 that computer-based protein structure prediction tools became available that approached the accuracy of experimentally-determined structures (below).²²⁹

²²⁵ EX1003, ¶ 218.

²²⁶ EX1003, ¶¶ 59-60, 206.

²²⁷ EX1003, ¶¶ 55, 58, 61-62.

²²⁸ EX1003, ¶ 212-14; EX1027, 6-10, Fig. 6.

²²⁹ EX1027, 6-10, Fig. 6; EX1003, ¶¶ 178, 214.

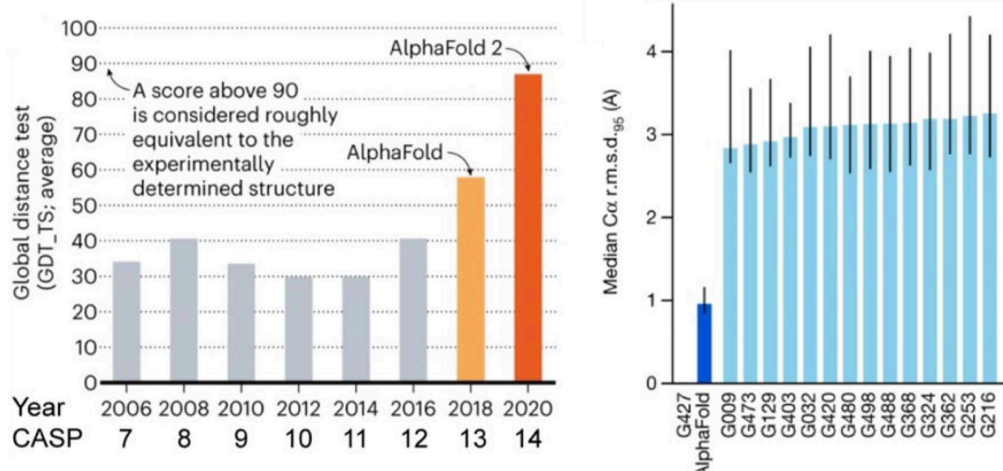


Figure 6. Left: progress of the CASP performance over the years for the best models and the most difficult targets.³⁸ Right: performance of AlphaFold2 relative to the top 15 entries by other groups in CASP14. Data are the median coordinate error and the 95% confidence interval of the median, estimated from 10 000 bootstrap samples.⁴¹

Moreover, the further away a modeled amino acid sequence is from an actual naturally occurring sequence and/or the original model's structure, the less reliable that model is.²³⁰ In addition, depending on the structural template used to produce the model, regions of the protein not supported by a corresponding structure could not be reliably used to assess particular changes.²³¹ And the time required to carry out rational design techniques to “practice” the full scope of the claimed genus would be unimaginable.²³²

²³⁰ EX1003, ¶¶ 178, 214, 253; EX1004, ¶¶ 156-157.

²³¹ EX1003, ¶¶ 178, 253; EX1004, ¶¶ 146-148; EX1012, 4, 8.

²³² EX1003, ¶¶ 51, 214; EX1059, 1225-26; EX1018, 378.

Consequently, a skilled artisan could not have used conventional rational design techniques to predict the which of the enormous number of human PH20 polypeptide sequences that incorporate the myriad possible combinations of between 2 and 20 modifications the claims encompass would be soluble and enzymatically active.²³³ Moreover, using such techniques to identify even a handful of soluble and active human PH20 polypeptides with more than 1 substitution would have taken an extreme amount of time and effort.²³⁴

(d) *Other Wands Factors and Conclusion*

The remaining *Wands* factors either indicate undue experimentation or are neutral. For example, 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 soluble human PH20 polypeptides being claimed.²³⁵ 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.

²³³ EX1003, ¶¶ 61-62, 178, 253.

²³⁴ EX1003, ¶¶ 178, 214.

²³⁵ EX1003, ¶¶ 61-62, 178, 239.

2. Only “Active Mutants” Have Credible Utility

The claims are also not enabled because they claim an unknown number of “inactive” mutants (which do not have a credible utility) and mutants that cannot be made or will not fold into a soluble human PH20 protein.

The only putative utility identified for “inactive mutants” (as “antigens in contraception vaccines”) is not scientifically credible.²³⁶ The disclosure cites two studies involving guinea pig PH20,²³⁷ but ignores other *evidence*—peer reviewed publications before 2011—that demonstrated that immunizing *other mammals* with their species’ PH20 did *not* cause contraception.²³⁸

Halozyme’s published clinical studies of unmodified human PH20₁₋₄₄₇ also showed no contraceptive effects in humans who were injected with unmodified PH20₁₋₄₄₇, reporting that “[a]lthough some antisperm antibodies are associated with

²³⁶ EX1001, 74:10-12, 194:49-195:2.

²³⁷ EX1001, 194:49-195:2; EX1022, 1142-43; EX1023, 1133-34.

²³⁸ See EX1019, 325, 331-33 (“recombinant mPH20 is not a useful antigen for inclusion in immunocontraceptive vaccines that target mice”); EX1020, 179-81 (“immunization [of rabbits] with reproductive antigens ... are unlikely to result in reduced fertility ...”); EX1021, 30310, 30314 (“PH-20 is not essential for fertilization, at least in the mouse ...”).

decreased fertility [], no evidence of negative effects on fertility could be determined in rHuPH20-reactive antibody-positive subjects of either sex.”²³⁹

Settled law holds that a claimed invention “must have ‘substantial utility’ and ‘specific benefit exist[ing] in currently available form’”—a theoretical or unproven utility is insufficient.²⁴⁰ Where an asserted utility is implausible (as here), credible evidence is required to support it.²⁴¹ There is none in the common disclosure:

- it identifies **no** “inactive mutants” that were demonstrated to be soluble;
- it identifies **no** “inactive mutants” within the scope of the claims that were demonstrated to confer contraceptive effects;
- it provides **no** guidance for selecting “inactive mutants” within the scope of the claims that possess contraceptive utility; and

²³⁹ EX1024, 87-88; *see also* EX1061, 1154; EX1003, ¶¶ 121-22.

²⁴⁰ *In re '318 Patent Infringement Litigation*, 583 F.3d. 1317, 1324 (Fed. Cir. 2009), citing *Brenner v. Manson*, 383 U.S. 519, 86 S.Ct. 1033 (1966) at 86 S.Ct. 1033.

²⁴¹ EX1003, ¶¶ 121-24.

- it identifies *no* epitopes or structures on naturally occurring PH20 proteins that induce antibody production that confers contraceptive effects, or that such epitopes/structures are preserved in every multiply-modified M320-substituted “inactive mutant” PH20 being claimed.²⁴²

Given this absence of information, a skilled artisan could not have reasonably predicted from the common disclosure whether *any* “inactive mutant” human PH20 polypeptide within the claim’s scope would cause contraceptive effects.²⁴³

There also is no basis for assuming that every modified human PH20 polypeptide that is not an “active mutant” is an “inactive mutant” useful for contraception. A skilled artisan would have considered it highly likely that some number of modified PH20 polypeptides within the $\sim 10^{57}$ mutants claimed cannot be produced and/or recovered.²⁴⁴ For example, instability caused by amino acid substitutions can induce cells to break down rather than secrete proteins, prevent proper folding, expose hydrophobic residues leading to aggregation, and cause

²⁴² EX1003, ¶¶ 123-124.

²⁴³ EX1003, ¶ 124.

²⁴⁴ EX1003, ¶ 115, 125.

other problems.²⁴⁵ Modified PH20 polypeptides that cannot be produced or are not properly folded will not retain the native protein structure of PH20 and cannot be “useful” “active” or “inactive mutants”—they have no utility.²⁴⁶

As explained in § V.A.1(b)(i), the common disclosure did not establish that ~3,380 properly folded “inactive mutant” PH20 polypeptides were actually produced. The actual number (if any) is unknowable: no measured activity levels or solubility testing results are reported for them, and no experimental evidence demonstrated “inactive mutant” proteins were in the supernatants tested for activity.²⁴⁷ And it did not even classify ~830 (12%) of the mutants.²⁴⁸

Even if only a fraction of a percent of the $\sim 10^{57}$ claimed multiply-modified PH20 polypeptides²⁴⁹ cannot be produced by the cells or will not properly fold, it would require an impossible amount of effort to find them—identifying each

²⁴⁵ *Id.*; EX1081, 895-897.

²⁴⁶ EX1003, ¶¶ 115, 125; *See Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1323 (Fed. Cir. 2005).

²⁴⁷ EX1003, ¶¶ 110-115; EX1001, 230:60-234:26, 255:51-256:67.

²⁴⁸ EX1003, ¶¶ 112, 114-15; EX1001, 234:26-255:51 (Table 9), 257:1-267:32 (Table 10).

²⁴⁹ 0.1% of $10^{43} = 1 \times 10^{39}$.

requires making and testing all $\sim 10^{57}$ mutants. Performing that scale of testing to find them independently demonstrates a lack of enablement.²⁵⁰

The common disclosure thus presents only a “research proposal” to discover “inactive mutants” with contraceptive utility, which does not enable this subgenus within the claims’ scope.²⁵¹

3. Dependent Claims 3-15 Are Not Enabled

(a) Claims 3-4

Claims 3 and 4 require the modified soluble human PH20 polypeptides to have increased activity (*i.e.*, >100% of unmodified PH20).

Claims 3 and 4 are not enabled for the same reasons that claims 1-2 are not enabled (*see* § V.B.1). Specifically, a skilled artisan could not have predicted which of the 10^{57+} of human PH20 polypeptides having up to 19 changes beyond a required change at position 320 would be soluble and exhibit increased activity

²⁵⁰ EX1003, ¶¶ 112, 115, 140-42; *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984); *Pharm. Res., Inc. v. Roxane Labs., Inc.*, 253 F. App’x. 26, 30 (Fed. Cir. 2007).

²⁵¹ *See Janssen Pharmaceutica N.V. v. Teva Pharms. USA, Inc.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009).

relative to unmodified PH20.²⁵² Instead, a skilled artisan would need to make-and-test each molecule in order to practice the “full scope” of the claims.

(b) Claims 5-15

Claims 5-15 employ the definition of the genus of modified soluble human PH20 polypeptides used in claim 1 to define nucleic acids, recombinant expression vectors, host cells, pharmaceutical compositions, methods of administering pharmaceutical compositions, and methods of manufacture. None of claims 5-15 limit the number of polypeptides in the claim 1 genus. They are therefore not enabled for the same reasons.²⁵³

C. The Original Claims of the '731 Application Do Not Cure the Written Description and Enablement Deficiencies

The original claims of the '731 Application provide no additional guidance demonstrating written description or enablement of the claimed genera of multiply-modified soluble human PH20 polypeptides. Those original claims claimed broad genera via sequence identity language (*e.g.*, 85% to SEQ ID NOS: 3, 7, or 32-66) (claims 1-3) or having up to “75 or more amino acid replacements” (claim 4). Dependent claims listed single positions (claim 12) or replacements (claims 13-16) in those polypeptides. And, while certain claims contemplated 2-3 particular

²⁵² EX1003, ¶¶ 161, 206-07.

²⁵³ *See, e.g., Idenix*, 941 F.3d at 1155, 1165.

combinations of amino acid replacements (from dozens listed), others encompassed substitutions at unspecified locations.²⁵⁴ The original claims do not provide § 112 support for the challenged claims.²⁵⁵

VI. Challenged Claims 1-2 and 5-15 Are Unpatentable Under § 103

Claims 1 and 2 encompass one specific modified PH20 polypeptide: D320K PH20₁₋₄₄₇. *See* § IV.D.2. Because this mutant would have been obvious from the '429 Patent in view of Chao and the knowledge of a skilled artisan, each of those claims is unpatentable.

Claims 5-15 are also obvious, as each recites attributes met by D320K PH20₁₋₄₄₇, or is suggested by the '429 Patent alone or with other prior art.

A. The Prior Art

The '429 Patent (EX1005) is owned by Patentee, was filed in 2003, and issued on Aug. 3, 2010.

Chao (EX1006) was published in 2007. Chao is not discussed in the common disclosure of the '773 Patent and '731 Application or in any rejection.

²⁵⁴ EX1026, at 335.

²⁵⁵ *See, e.g., Ariad Pharms.*, 598 F.3d at 1349; *Fiers v. Revel*, 984 F.2d 1164, 1170-71 (Fed. Cir. 1993).

Knowledge of the skilled artisan relevant to obviousness is described in the testimony of Drs. Hecht (EX1003) and Park (EX1004), and is also documented in the prior art, including Patentee's earlier-published application, WO297 (EX1007).

B. Because D320K PH20₁₋₄₄₇ Would Have Been Obvious, Claims 1-2 Are Unpatentable

Patentee's '429 Patent would have motivated a skilled artisan to produce modified soluble human PH20₁₋₄₄₇ polypeptides having a single amino acid substitution in non-essential regions of the protein. Guided by her familiarity with rational protein design and the teachings of the '429 Patent and Chao, the artisan would have known what regions in PH20₁₋₄₄₇ are non-essential, and which single amino-acid substitutions in them would that have been obvious to make and would have been tolerated (*i.e.*, a PH20₁₋₄₄₇ with that single substitution would retain its enzymatic activity). D320K PH20₁₋₄₄₇ is one such example. Because claims 1-2 encompass this obvious variant of PH20₁₋₄₄₇, each is unpatentable.

1. Patentee's '429 Patent Motivates a Skilled Artisan to Make Single Amino Acid Substitutions in Non-Essential Regions of PH20₁₋₄₄₇

Patentee's '429 Patent, filed in 2003, describes its invention as soluble PH20 hyaluronidase glycoproteins ("sHASEGPs") that are enzymatically active at

neutral pH.²⁵⁶ It exemplifies and claims one such “sHASEGP” that terminates at position 447 (positions 36-482 of SEQ ID NO: 1).²⁵⁷

The '429 Patent explains that sHASEGPs are useful in human therapy and illustrates administering pharmaceutical compositions of them, alone or with other therapeutic agents (*e.g.*, antibodies, chemotherapeutics) to treat cancer and hyaluronidase disorders.²⁵⁸ The FDA approved Hylenex[®] (PH20₁₋₄₄₇) in 2005,²⁵⁹ which would have induced a skilled artisan to focus on this particular PH20 polypeptide to practice the '429 Patent's teachings.²⁶⁰

Patentee's '429 Patent defines sHASEGPs as including PH20₁₋₄₄₇ “with amino acid substitutions that do not substantially alter activity” of the protein:²⁶¹

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

²⁵⁶ EX1005, 6:4-10, 10:30-59.

²⁵⁷ EX1005, 86:18-33, 86:64-87:13, 88:8, 89:52-90:15, 153:36-40.

²⁵⁸ EX1005, 8:25-9:4, 54:40-65, 56:34-57:36, 60:38-61:4, 63:41-61, 74:10-29, 76:19-77:36, 99:28-100:47.

²⁵⁹ EX1049, 1.

²⁶⁰ EX1003, ¶ 219.

²⁶¹ EX1005, 9:65-10:13; *see also id.* at 18:64-19:6 (“equivalent” proteins).

the resulting molecule. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity ...²⁶²

The '429 Patent explains that single amino acid substitutions can include “conservative” substitutions in Table 1, but “[o]ther substitutions are also permissible and can be determined empirically or in accord with known conservative substitutions.”²⁶³

The '429 Patent thus teaches making a *particular* type of modification (a single amino acid substitution) in *particular* locations (non-essential regions of PH20) in a *particular* PH20 (PH20₁₋₄₄₇) to yield equivalents of PH20₁₋₄₄₇ (*i.e.*, those that do not substantially alter the activity or function of PH20₁₋₄₄₇).²⁶⁴ It also motivates skilled artisans to undertake this effort to design and produce such singly-substituted PH20₁₋₄₄₇ proteins because it assures them their efforts will be successful.²⁶⁵ A skilled artisan thus would have expected a PH20₁₋₄₄₇ with a single

²⁶² EX1005, 16:14-22.

²⁶³ EX1005, 16:24-36.

²⁶⁴ EX1003, ¶ 230; EX1004, ¶ 32.

²⁶⁵ EX1003, ¶ 231; EX1005, 16:4-21.

amino acid substitution in a non-essential region to have the same therapeutic utilities the '429 Patent identifies for wild-type PH20₁₋₄₄₇ and other sHASEGPs.²⁶⁶

2. Chao Provides Information Useful for Engineering the Changes to PH20₁₋₄₄₇ that the '429 Patent Suggests

By 2011, a skilled artisan looking to implement the '429 Patent's suggestion to make single-amino acid modifications in non-essential regions of PH20₁₋₄₄₇ would have recognized such changes could best be accomplished using rational design techniques. She thus would have (i) identified the non-essential in PH20, and (ii) determined which substitutions to make in which positions in those non-essential regions.²⁶⁷ To do so, a skilled artisan would have looked for published guidance on the structure of human hyaluronidase enzymes (e.g., PH20).²⁶⁸ Chao (EX1006) provides that guidance—it reported an experimentally determined structure for human HYAL1 and provided new insights into the shared characteristics of human hyaluronidase enzymes.²⁶⁹

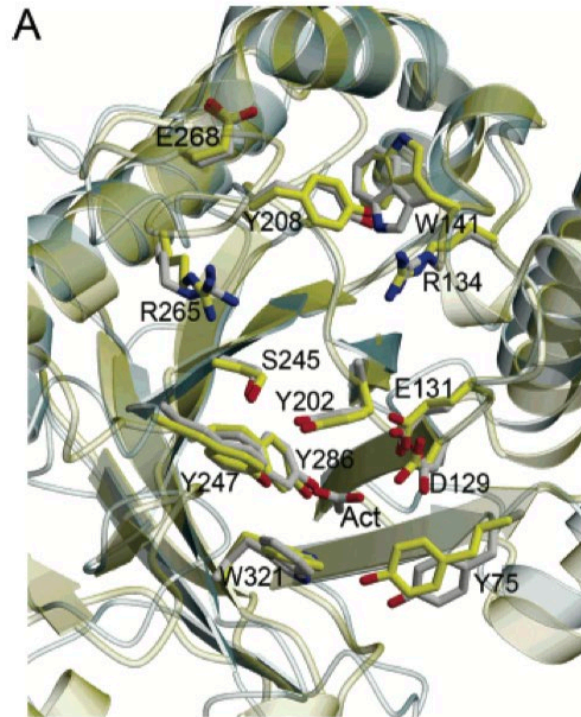
²⁶⁶ EX1003, ¶¶ 223-26, 231, 247.

²⁶⁷ EX1003, ¶ 236-38.

²⁶⁸ EX1003, ¶¶ 89, 233-35; EX1004, ¶ 88.

²⁶⁹ EX1003, ¶¶ 82-89; EX1004, ¶ 88; EX1006, 6912-17.

Chao showed that human and non-human hyaluronidases share a highly conserved active site and identified residues that interact with HA.²⁷⁰



Chao also provided an alignment of the five human hyaluronidases (Figure 3, below), and identified secondary structures (*e.g.*, β -sheets, α -helices), invariant conserved positions (blue), residues involved in catalysis (red), conserved cysteines that form disulfide bonds (gold), conserved glycosylated asparagine

²⁷⁰ EX1006, 6917 (Figure 4A); *see also id.* at 6914-16, Figure 2C; EX1004, ¶¶ 89-91; EX1003, ¶¶ 82-83; *also* EX1005, 4:12-22, 86:49-53, 88:14-24, 2:6-67, 4:11-22.

residues (turquoise), and “conservative replacements” showing variance across the aligned sequences (blue boxes).²⁷¹

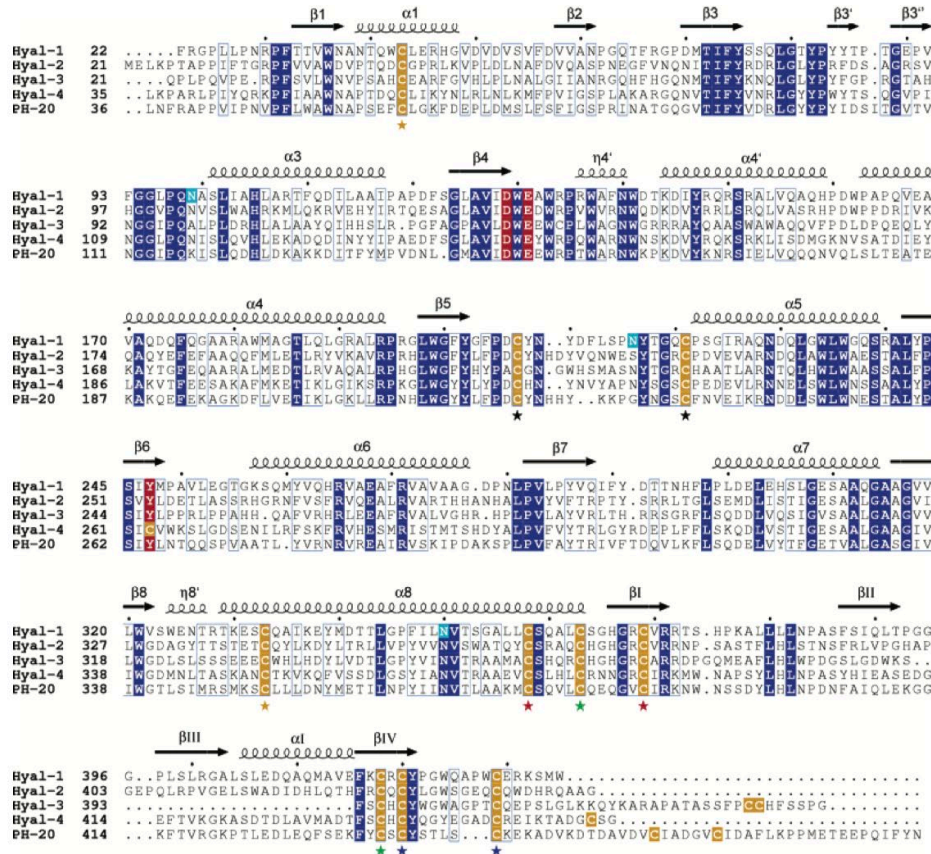


FIGURE 3: Structure-based sequence alignment of human hyaluronidases. Invariant residues are shown in blue except for three key catalytic residues that are colored red. Residues exhibiting conservative replacements are blocked in blue. Pairs of cysteine residues that form disulfide bonds are indicated by stars with matching colors. Secondary structure units are labeled as in Figure 2B.

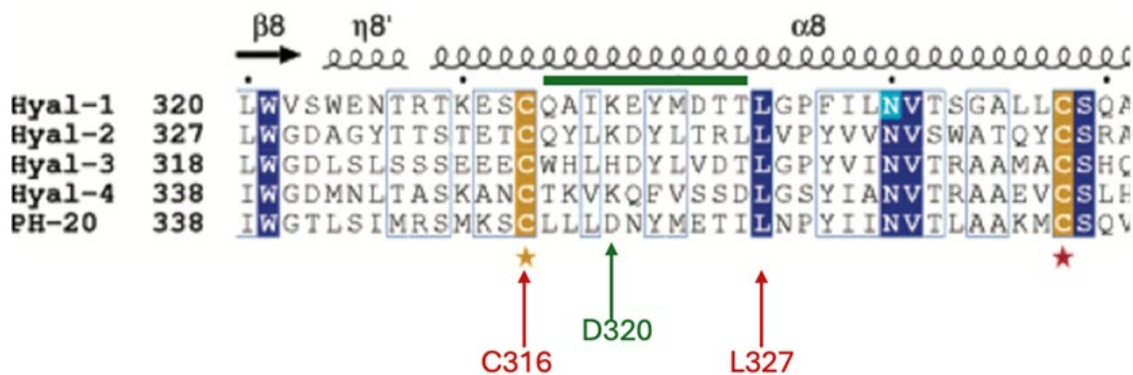
Chao also described “a novel, EGF-like domain” in the C-terminal region of human hyaluronidases “closely associated” with the catalytic domain (*see* § IV.A.2), and its characteristic pattern (in PH20 at positions 337-409).²⁷²

²⁷¹ EX1006, 6916; EX1003, ¶¶ 84, 235; EX1004, ¶ 92.

²⁷² EX1006, 6911; EX1004, ¶¶ 97-98; EX1003, ¶¶ 85, 88.

hyaluronidase protein sequences published by December 29, 2011.²⁷⁶ From Chao and that alignment he identified essential (Appendix D-3) and non-essential (Appendix D-2) residues in PH20.²⁷⁷

Dr. Park's analysis and Chao's Figure 3 both identify position 320 as being within one of the non-essential regions in PH20₁₋₄₄₇ (*i.e.*, in between C316 and L327) (below).²⁷⁸



²⁷⁶ EX1004, ¶¶ 27, 138-141; EX1053; EX1054; EX1055; EX1056; EX1064, 1, 4, 10, 23-28.

²⁷⁷ EX1004, ¶¶ 28-32, 142-143, Appendix D; EX1057; EX1058; EX1043, 1-2, 4-5; EX1065, 1, 4.

²⁷⁸ EX1003, ¶ 241; EX1004, ¶¶ 31-32, Appendix D-2; EX1006, 6916.

Thus, using information in the '429 Patent and Chao, and publicly known before December 2011, a skilled artisan would have readily identified position 320 as being a position within a non-essential region PH20₁₋₄₄₇.²⁷⁹

4. A Skilled Artisan Would Have Viewed Lysine as an Obvious Single Amino Acid Substitution for Aspartic Acid at Position 320 of PH20₁₋₄₄₇

The MSA reveals a second powerful insight: it identifies *which* amino acids have been tolerated at specific positions within naturally occurring structurally related hyaluronidase enzymes.²⁸⁰ This derives from evolutionary selection principles, which over the course of millions of years, function to eliminate from the genome of organisms those variations in the sequences of a protein that do not yield stable and active forms of the protein.²⁸¹

²⁷⁹ EX1003, ¶ 245; EX1004, ¶¶ 31-32, 104, Appendix D-2; EX1005, 16:14-22, 16:24-36; EX1006, 6916.

²⁸⁰ EX1003, ¶ 238; EX1004, ¶¶ 21-22.

²⁸¹ EX1003, ¶ 238; EX1004, ¶¶ 25, 31, 41-42; EX1017, 224 (evolutionarily conserved sequences useful for determining protein structure and function); EX1014, 351.

Using a MSA, a skilled artisan can readily compile a list of amino acids tolerated at each position within each non-essential regions of PH20.²⁸² Dr. Park did this: he identified the different amino acids that occur at positions corresponding to position 320 in PH20 in homologous hyaluronidases, and how many proteins contain each residue (below).²⁸³

		AA at position 355/320 in PH20 ₁₋₄₄₇		Most frequent AA at position in set of proteins	
wt 355:	D	10.22	K	57.95	
res394:	K	51	57.95] % of occurrence of AA in set of proteins
res394:	D	9	10.22		
res394:	H	9	10.22		
res394:	R	5	5.68		
res394:	N	5	5.68		
res394:	Q	4	4.54		
res394:	S	2	2.27		
res394:	G	2	2.27		
res394:	E	1	1.13		

The wild-type residue at position 320 in PH20 is aspartic acid (D), which occurs in ~10% of the proteins (including PH20). The most prevalent amino acid found at position 320 in this set of homologous sequences is lysine (K) (57.95%), which is present in 51 different hyaluronidase proteins.²⁸⁴

²⁸² EX1003, ¶¶ 238-39; EX1004, ¶¶ 21-22.

²⁸³ EX1004, ¶¶ 30-32, 41-43, 106, 116, Appendix D-1; EX1003, ¶¶ 239, 241-42.

²⁸⁴ EX1004, ¶ 116; EX1003, ¶ 242.

A skilled artisan would have considered position 320 to be a position within a non-essential region of PH20₁₋₄₄₇ at which a single amino acid substitution could be made pursuant to the guidance in the '429 Patent.²⁸⁵ The skilled artisan also would have selected lysine (K) as an obvious choice for such a single substitution at position 320 in PH20₁₋₄₄₇.²⁸⁶

First, lysine is the most prevalent amino acid at positions corresponding to 320 in PH20: it occurs in nearly 60% of the 88 homologous hyaluronidase enzymes known by 2011 (51 different naturally occurring hyaluronidase enzymes) and in 3 of the 5 human hyaluronidases (as shown in Chao Figure 3, above).²⁸⁷ Lysine's high frequency of occurrence at positions corresponding to 320 in PH20 in many other naturally occurring hyaluronidases would have motivated a skilled artisan to consider it for a substitution in position 320 of PH20.²⁸⁸

Second, Chao shows that position 320 is within an α -helix structure designated " $\alpha 8$ " within the non-essential region of PH20 between positions C316

²⁸⁵ EX1003, ¶¶ 241, 245.

²⁸⁶ EX1003, ¶¶ 245-46; EX1004, ¶¶ 41-42, 106, 116.

²⁸⁷ EX1004, ¶¶ 43, 106, 116; EX1003, ¶¶ 242, 245.

²⁸⁸ EX1003, ¶ 246; EX1004, ¶ 116.

Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity.²⁹²

Patentee also secured claims in the '429 patent to modified PH20₁₋₄₄₇ proteins with at least one substitution (*e.g.*, claim 1), despite not providing examples of PH20 proteins with any substitutions. Patentee, thus, made and relied on its statements that a skilled artisan would have expected *any* single amino acid substitution in *any* non-essential position of PH20₁₋₄₄₇ to not substantially affect the activity of the enzyme. Patentee should not be permitted to now contend a skilled artisan would not have reasonably expected that the D320K substitution in PH20₁₋₄₄₇ would yield an enzyme with substantially the same activity as unmodified PH20₁₋₄₄₇.

(b) Skilled Artisans Would Reasonably Expect D320K Substitution to be Tolerated in PH20₁₋₄₄₇

Independently, a skilled artisan would have reasonably expected human PH20 with the D320K substitution to be soluble and to retain hyaluronidase activity.

Both experts noted that many naturally occurring homologous hyaluronidase proteins contain lysine at positions corresponding to position 320 in PH20—

²⁹² EX1005, 16:17-20.

including, as Chao show, in 3 of the 5 human hyaluronidases. Dr. Park's MSA also shows that many (8) different amino acids occur in homologous proteins at positions corresponding to position 320 in PH20.²⁹³ The diversity of characteristics of those amino acids (*e.g.*, large or small side chains, high or low helix propensities, net positive, negative, or zero charges, etc.) suggests many different kinds of amino acids can be tolerated at position 320 in PH20.²⁹⁴

Consequently, a skilled artisan would expect the D320K substitution to be tolerated in PH20.²⁹⁵

(c) A PH20 Structural Model Confirms that PH20₁₋₄₄₇ Would Tolerate Lysine at Position 320

Dr. Park assessed whether single amino acid substitutions in PH20₁₋₄₄₇ would be tolerated, including D320K, using a PH20 protein structural model generated by SWISS-MODEL using Chao's HYAL1 structure as the template, as would have been done in 2011 by a skilled artisan.²⁹⁶ He explains that his PH20 model was reliable in the region of position 320 of PH20 based on QMEAN

²⁹³ EX1004, ¶ 106.

²⁹⁴ EX1003, ¶ 243; EX1004, ¶ 106.

²⁹⁵ EX1003, ¶¶ 245-46; EX1004, ¶¶ 70, 106, 116.

²⁹⁶ EX1004, ¶¶ 39-40, 144-145; EX1003, ¶¶ 249-253; EX1006, 6915, Figure 2; EX1017, 229; EX1012, 1-2, 4; EX1014, 348, 370; EX1038, 3382.

values,²⁹⁷ and would be very similar to a PH20 model generated by SWISS-MODEL in 2011 (*e.g.*, it used 165 conserved positions in the backbone of the two proteins).²⁹⁸ He also devised a consistent, objective methodology for assessing substitutions using the PH20₁₋₄₄₇ model.²⁹⁹ Factors he considered included, *inter alia*, the number of neighboring residues at position 320 (*i.e.*, those within 5 Å), the various possible interactions between neighbors (*e.g.*, hydrophobic, charged, van der Waals, steric, etc.), and solvent accessibility.³⁰⁰ Where interactions were observed, Dr. Park assessed the impact of them (*e.g.*, hydrophobic-hydrophilic, effects on secondary structures, size related issues such as steric clashes or creation/filling of “holes” in the structure).³⁰¹

²⁹⁷ EX1004, ¶¶ 146-148 (satisfactory local and global QMEAN values); EX1037, 346-47; EX1069, 3; EX1012, 4, 8.

²⁹⁸ EX1004, ¶¶ 149-150, 154; EX1038, 3382-84; EX1017, 229-30; EX1012, 1-2; EX1014, 348, 370; EX1066, 5-11.

²⁹⁹ EX1004, ¶¶ 102-103; *see generally id.* at § IV.C (description of Dr. Park’s methodology); EX1003, ¶¶ 239-40.

³⁰⁰ EX1004, ¶¶ 44-47, 53-60, 65-85, Appendix D-5; EX1035, 1408, Table 2; EX1043, 2, Table 1.

³⁰¹ EX1004, ¶¶ 62-63, 85.

Dr. Park assessed the environment of position 320 visually by comparing the wild-type with the version incorporating substituted amino acids at position 320 using functionality within the viewer (PyMol) and as a modeled sequence generated from the PH20₁₋₄₄₇ sequence incorporating the single substitution in SWISS-MODEL.³⁰² These technologies were available in 2011.³⁰³ He used his methodology to assess substitutions representing diverse interactions, and confirmed it provided a consistent, objective and unbiased evaluation of substitutions.³⁰⁴

Dr. Park assigned a score for each substitution reflecting the aggregate effect of the interactions he observed (below).³⁰⁵

<i>Score</i>	<i>Expected Impact</i>	<i>Expected Toleration</i>
1	Significantly Destabilized	Likely Not Tolerated
2	Neutral or Minor Impacts	Tolerated
3	Improved Stability	Tolerated

³⁰² EX1004, ¶¶ 61, 107, 115, 118, 122, 159-161; EX1003, ¶¶ 249, 251.

³⁰³ EX1004, ¶¶ 144, 149-150, 158, 160-162; EX1066, 1, 4, 7, 17, 25, 27, 35, 39, 41; EX1067, 1, 6-7, 53-57, 61-62; EX1012, 1-4; EX1003, ¶¶ 20-22.

³⁰⁴ EX1004, ¶¶ 102-103; EX1003, ¶¶ 239-240.

³⁰⁵ EX1004, ¶¶ 85-87.

Dr. Park assigned a score of 3 for the D320K substitution in PH20₁₋₄₄₇, indicating it would be expected to confer improved stability.³⁰⁶ He observed that in the wild-type environment, there is a deep hydrophobic pocket around position 320 that limits solvent accessibility to the side chains, but that it is exposed to solvent at the top.³⁰⁷ He also observed that there is a negative surface charge at position 320 that creates electrostatic repulsion with the charged carboxyl group of D320.³⁰⁸ When the lysine was substituted in position 320, Dr. Park observed that: (i) it introduces a stabilizing salt-bridge with E324 (left image), and a hydrogen bond to the main carbonyl group of P32, (ii) the long aliphatic chain of lysine participates in hydrophobic interactions with P32 and L317 residues (right image), and (iii) its positive charge offsets nearby negative charges.³⁰⁹ Overall, Dr. Park found that the D320K substitution would be stabilizing, meaning that D320K PH20₁₋₄₄₇ would be expected to retain the hyaluronidase activity of the unmodified PH20₁₋₄₄₇.³¹⁰

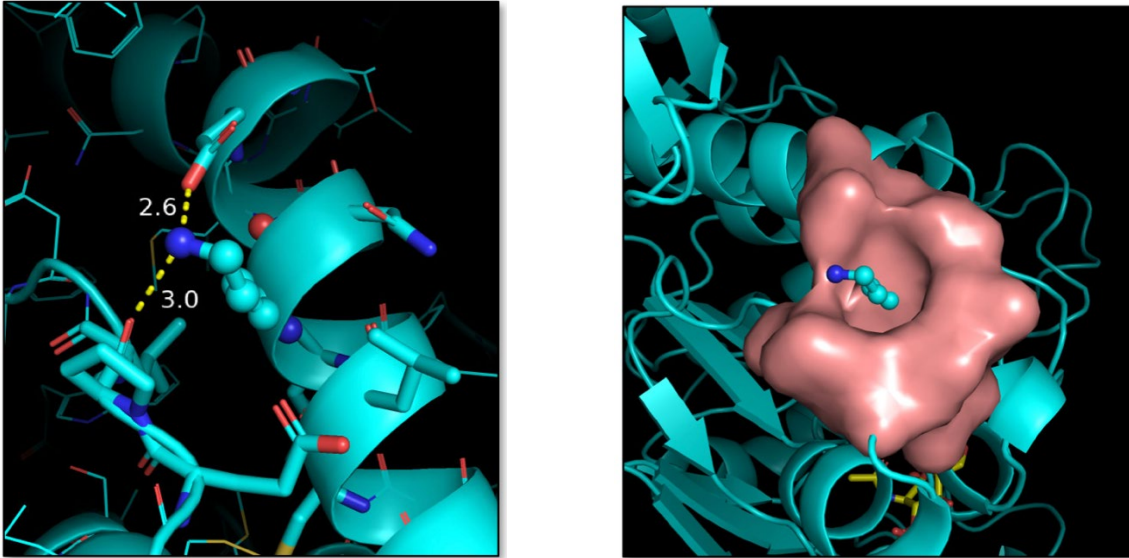
³⁰⁶ EX1004, ¶ 123, Appendix C.

³⁰⁷ EX1004, ¶ 110.

³⁰⁸ EX1004, ¶¶ 112-114.

³⁰⁹ EX1004, ¶¶ 119-121, 123.

³¹⁰ EX1004, ¶ 123.



Dr. Park's visualization-based assessment was a prevalent technique used in 2011.³¹¹ Similarly, his technique of assessing interactions between neighbors and assigning an overall score reflecting the aggregate effects of those interactions is consistent with methods reported in peer review publications.³¹²

³¹¹ EX1017, 228 (“... a structural biologist’s intuition is often an important tool in the design of the desired variants, an approach that may be termed structure-based protein design to borrow a term from the drug design field. Visualization of the known reference structure is a key component of this.”); EX1004, ¶¶ 22, 33-36; EX1003, ¶¶ 250-52.

³¹² EX1004, ¶¶ 48-52; EX1031, 459, 462-64, 469-71, Table 3; EX1032, 265-66; EX1003, ¶ 252.

Dr. Hecht reviewed Dr. Park's analysis and conclusions concerning the D320K single substitution and agreed with them.³¹³

The common disclosure defines an "active mutant" as a modified PH20 polypeptide with at least ~40% of the activity of unmodified PH20₁₋₄₄₇.³¹⁴ Drs. Hecht and Park each independently concluded that the D320K substitution would have been tolerated by PH20₁₋₄₄₇.³¹⁵ A skilled artisan thus would have reasonably expected that the D320K PH20₁₋₄₄₇ polypeptide would exhibit at least 40% of the activity of unmodified PH20₁₋₄₄₇.³¹⁶

(d) D320K PH20₁₋₄₄₇ Would Be Expected to Maintain Solubility

The claims require a "soluble human PH20 polypeptide." The '429 Patent indicates that PH20₁₋₄₄₇ is a soluble form of the PH20 protein because it truncates the C-terminal residues above position 448 (483) containing the GPI anchor sequence (i.e., it is C-terminally truncated).³¹⁷ A skilled artisan would have expected that changing aspartic acid (D) to lysine (K) at position 320 would not

³¹³ EX1003, ¶¶ 241, 254.

³¹⁴ EX1001, 73:65-74:6; *also id.* at 77:54-58.

³¹⁵ EX1003, ¶¶ 254-57; EX1004, ¶¶ 17, 123.

³¹⁶ EX1003, ¶ 257.

³¹⁷ EX1005, 3:57-62; 87:52-88:24.

affect the solubility of PH20₁₋₄₄₇ as it would not meaningfully alter the overall structure of the protein, as discussed above.³¹⁸

Based on the '429 Patent, Chao, and information available in 2011, the D320K PH20₁₋₄₄₇ mutant polypeptide would have been obvious to a skilled artisan in 2011. And because claims 1-2 encompass this single-substitution mutant, each claim is unpatentable.

C. Dependent Claims 5-15 Are Obvious

Each of claims 5-15 defines subject matter that would have been obvious to a skilled artisan.

1. Claims 5-7 and 15

Claims 5-7 specify a nucleic acid encoding any modified soluble human PH20 polypeptide of claim 1, a recombinant expression vector comprising that nucleic acid, and a host cell comprising that vector. Claim 15 similarly claims a method of recombinantly producing a genus that includes D320K PH20₁₋₄₄₇ by preparing a plasmid containing a cDNA encoding it, transfecting the plasmid into a host cell, culturing the cells, and harvesting the protein from the cell culture.

The '429 Patent teaches the recombinant production of PH20₁₋₄₄₇ in CHO cells comprising (i) preparing a nucleic acid encoding PH20₁₋₄₄₇, (ii) inserting it

³¹⁸ EX1003, ¶¶ 220, 227, 246-47.

into a plasmid expression vector, and (iii) transfecting CHO cells with the plasmid to produce the PH20₁₋₄₄₇ protein.³¹⁹ It also teaches “nucleic acid molecules that encode a polypeptide ... that have at least” 95% sequence identity with a full length PH20 (*i.e.*, up to 22+ substitutions).³²⁰

From their training and experience, and the guidance in the '429 Patent, a skilled artisan would have found it obvious to prepare and insert into a plasmid a nucleic acid encoding a single-replacement (*e.g.*, D320K) PH20₁₋₄₄₇, transfect a CHO host cell with it, express and then harvest the protein from the cell culture.³²¹ For example, Arming and Zhang both reported recombinant production of single-substitution forms of active soluble PH20 polypeptides.³²²

2. Claims 8-14

Claims 8-12 specify a pharmaceutical composition comprising any modified soluble human PH20 polypeptide in the genus of claim 1, alone (claim 8) or in combination with a therapeutically active agent (9), which may be selected from several types of active agents (10) such as an antibody (11), or “a small molecule

³¹⁹ EX1005, 89:54-90:15, 90:19-91:67.

³²⁰ EX1005, 11:60-66.

³²¹ EX1003, ¶¶ 222, 227.

³²² EX1011, 810-811; EX1010, 9433-35.

drug” (12). Claims 13-14 concern methods of administering the compositions of claim 9 parenterally (13) and subcutaneously (14).

The '429 Patent provides extensive guidance concerning and claims pharmaceutical compositions comprising soluble, neutral PH20 polypeptides (*e.g.*, PH20₁₋₄₇₇), alone or in combination with other therapeutic agents including antibodies and small molecule drugs.³²³ It similarly describes and claims methods of administering them subcutaneously, which is a form of parenteral administration.³²⁴

A skilled artisan would appreciate that a single-replacement PH20₁₋₄₄₇ polypeptide with similar expected activity to PH20₁₋₄₄₇ (such as the D320K mutant) would be equivalently useful in the therapeutic compositions and methods of administration described in the '429 Patent for PH20₁₋₄₇₇.³²⁵ Claims 8-12 also impose no restrictions on the makeup of the pharmaceutical compositions, and claim only categories of therapeutic agents to be used in combinations. A skilled

³²³ EX1005, 8:60-9:4, 54:52-55:35, 56:28-57:21, 55:61-56:9, 73:4-20, claims 14, 29, 33.

³²⁴ EX1005, 8:25-38, 56:28-56, 57:22-36, 58:59-59:12, 63:40-64:4, 76:18-77:37, claim 27.

³²⁵ EX1003, ¶¶ 223, 246, 257.

artisan, thus, would have found such agents and methods of administration to have been obvious.³²⁶

D. There Is No Nexus Between the Claims and Any Evidence of Putative Secondary Indicia

Evidence of secondary indicia cannot support non-obviousness if it does not have nexus to the claims. Nexus requires any such evidence to be commensurate with the scope of the claims. It is not here.

Patentee may contend that the D320K PH20₁₋₄₄₇ variant has unexpectedly high hyaluronidase activity as a single substitution mutant. Demonstrating that result for one mutant out of the $\sim 10^{57}$ modified soluble human PH20 polypeptides encompassed by the claims utterly fails to establish nexus. Per § V.A.1, the single-substitution D320K PH20₁₋₄₄₇ mutant is not representative of the numerous, structurally different multiply-modified proteins being claimed.

If Patentee advances evidence or arguments concerning nexus, that issue should be deferred until after institution.

VII. Discretionary Denial Issues

If Halozyme contends discretionary denial is warranted, Merck reserves the right to respond separately pursuant to the Acting Director's March 26, 2025 Memorandum.

³²⁶ EX1003, ¶ 223.

VIII. CONCLUSION

For the foregoing reasons, the challenged claims are unpatentable.

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EXHIBIT LIST

No.	Exhibit Description
1001	U.S. Patent No. 12,195,773
1002	File History of U.S. Patent No. 12,195,773
1003	Declaration of Dr. Michael Hecht
1004	Declaration of Dr. Sheldon Park
1005	U.S. Patent No. 7,767,429
1006	Chao et al., "Structure of Human Hyaluronidase-1, a Hyaluronan Hydrolyzing Enzyme Involved in Tumor Growth and Angiogenesis," <i>Biochemistry</i> , 46:6911-6920 (2007)
1007	WO 2010/077297, published 8 July 2010
1008	Stern et al., "The Hyaluronidases: Their Genomics, Structures, and Mechanisms of Action," <i>Chem. Rev.</i> 106:818-839 (2006)
1009	Jedzrejas et al., "Structures of Vertebrate Hyaluronidases and Their Unique Enzymatic Mechanism of Hydrolysis," <i>Proteins: Structure, Function and Bioinformatics</i> , 61:227-238 (2005)
1010	Zhang et al., "Hyaluronidase Activity of Human Hyal1 Requires Active Site Acidic and Tyrosine Residues," <i>J. Biol. Chem.</i> , 284(14):9433-9442 (2009)
1011	Arming et al., "In vitro mutagenesis of PH-20 hyaluronidase from human sperm," <i>Eur. J. Biochem.</i> , 247:810-814 (1997)
1012	Bordoli et al., "Protein structure homology modeling using SWISS-MODEL workspace," <i>Nature Protocols</i> , 4(1):1-13 (2008)
1013	Frost, "Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration," <i>Expert Opinion on Drug Delivery</i> , 4(4):427-440 (2007)
1014	Branden & Tooze, "Introduction to Protein Structure," Second Ed., Chapters 1-6, 11-12, 17-18 (1999)
1015	Table Associating Citations from the '773 Patent (EX1001) to Corresponding Citations in the '731 Application (EX1026)

No.	Exhibit Description
1016	Steipe, "Consensus-Based Engineering of Protein Stability: From Intrabodies to Thermostable Enzymes," <i>Methods in Enzymology</i> , 388:176-186 (2004)
1017	Green, "Computer Graphics, Homology Modeling, and Bioinformatics," <i>Protein Eng'g & Design</i> , Ch. 10, 223-237 (2010)
1018	Chica et al., "Semi-rational approaches to engineering enzyme activity: combining the benefits of directed evolution and rational design," <i>Curr. Opin. Biotechnol.</i> , (4):378-384 (2005)
1019	Hardy et al., "Assessment of contraceptive vaccines based on recombinant mouse sperm protein PH20," <i>Reprod.</i> , 127:325-334 (2004)
1020	Pomering et al., "Restricted Entry of IgG into Male and Female Rabbit Reproductive Ducts Following Immunization with Recombinant Rabbit PH-20," <i>Am. J. Reprod. Immunol.</i> , (3):174-82 (2002)
1021	Baba et al., "Mouse Sperm Lacking Cell Surface Hyaluronidase PH-20 Can Pass through the Layer of Cumulus Cells and Fertilize the Egg," <i>J. Biol. Chem.</i> , 277(33):30310-4 (2002)
1022	Primakoff et al., "Reversible Contraceptive Effect of PH-20 Immunization in Male Guinea Pigs," <i>Biol Reprod.</i> , 56(5):1142-6 (1997)
1023	Tung et al., "Mechanism of Infertility in Male Guinea Pigs Immunized with Sperm PH-20," <i>Biol. Reprod.</i> , 56(5):1133-41 (1997)
1024	Rosengren et al., "Recombinant Human PH20: Baseline Analysis of the Reactive Antibody Prevalence in the General Population Using Healthy Subjects," <i>BioDrugs</i> , 32(1):83-89 (2018)
1025	U.S. Patent No. 9,447,401
1026	U.S. Patent Application No. 13/694,731
1027	2024 Chemistry Nobel Prize Background
1028	Bordier, "Phase Separation of Integral Membrane Proteins in Triton X-114 Solution," <i>J. Biol. Chem.</i> , 256:1604-1607 (1981)

No.	Exhibit Description
1029	Gmachl et al., "The human sperm protein PH-20 has hyaluronidase activity," FEBS Letters, 3:545-548 (1993)
1030	Sills, "Retraction," Science, 319:569 (2008)
1031	Yue et al., "Loss of Protein Structure Stability as a Major Causative Factor in Monogenic Disease," J. Mol. Biol., 353:459-473 (2005)
1032	Wang & Moul, "SNPs, Protein Structure, and Disease," Hum. Mutation, 17:263-270 (2001)
1033	Marković-Housley et al., "Crystal Structure of Hyaluronidase, a Major Allergen of Bee Venom," Structure, 8:1025-1035 (2000)
1034	"Negative Results," Nature: Editorials, 453:258 (2008)
1035	Lins et al., "Analysis of Accessible Surface of Residues in Proteins," Protein Sci., 12:1406-1417 (2003)
1036	Hayden, "Chemistry: Designer Debacle," Nature, 453:275-278 (2008)
1037	Benkert et al., "Toward the Estimation of the Absolute Quality of Individual Protein Structure Models," Bioinformatics, 27:343-350 (2010)
1038	Schwede et al., "SWISS-MODEL: An Automated Protein Homology-Modeling Server," Nucleic Acids Res., 31:3381-3385 (2003)
1039	Alberts, "Molecular Biology of the Cell," Fifth Edition, Chapter 3 (2007).
1040	He et al., "NMR Structures of Two Designed Proteins with High Sequence Identity but Different Fold and Function," PNAS, 105:14412-14417 (2008)
1041	Alexander et al., "A Minimal Sequence Code for Switching Protein Structure and Function," PNAS, 106:21149-21154 (2009)
1042	Ruan et al., "Design and Characterization of a Protein Fold Switching Network," Nature Comm., 14 (2023)
1043	Sievers et al., "Fast, Scalable Generation of High-Quality Protein Multiple Sequence Alignments Using Clustal Omega," Molecular Sys. Biology, 7.1 (2011)

No.	Exhibit Description
1044	Mihel, "PSAIA – Protein Structure and Interaction Analyzer," BMC Structural Biology, 8:21 (2008)
1045	Redline Comparison of the '731 and '773 Specifications
1046	Beasley & Hecht, "Protein Design: The Choice of <i>de Novo</i> Sequences," J. Biological Chemistry, 272:2031-2034 (1997)
1047	Xiong et al., "Periodicity of Polar and Nonpolar Amino Acids is the Major Determinant of Secondary Structure in Self-Assembling Oligomeric Peptides," PNAS, 92: 6349-6353 (1995)
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1052	U.S. Patent Application No. 61/796,208
1053	Hom_pre2011
1054	Hom_pre2011_header
1055	Hom_pre2011_header_clean
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1058	Ph20_pre2011 Alignment html
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1062	[Reserved]

No.	Exhibit Description
1063	[Reserved]
1064	Collection of BLAST Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20111022151531/http://www.clustal.org/omega/
1065	Collection of Clustal Omega Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20111022151531/http://www.clustal.org/omega/
1066	Collection of SWISS-MODEL Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20110519141121/http://swissmodel.expasy.org/?pid=smh01&uid=&token=
1067	Collection of PyMol Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20110701072314/http://pymol.org/
1068	Declaration of Jeffrey P. Kushan
1069	Swiss Model Printout of PH20 Model
1070	Swiss Model Printout of PH20 Model with D320K Mutation
1071	Swiss Model Printout of PH20 Model with D320H Mutation
1072	Swiss Model Printout of PH20 Model with D320R Mutation
1073	[Reserved]
1074	[Reserved]
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1080	Bookbinder et al., "A Recombinant Human Enzyme for Enhanced Interstitial Transport of Therapeutics," J. Controlled Release, 114:230-241 (2006)
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CERTIFICATE OF COMPLIANCE

I hereby certify that this brief complies with the type-volume limitations of 37 C.F.R. § 42.24, because it contains 18,385 words (as determined by the Microsoft Word word-processing system used to prepare the brief), excluding the parts of the brief exempted by 37 C.F.R. § 42.24.

Dated: June 6, 2025

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on this 6th day of June, 2025, I caused to be served a true and correct copy of the foregoing and any accompanying exhibits by FedEx on the following counsel:

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