

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. IPR2026-00313
U.S. Patent No. 11,041,149

PETITION FOR INTER PARTES REVIEW

TABLE OF CONTENTS

I.	Introduction.....	1
II.	Compliance with IPR Requirements	5
A.	Certification of Standing	5
B.	Mandatory Notices	5
1.	<i>Real Party-in-Interest</i>	<i>5</i>
2.	<i>Related Proceedings</i>	<i>6</i>
3.	<i>Counsel and Service Information</i>	<i>6</i>
III.	Ground.....	7
IV.	Background on the '149 Patent	8
A.	Field of the Patent.....	8
1.	<i>Protein Structures</i>	<i>8</i>
2.	<i>Hyaluronidase Enzymes.....</i>	<i>13</i>
3.	<i>Protein Engineering.....</i>	<i>16</i>
B.	Person of Ordinary Skill in the Art	18
C.	Prosecution History	18
D.	The Challenged Claims.....	19
1.	<i>The Claim Parameters Define an Immense and Diverse Sequence Space</i>	<i>20</i>
2.	<i>The Claims Encompass or Require “Active Mutants”</i>	<i>23</i>
E.	Instituted PGR Challenges	26
V.	The Challenged Claims Are Not Entitled to Benefit of or Priority to Earlier-Filed Applications	28
A.	The Claims Are Not Supported by the Written Description of Prior Applications	30
1.	<i>The Disclosure Does Not Describe the Genera Defined by Claims 1-17.....</i>	<i>35</i>

(a)	The Claims Capture Structurally Diverse Enzymatically Active Modified PH20 Polypeptides.....	37
(b)	Examples in the Disclosure Show Unpredictability and a Limited Investigation of Types of Mutations.....	39
(i)	Examples Show Unpredictable Effects from Even Single Mutations	39
(ii)	Unpredictable and Unexplained Effects of Single Substitutions	42
(c)	The '731 Application Does Not Describe Species Reflecting the Diversity of Multiply-Modified PH20s Being Claimed	46
(i)	Singly-Substituted PH20 ₁₋₄₄₇ Active Mutants Are Not Representative of Multiply-Modified PH20s	46
(ii)	The '731 Application Discourages Multiply-Modified Active PH20s with Substitutions that Individually Render PH20 ₁₋₄₄₇ Inactive.....	49
(iii)	No Multiply-Modified Active PH20s with Significant C-terminal Truncations.....	50
(iv)	Disclosure Does Not Demonstrate Possession of Multiply-Modified Active PH20s	54
(d)	The Research Plan in the '731 Application Does Not Identify Any Multiply-Modified PH20 Polypeptides with Hyaluronidase Activity.....	55
(e)	The '731 Application Does Not Identify a Structure-Function Relationship for Multiply-Modified, PH20 Polypeptides with Activity or Increased Activity	58
(f)	The Claims Capture Multiply-Modified PH20 Polypeptides that the '731 Application Excludes from the Class of Enzymatically Active PH20 Proteins	62
2.	<i>Lack of an Express Activity Limitation Does Not Save Claim 17</i>	63
3.	<i>Dependent Claims 10-16 Lack Written Description.....</i>	64
B.	The Claims Are Not Enabled by the '731 Application	65

1.	<i>Claims 1-9 and 17 Are Not Enabled</i>	67
(a)	Extreme Scope of the Claims	68
(b)	Limited Working Examples and Only a Research Plan for Discovering Folded and Active Mutant PH20 Polypeptides.....	72
(c)	Making Multiple Changes to PH20 Polypeptides Was Unpredictable.....	77
(d)	Other Wands Factors and Conclusion	81
2.	<i>Claims 10-16 Are Not Enabled</i>	82
3.	<i>Even if Claim 17 Encompasses Inactive Mutants, It Is Not Enabled</i>	82
C.	The Original Claims of the '731 Application Do Not Cure the Written Description and Enablement Deficiencies	85
VI.	US-275 Anticipates Every Claim of the '149 Patent	85
VII.	Conclusion	93

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>In re '318 Patent Infringement Litigation</i> , 583 F.3d 1317 (Fed. Cir. 2009)	66
<i>AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.</i> , 759 F.3d 1285 (Fed. Cir. 2014)	31, 33, 56
<i>Amgen Inc. v. Sanofi</i> , 598 U.S. 594 (2023).....	65, 67, 71, 76
<i>Arbutus Biopharma Corp. v. ModernaTX, Inc.</i> , 65 F.4th 656 (Fed. Cir. 2023)	91, 92
<i>Ariad Pharms., Inc. v. Eli Lilly & Co.</i> , 598 F.3d 1336 (Fed. Cir. 2010) (<i>en banc</i>)	30, 31, 32, 56
<i>Arthrex, Inc. v. Smith & Nephew, Inc.</i> , 35 F.4th 1328 (Fed. Cir. 2022)	28, 29
<i>Atlas Powder Co. v. E.I. du Pont De Nemours Co.</i> , 750 F.2d 1569 (Fed. Cir. 1984)	67, 84
<i>Baxalta Inc. v. Genentech, Inc.</i> , 579 F. Supp. 3d 595 (D. Del. 2022) <i>aff'd</i> 81 F.4th 1362 (Fed. Cir. 2023)	66, 76
<i>Boehringer Ingelheim Animal Health USA Inc. v. Kan. State Univ. Research Found.</i> , PGR2020-00076, Paper 42, 6 (P.T.A.B. Jan. 31, 2022).....	34, 35, 65
<i>Boston Sci. Corp. v Johnson & Johnson</i> , 647 F.3d 1353 (Fed. Cir. 2011)	61
<i>Crown Operations Intern. Ltd v. Solutia Inc.</i> , 389 F.3d 1367 (Fed. Cir. 2002)	67
<i>Duke Univ. v. Sandoz Inc.</i> , 160 F.4th 1305 (Fed. Cir. 2025)	30

<i>In re Fisher</i> , 421 F.3d 1365 (Fed. Cir. 2005)	66
<i>Gentry Gallery, Inc. v. Berkline Corp.</i> , 134 F.3d 1473 (Fed. Cir. 1998)	62
<i>Halozyme, Inc. v. Merck Sharp & Dohme Corp.</i> , Case No. 2-25-cv-03179 (D.N.J.)	6
<i>Idenix Pharm., LLC v. Gilead Sciences, Inc.</i> , 941 F.3d 1149 (Fed. Cir. 2019)	<i>passim</i>
<i>Indivior UK Ltd. v. Dr. Reddy's Labs. S.A.</i> , 18 F.4th 1323 (Fed. Cir. 2021)	29
<i>Janssen Pharmaceutica N.V. v. Teva Pharms. USA, Inc.</i> 583 F.3d 1317 (Fed. Cir. 2009)	84
<i>In re Kirk</i> , 376 F.2d 936 (C.C.P.A. 1967)	66
<i>Merck Sharp & Dohme LLC v. Halozyme, Inc.</i> , PGR2025-00046, Paper 18 (P.T.A.B. Oct. 10, 2025)	27
<i>Novozymes et al., v. DuPont Nutrition Biosciences et al.</i> , 723 F.3d 1336 (Fed. Cir. 2013)	32, 33
<i>Pharm. Res., Inc. v. Roxane Labs., Inc.</i> , 253 F. App'x. 26 (Fed. Cir. 2007)	84
<i>Reckitt Benckiser v. Ansell Healthcare</i> , IPR2017-00063, Paper 38, 5, 15-16 (P.T.A.B. Jan. 30, 2018)	29
<i>Regents of Univ. of Minn. v. Gilead Sciences, Inc.</i> , 61 F.4th 1350 (Fed. Cir. 2023)	31
<i>Tianma Microelectronics Co., Ltd. v. LG Display Co., Ltd.</i> , IPR2025-01579, Paper 12 (March 18, 2026)	5
<i>Tronzo v. Biomet, Inc.</i> , 156 F.3d 1154 (Fed. Cir. 1998)	28

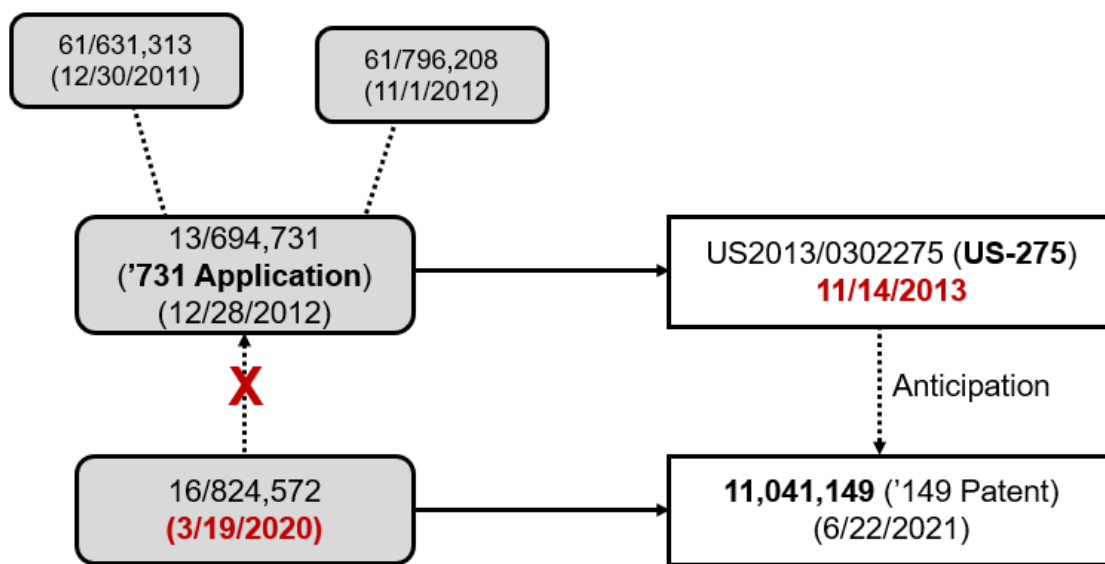
<i>In re Wands</i> , 858 F.2d 731 (Fed. Cir. 1988)	<i>passim</i>
<i>Wyeth & Cordis Corp. v. Abbott Labs</i> , 720 F.3d 1380 (Fed. Cir. 2013)	65, 76
<i>Zenon Envtl., Inc. v. United States Filter Corp.</i> , 506 F.3d 1370 (Fed. Cir. 2007)	29

Statutes

35 U.S.C. § 102	7, 8
35 U.S.C. § 102(a)(1)	85
35 U.S.C. § 102(b)	<i>passim</i>
35 U.S.C. § 112, second paragraph	<i>passim</i>
35 U.S.C. § 120	1, 28

I. Introduction

Petitioner Merck Sharp & Dohme LLC (“Merck”) requests *inter partes* review of U.S. Patent No. 11,041,149 (“’149 Patent”). Claims 1-17 (the “challenged claims”) are not entitled to the benefit of U.S. Application No. 13/694,731 (the “’731 Application”) under 35 U.S.C. § 120, as they are not supported by that application’s disclosure as § 112 requires.¹ As such, US-275,² which published the contents of the ’731 Application on November 14, 2013, is prior art that anticipates each of these claims (illustrated below).



¹ The claims are also not entitled to priority to U.S. Application Nos. 61/796,108 or 61/631,313. See § V.A.

² EX1004 (US2013/0302275) (“US-275”).

The written description and enablement deficiencies of all claims relative to the '731 Application mirror those of claims in fourteen other patents in the same family for which post-grant review (PGR) proceedings have been instituted. *See infra* § II.B.2. Claims 1-17 of the '149 Patent define modified human PH20 polypeptides that (i) ***must have*** one amino acid substitution/replacement at position 313, and (ii) ***may have*** up to between 20 and 41 ***optional additional*** substitutions at ***any*** of 430+ positions to ***any*** of 19 other amino acids. The challenged claims share these parameters with the claims of U.S. Patent No. 12,091,692 (“‘692 Patent”), the subject of instituted PGR2025-00046, and claims 1-16 add a requirement of “increased hyaluronidase activity.” Tellingly, Patentee has statutorily disclaimed claims in 13 of these other PGR-challenged patents that explicitly require the modified PH20s to possess activity or other functional properties.³ And challenged claim 17—the only claim that does not expressly recite

³ PGR2025-00003, EX2003 (claims 5-7); PGR2025-00004, EX2003 (claims 5-6); PGR2025-00006, EX2003 (claims 5-7); PGR2025-00009, EX2003 (claims 4-5, 15); PGR2025-00017, EX2003 (claims 4-5, 16); PGR2025-00024, EX2003 (claims 4-5, 16); PGR2025-00030, EX2003 (claims 4-5); PGR2025-00033, EX2003 (claims 4-5, 35); PGR2025-00039, EX2003 (claims 5-6);

“increased hyaluronidase activity”—is, in fact, nearly identical to claim 15 of the PGR-instituted '692 Patent, with just one word of difference (“replacement” vs. “modification”) that is immaterial to the § 112 issues.

The challenged claims here require an unidentified (and unknowable) genus of enzymatically active modified PH20 polypeptides within a massive “sequence space” (*i.e.*, sets of 10^{60} - $10^{113}+$ distinct amino acid sequences).⁴ Determining which are enzymatically active PH20s with increased hyaluronidase activity requires producing and testing them, an impossible task that would consume an aggregate mass ($\sim 8.63 \times 10^{38}$ kg) that exceeds that of Earth ($\sim 6 \times 10^{24}$ kg)!⁵

The '731 Application fails to provide adequate written description support for the claims. The examples it describes have only **one** amino acid substitution in **one** sequence (*i.e.*, PH20₁₋₄₄₇). Of those $\sim 6,700$ single-substitution PH20₁₋₄₄₇ mutants, ~ 800 exhibited $>100\%$ activity. But there are **no examples** of **any multiply**-modified PH20₁₋₄₄₇ polypeptides (with or without increased activity). The

PGR2025-00042, EX2003 (claims 4, 6); PGR2025-00046, EX2003 (claims 4, 6); PGR2025-00050, EX2003 (claims 4-5); PGR2025-00053 (claim 4).

⁴ EX1003, ¶¶ 184-186, 189, 196-197; *see also id.* ¶ 34.

⁵ EX1003, ¶¶ 186-189, 238; *see also, e.g.*, EX1039, 136-37 (10^{390} forms of a polypeptide possible from 300 residue sequence).

disclosure also does not identify or describe common structural features shared by enzymatically active ***multiply-modified*** PH20s (much less those with increased activity). At most, the disclosure supplies a prophetic, make-and-test, research plan to ***discover*** such PH20 polypeptides with increased activity. And given that POSAs could not even ***estimate*** what portion of the claims' sequence space will properly fold, the '731 Application cannot demonstrate possession of the claimed ***multiply-modified*** PH20 polypeptides with increased activity.

The '731 Application also does not enable the claims. It provides ***no examples*** of multiply-modified PH20 polypeptides with hyaluronidase activity and does not otherwise guide a POSA to select combinations of changes (substitutions, deletions and additions) that will yield properly folded, enzymatically active PH20s. Instead, it provides only a prophetic method that requires producing 10^{60} - 10^{113+} mutants and screening them to discover which (if any) exhibit hyaluronidase activity (or increased activity). The POSA is left to navigate the unpredictable effects that combinations of mutations have on polypeptides—including on their production, folding, stability, and enzymatic activity. The impossible scale of experimentation required to practice the full scope of the claims renders them non-enabled.

These written description and enablement deficiencies prevent the claims from being entitled to the benefit of the filing date of the '731 Application or either

of the provisional applications. US-275 is thus prior art to these claims. And because US-275 discloses several position 313 single-substitution PH20₁₋₄₄₇ mutants that exhibited increased activity (including M313K) that fall within the scope of the challenged claims, it anticipates every claim. Institution and a final written decision finding the claims unpatentable is warranted.

II. Compliance with IPR Requirements

A. Certification of Standing

Petitioner certifies (i) this Petition for *inter partes* review is filed within one year of service of a complaint alleging infringement of the '149 Patent and (ii) it is not barred or estopped from requesting this IPR. Petitioner and its privies have not filed a civil action challenging the validity of any claim of the '149 Patent.

B. Mandatory Notices

1. Real Party-in-Interest

Merck Sharp & Dohme LLC is the real party-in-interest for this Petition. Pursuant to the Director's instructions in *Tianma Microelectronics Co., Ltd. v. LG Display Co., Ltd.*, IPR2025-01579, Paper 12 (March 18, 2026), Petitioner further states that it is a wholly owned subsidiary of Merck & Co., Inc. Merck & Co., Inc. has no parent corporation, and no publicly held corporation owns 10% or more of its stock.

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, PGR2025-00050, PGR2025-00052, PGR2025-00053, PGR2025-00087, IPR2026-00312, and IPR2026-00314 are related proceedings.

On April 24, 2025, Patent Owner filed a complaint in *Halozyyme, Inc. v. Merck Sharp & Dohme Corp.*, Case No. 2-25-cv-03179 (D.N.J.), alleging infringement of, *inter alia*, the '149 Patent.

3. Counsel and Service Information

<u>Lead Counsel</u>	<u>Backup Counsel</u>	
Jeffrey P. Kushan Reg. No. 43,401 Sidley Austin LLP 1501 K Street, N.W. Washington, DC 20005 jkushan@sidley.com (202) 736-8914	Blaine M. Hackman Reg. No. 67,479 Dechert LLP Three Bryant Park 1095 Avenue of the Americas New York, NY 10036 blaine.hackman@dechert.com (917) 388-8306	Leif Peterson <i>Pro Hac Vice</i> forthcoming Sidley Austin LLP 1 S Dearborn Street Chicago, IL 60603 leif.peterson@sidley.com (312) 853-7190
	Katherine A. Helm <i>Pro Hac Vice</i> forthcoming Dechert LLP Three Bryant Park 1095 Avenue of the Americas New York, NY 10036 khelm@dechert.com (212) 698-3500	Sue Wang <i>Pro Hac Vice</i> forthcoming Sidley Austin LLP 101 California Street San Francisco, CA 94111

	Brian M. Goldberg <i>Pro Hac Vice</i> forthcoming Dechert LLP Cira Centre 2929 Arch Street Philadelphia, PA 19104 Brian.Goldberg@dechert.com (212) 698-3500 Mark Stewart Reg. No. 43,936 Merck Sharp & Dohme LLC 126 E. Lincoln Ave. Rahway, New Jersey 07065 mark.stewart@merck.com (732) 594-6302	sue.wang@sidley.com (415) 772-1243 Amy Mahan Reg. No. 75,997 Sidley Austin LLP 60 State Street Boston, MA 02109 amy.mahan@sidley.com (617) 223-0451 Christine M. Engen <i>Pro Hac Vice</i> forthcoming Sidley Austin LLP 1501 K Street, N.W. Washington, D.C. 20005 christine.engen@sidley.com (202) 736-8208 Amit Bhatla <i>Pro Hac Vice</i> forthcoming Sidley Austin LLP 1501 K Street, N.W. Washington, D.C. 20005 abhatla@sidley.com (202) 736-8075
--	--	--

Petitioner consents to service via e-mail at the email addresses listed above and at HalozymePGRs@sidley.com and Merck-Halozyme-Dechert@dechert.com.

III. Ground

Claims 1-17 are anticipated under 35 U.S.C. § 102 by US-275.

Petitioner's ground is supported by the evidence submitted with this Petition, including testimony from Dr. James Naismith (EX1003).

The full-length PH20 protein (SEQ ID NO: 6) includes a 35 amino acid signal sequence, and mature forms of PH20 differ from SEQ ID NO: 6 by 35 residues.⁶ "PH20_{1-n}" refers to a sequence of 1-n residues in PH20 (*e.g.*, PH20₁₋₄₄₇ is SEQ ID NO: 3, PH20₁₋₄₆₅ is SEQ ID NO: 35).

"AxxxB" is used to identify the position of a substitution (*e.g.*, the replacement of the methionine (M) with lysine (K) position 313 is "M313K." If the replacement is in SEQ ID NO: 3, then the modified PH20 polypeptide would be written as "M313K PH20₁₋₄₄₇."

IV. Background on the '149 Patent

A. Field of the Patent

The '149 Patent concerns the human PH20 hyaluronidase enzyme and making structurally altered forms of that protein that retain or enhance enzymatic activity.⁷

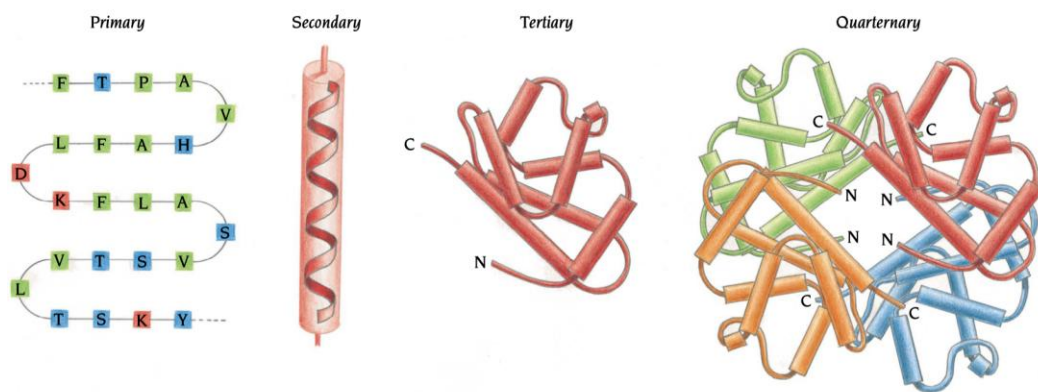
1. Protein Structures

Proteins are comprised of sequences of amino acids. A protein's activity derives from its unique, three-dimensional structure, which results when the amino

⁶ EX1003, ¶ 16.

⁷ EX1026, 1:20-22; *see also* EX1003, ¶ 35.

acid sequence folds to adopt the native state of the protein.⁸ That, in turn, is dictated by specific and often characteristic patterns of amino acids within its sequence. Those patterns of amino acids induce formation and maintenance of various secondary structures and higher-order structural motifs that are packed into compact domains that define the protein's overall structure (its “tertiary structure”).⁹



For example, secondary structures (α -helices, β -strands) are formed and stabilized by different but characteristic patterns of amino acids (below).¹⁰ “Loops” between sequences defining secondary structures are important too; they direct and

⁸ EX1003, ¶¶ 36-37.

⁹ EX1014, 3-4, 24-32, Figure 1.1; EX1039, 136-37 (Figure 3-11); EX1003, ¶¶ 37-39, 42-46.

¹⁰ EX1039, 134; EX1014, 14-22, Figures 2.2, 2.5, Table 2.1; EX1046, 2031-32; EX1003, ¶¶ 42-45.

facilitate positioning of the various secondary structures into higher-order structural motifs and the protein's overall structure.¹¹

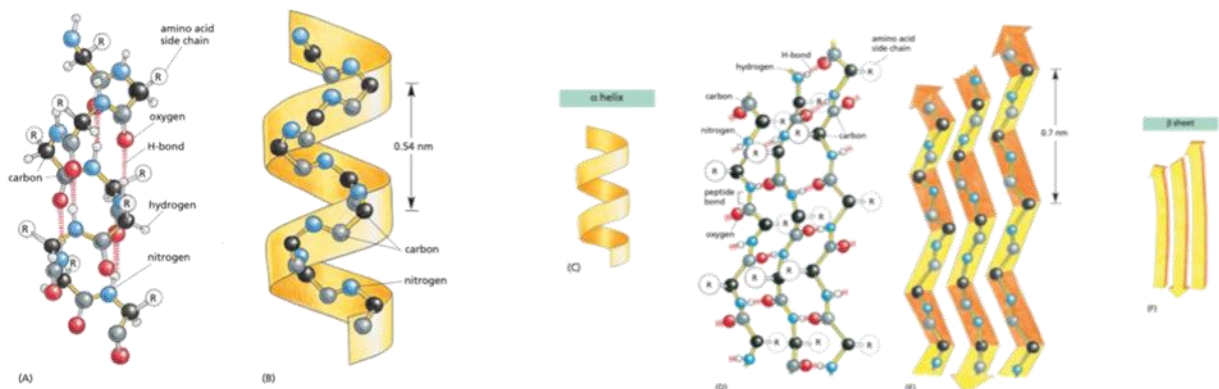


Figure 3-7 The regular conformation of the polypeptide backbone in the α helix and the β sheet. <GTAG> <TGCT> (A, B, and C) The α helix. The N-H of every peptide bond is hydrogen-bonded to the C=O of a neighboring peptide bond located four peptide bonds away in the same chain. Note that all of the N-H 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).

A PH20 polypeptide must fold into the tertiary structure of the wild-type human PH20 protein to have enzymatic activity.¹² During folding, however, it can adopt an immense number of intermediate conformations, each with different energetic states, which can slow or prevent the polypeptide from properly folding.

¹¹ EX1003, ¶¶ 43-46; EX1014, 21-22.

¹² EX1003, ¶¶ 48, 110, 203-204; EX1026, 118:7-8, 118:16-119:25, 55:28-33.

For example, if the polypeptide does not fold efficiently, it will be degraded by the cell or can form aggregates (below).¹³

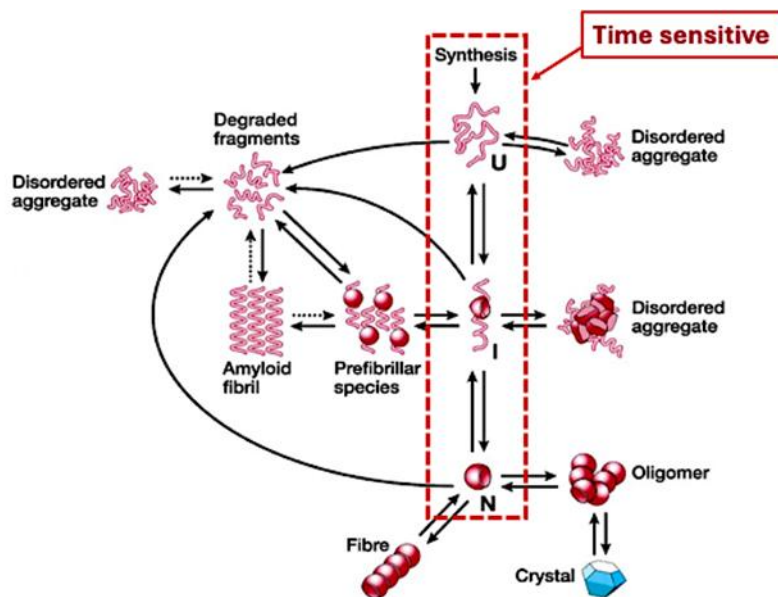


Fig. 5. Schematic representation of some of the states accessible to a polypeptide chain following its synthesis on a ribosome. The relative populations of the different states depend on the kinetics and thermodynamics of the various equilibria shown in the diagram. In living systems the fate of a given protein molecule is closely regulated by molecular chaperones and other quality control mechanisms, rather as metabolic pathways in cells are controlled by enzymes and associated molecules such as cofactors. From [36].

Changes to an enzyme's amino acid sequence can prevent it from being synthesized, properly folding, and/or remaining folded. Mutations can disrupt secondary structures and higher order motifs necessary to its tertiary structure, alter the spatial positioning of residues required for enzymatic activity or substrate

¹³ EX1003, ¶¶ 81-88; EX1136, 11 (Figure 5); *see also* EX1137, 888 (Figure 4); EX1138, 11 (Figure 2); EX1139, 351 (Figure 2); EX1131, 38:18–39:23, 43:3–23, 98:10-13.

binding, and/or destabilize the enzyme's structure.¹⁴ Unstable proteins can unfold, misfold and/or form aggregates.¹⁵ Even a single modification can cause these effects.¹⁶

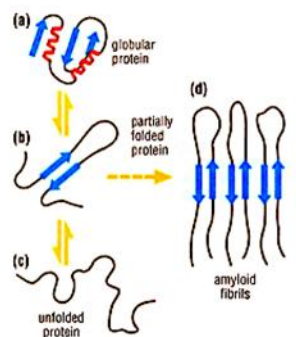


Figure 4-53 A possible mechanism for the formation of amyloid fibrils by a globular protein The correctly folded protein (a) is secreted from the cell. Under certain conditions, or because it contains a mutation, the protein unfolds partially (b) or completely (c); the unfolded forms can also refold partially or completely. The partially unfolded form is prone to aggregation, which results in the formation of fibrils (d) and other aggregates that accumulate in the extracellular space.

Making multiple changes to a protein's sequence can exacerbate these problems, especially when they are in or affect the same region(s) of the protein.¹⁷ For example, multiple changes can change the characteristic patterns, spacing and/or types of amino acids required to induce formation and stability of the enzyme's secondary structures, which can disrupt the formation, shape, or positioning of the secondary structures and structural motifs that make up the

¹⁴ EX1003, ¶¶ 41, 52, 77-81, 89-95 ; EX1136, 3-7; EX1144.

¹⁵ EX1003, ¶¶ 48, 52, 83, 195.

¹⁶ EX1003, ¶¶ 54-58, 72; EX1209, 160; EX1140, 329 (Fig. 1); EX1152, 80.1, 80.3; EX1158, 1, Abstract; EX1155, 10607; EX1156, 16419.

¹⁷ EX1003, ¶¶ 58, 73-75; EX1157, 808.

enzyme's tertiary structure.¹⁸ Multiple changes in different regions of the amino acid sequence can cause unfavorable spatial or long-distance interactions that destabilize or impair folding.¹⁹ Also, single mutations that are tolerated alone often are not tolerated in combination, and that increases with the number of mutations being combined.²⁰ Consequently, in 2011-2012, predicting the effects of more than a few substitutions was beyond the capacity of POSAs and computational tools available in the 2011-2012 timeframe.²¹

2. Hyaluronidase Enzymes

PH20 is one of five human hyaluronidases and is homologous—evolutionarily related to—hyaluronidases in many species.²² PH20 breaks down hyaluronan (“HA”) by selectively hydrolyzing glycosidic linkages.²³ Wild-type

¹⁸ EX1003, ¶¶ 41, 44, 73-78, 96; EX1047, 6349; EX1046, 2034; *see also* EX1040, 14412-13; EX1041, 21149-50; EX1042, 1-3.

¹⁹ EX1003, ¶¶ 46, 75-78, 80, 178.

²⁰ EX1003, ¶¶ 76-79, 97; EX1151, 743-44; EX1146, 22381-82; EX1160, 383-85.

²¹ EX1003, ¶¶ 99, 104-109; EX1027 at 8-11.

²² EX1007, 10:18-30; EX1006, 6911, 6916 (Figure 3); EX1003, ¶¶ 16, 119.

²³ EX1003, ¶ 119; EX1008, 819.

PH20 exists naturally as a GPI anchored protein; deletion of its GPI-anchoring sequence yields a soluble, neutral active enzyme.²⁴

Many essential residues in PH20 were identified before 2011-2012. Several are in the shared catalytic site of the protein;²⁵ mutating certain residues in or near that site can abolish enzymatic activity.²⁶ Conserved cysteine residues that stabilize the protein structure are also essential,²⁷ as are certain conserved asparagine residues involved in glycosylation.²⁸

In 2007, Chao reported an experimentally-determined structure of human Hyal-1, and illustrated shared secondary structures and conserved residues in human hyaluronidases.²⁹ Chao also showed that human and non-human hyaluronidases share a highly conserved active site and identified residues that

²⁴ EX1005, 2:40-61, 87:52-88:24; EX1013, 430-32 (Figure 2); EX1003, ¶¶ 141, 257-259; EX1029, 546 (Figure 1).

²⁵ EX1006, 6914-16, Figure 3; EX1007, 35:28-36:10; EX1011, 810-14; EX1008, 824-25; EX1009, 232-36.

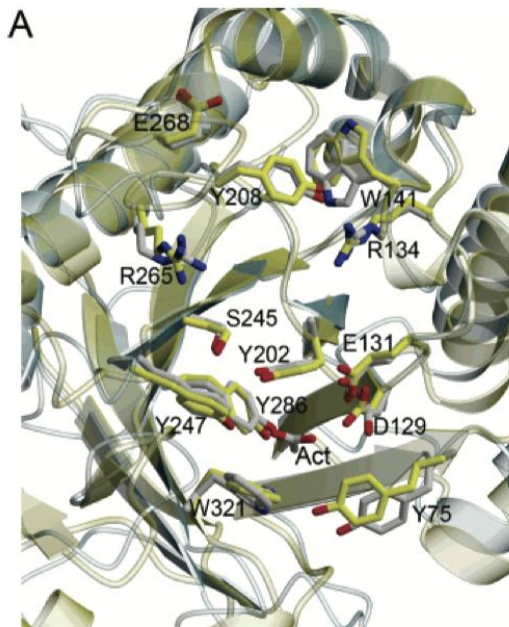
²⁶ EX1011, 812-14; EX1010, 9435-39 (Table 1).

²⁷ EX1006, 6914-16 (Figure 3); EX1011, 810-11; EX1005, 88:21-23.

²⁸ EX1005, 7:9-27; EX1007, 36:12-20; EX1010, 9433, 9435-40.

²⁹ EX1006, 6914-18.

interact with HA, *inter alia*, by superimposing Hyal-1 and bee venom hyaluronidase structures.³⁰



Among Chao's findings was that human hyaluronidases (including PH20) contain "a novel, EGF-like domain" in their C-terminal region³¹ that is "closely

³⁰ EX1006, 6912-6913, 6916-18 (Figure 4A); *see also id.* at 6914-16 (Figure 2C); EX1033, 1026 (Figure 1), 1028-29; EX1010, 9434, 9436 (Figure 1); EX1003, ¶¶ 123-125.

³¹ EX1006, 6911, 6917, 6913 ("The HyalEGF-like fold does not resemble the Hyal-1 C-terminal domain fold predicted by *ab initio* approaches (33).") (citing EX1009). *Also id.* at 6911-6913, 6915-6918 (Figures 2A, 2D, 4B); EX1010, 9434, 9436; EX1003, ¶¶ 126-29, 131.

associated” with the catalytic domain.³² Chao identified a characteristic pattern of residues for this “Hyal-EGF” domain (positions 337-409 in PH20).³³ The Hyal-EGF domain also is necessary for enzymatic activity—deletion of it “abolished” activity in Hyal-1, while bee venom hyaluronidase exhibits activity without it.³⁴

3. Protein Engineering

There are two general approaches used to engineer changes into proteins.³⁵ In “rational design,” POSAs employed computational tools—*e.g.*, sequence alignments and protein structure models—to study the protein and identify potential changes.³⁶ For proteins without a known structure, a homology model could be generated using a known structure of a homologous protein.³⁷ With varying confidence and important limitations, a POSA could use a homology

³² EX1006, 6911, 6913, 6914, 6917, 6918; see EX1003, ¶¶ 128-130; EX1079, 84.

³³ EX1006, 6911-6912 (Figure 3); EX1003, ¶¶ 128, 131.

³⁴ EX1010, 9439, 9441; EX1033, 1025; EX1003, ¶¶ 134-137, 192.

³⁵ EX1003, ¶¶ 59-61.

³⁶ EX1016, 181-82; EX1017, 223, 236; EX1003, ¶¶ 62-63, 99-100.

³⁷ EX1017, 228-30; EX1031, 461, 463, 469-71; EX1014, 351-52; EX1032, 265-66; EX1003, ¶¶ 101-105.

model to assess potential effects of changing one or a few amino acids within the local environment of the changes.³⁸ POSAs, however, could not use rational design techniques and homology models to predict the effects of making more than a few concurrent changes or of certain types of interactions (*e.g.*, long-distance or electrostatic), given the complexity of interrelated interactions and the limits of protein modeling tools.³⁹

“Directed evolution” techniques arose due to the limits of rational design.⁴⁰ 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.⁴¹ Importantly, until a desired mutant is made, found, and tested, whether it exists and its sequence are unknown.⁴² The disclosure embodies this approach.⁴³

³⁸ EX1003, ¶¶ 105-106, 132-133.

³⁹ EX1003, ¶¶ 64, 77, 105-108, 132-133, 138, 210; EX1027, 6-11 (Figure 6).

⁴⁰ EX1003, ¶ 65; EX1059, 1225-26; EX1018, 378.

⁴¹ EX1003, ¶¶ 66-68; EX1059, 1225-26; EX1018, 378.

⁴² EX1003, ¶ 66.

⁴³ EX1003, ¶¶ 68-71, 239-240, 253-54.

B. Person of Ordinary Skill in the Art

In 2011-2012 (*i.e.*, the filing date of the '731 Application and the provisional applications incorporated-by-reference thereto), a POSA 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 as techniques used to analyze protein structure (*i.e.*, sequence searching and alignments, protein modeling software, etc.).⁴⁴

C. Prosecution History

During examination, the claims of the '149 Patent were rejected under pre-AIA 35 U.S.C. § 112, second paragraph as being indefinite and for obviousness-type double patenting ("ODP") over the '400 Patent.⁴⁵ The indefiniteness rejection was overcome with an amendment to the claims and argument, and a terminal

⁴⁴ EX1003, ¶ 12-13.

⁴⁵ EX1002, 506-512.

disclaimer was filed to overcome the ODP rejection.⁴⁶ The prosecution history contains no indication that the Examiner considered written description or enablement issues, including a failure to establish a priority date earlier than the '149 Patent's filing date, when reviewing the challenged claims.

If Patentee contends discretionary denial is warranted, Petitioner reserves the right to respond separately pursuant to the Acting Director's March 26, 2025 Memorandum.⁴⁷

D. The Challenged Claims

The claim terms "PH20" and "modified PH20 polypeptide" are expressly defined in the disclosure.⁴⁸ The latter requires "at least one modification" to a PH20; the former requires the PH20 to be folded (*i.e.*, like native PH20).⁴⁹ All but

⁴⁶ *Id.*, 556, 564-578.

⁴⁷ <https://www.uspto.gov/sites/default/files/documents/InterimProcesses-PTABWorkloadMgmt-20250326.pdf>;
<https://www.uspto.gov/patents/ptab/faqs/interim-processes-workload-management>.

⁴⁸ EX1026, 50:31-32; 54:5-8.

⁴⁹ EX1003, ¶¶ 201-204.

one of the claims also expressly require the modified PH20s to “exhibit[] increased hyaluronidase activity,” which requires the modified PH20 to be properly folded.⁵⁰

A clear understanding of the ***breadth*** of the claims also is important. Each claims an unknown (and unknowable) number of folded and “active” mutants that are within a massive “sequence space” of between 10^{60} - 10^{113} different amino acid sequences. Because the disclosure does not identify—much less describe and enable—those claimed folded and “active” PH20s, the claims are not supported under § 112(a).

1. The Claim Parameters Define an Immense and Diverse Sequence Space

Parameters in the claims set boundaries that capture an immense number of structurally distinct amino acid sequences, of which an unknown portion will fold into “modified PH20 polypeptides” with hyaluronidase activity.⁵¹

Per independent claim 1, each polypeptide in this “sequence space”:

- ***must*** contain one ***amino acid replacement at position 313***; and

⁵⁰ EX1003, ¶¶ 179, 200, 203-207; see Declaration of Gregory A. Petsko, PGR2025-00003 (U.S. Patent No. 11,952,600), EX2070, 51, 128 (n.12), 345 (“POSAs think of PH20 as a folded protein.”) (Sept. 22, 2025).

⁵¹ EX1003, ¶¶ 194-97.

- **may** contain additional replacements, provided each polypeptide retains **at least 91% sequence identity** to one of 37 unmodified sequences (SEQ ID NOs: 3, 7, or 32-66), ranging in length from 430 (SEQ ID NO: 32) to 474 residues (SEQ ID NO: 7).

Certain dependent claims alter these parameters by restricting the sequence identity requirement (e.g., 95%, claims 7-8), the available unmodified SEQ ID NOs (claims 4-6, 8, 17), and/or restricting the permitted substitutions at position 313 (claims 2-5).

Assuming use of the longest-recited unmodified SEQ ID in each claim, those parameters translate into between 10^{60} - 10^{113} possible sequences (below):⁵²

⁵² EX1003, ¶ 186.

Claims	Max Length	Seq. Id. %	Max Changes	Pos. 313 Choices	# of Distinct Polypeptides
1, 9-16	474	91	42	19	1.20×10^{113}
2	474	91	42	8	5.05×10^{112}
3	474	91	42	1	6.32×10^{111}
4	433	91	38	1	1.00×10^{101}
5	465	91	41	8	1.13×10^{110}
6	465	91	41	19	2.68×10^{110}
7	474	95	23	19	9.85×10^{66}
8	433	95	21	19	9.65×10^{60}
17	447	91	40	19	2.65×10^{107}

Importantly, the sequence identity percentage claim parameter imposes ***no constraints*** on the location or nature of modifications (other than one substitution)—it is a ***mathematical*** boundary that captures sequences with up to 21 to 42 modifications, including any combination of: (i) substitutions, each to any of 19 other amino acids, (ii) deletions, and/or (iii) additions (to any of 20 amino acids).⁵³ With one exception,⁵⁴ each modified PH20 can include modifications at

⁵³ EX1026, 53:1-3, 68:18-34, 86:23-31, 88:12-15, 88:29-89:2, 114:19-24, 115:12-17, 144:9-14, 65:4-13; EX1003, ¶¶ 182-83, 190.

⁵⁴ EX1026, 88:29-89:2.

any position(s) in its amino acid sequence—conserved or non-conserved positions, surface or buried residues, within the active site or at substrate binding locations.⁵⁵

2. The Claims Encompass or Require “Active Mutants”

The disclosure describes two mutually exclusive categories of modified PH20: “active mutants” and “inactive mutants.”⁵⁶ It then classifies single-substitution mutants into tables of “active” or “inactive” mutants using the >40% threshold (Tables 3 and 9) or <20% threshold (Tables 5 and 10).⁵⁷ No examples of an “active mutant” modified PH20 polypeptide have two or more specific

⁵⁵ EX1003, ¶¶ 182-83; EX1130, 54:2–11, 90:25–91:12; EX1131, 55:22–56:23.

⁵⁶ EX1026, 86:12-18, 130:29-131:3, 272:3-5.

⁵⁷ EX1026, 251:1-4 (“Active mutants were selected whereby **at least one duplicate sample** exhibited greater than 40% of wildtype activity ...”); *id.* at 251:6-9 (Table 9 “...sets forth the **average hyaluronidase activity** of tested duplicates...”); 272:20-22 (“reconfirmed inactive mutants are set forth in Table 10.”), 56:24-27 (“increased activity” “means that, when tested under the same conditions, the modified PH20 hyaluronidase exhibits greater hyaluronidase activity...”); EX1003 ¶¶ 164-68.

substitutions,⁵⁸ much less one that contains: (i) a first substitution in Tables 3 or 9 **plus** (ii) a second substitution in Tables 5 and 10.

The common disclosure also portrays “active” and “inactive” mutants as having utilities with mutually exclusive properties. “Active mutants” have a variety of therapeutic uses ***because they possess hyaluronidase activity.***⁵⁹ However, the common disclosure identifies only one utility for “inactive mutants”: “antigens in contraception vaccines.”⁶⁰

Each claim encompasses (and all but one claim expressly requires) properly folded “active mutant” modified PH20 polypeptides meeting the sequence identity parameters of the claims.

Claims 1-16 require modified PH20 polypeptides with “increased hyaluronidase activity” (>100%) relative to an unmodified PH20.⁶¹ Claim 9 requires $\geq 120\%$ activity.

⁵⁸ *E.g.*, EX1003, ¶¶ 209-220.

⁵⁹ EX1026, 197:20-27; EX1003, ¶¶ 201-07.

⁶⁰ EX1026, 86:20-22 (“Also provided are modified PH20 polypeptides that are inactive, ***and*** that can be used, for example, as antigens in contraception vaccines.”); EX1003, ¶ 282-284; EX1060, 1711.

⁶¹ EX1026, 19:1-9, 108:24-109:8.

Regarding claim 17, the common disclosure's description of modified PH20 polypeptides indicates that they, at a minimum, encompass folded "active mutants." For example, it defines a "modified PH20 polypeptide" as "a PH20 polypeptide that contains at least one amino acid modification," but explains it can "have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide ***exhibits hyaluronidase activity***."⁶² This aligns with its prophetic methodology for discovering multi-modified PH20 polypeptides, which selects "active mutants" with one substitution, randomly introduces another, and then screens to find "double mutants" that ***retained*** hyaluronidase activity.⁶³ Further, the claims reference SEQ ID NOs: 591-598, which correspond to the M313A, M313G, M313H, M313K, M313P, M313R, M313T, and M313Y mutants that are all classified as "active" in the disclosure (see Table 9 below).

⁶² EX1026, 54:5-14, 53:13-19; EX1003, ¶ 203.

⁶³ EX1026, 150:1-26; *id.*, 47:11-18.

M313A	591	1.34
M313E		0.63
M313G	592	0.56
M313H	593	1.23
M313K	594	2.85
S312L		0.38
M313L		1.05
M313P	595	1.11
M313R	596	2.30
M313S		0.88
M313T	597	0.67
M313V		0.99
M313Y	598	1.12

Patentee may contend that claim 17 encompasses both “active” and “inactive” mutants, but that only compounds the § 112 problems. First, every claim still encompasses (and therefore must, but fails to, describe and enable) the subgenus of “active mutants.”⁶⁴ Second, analogous § 112 problems exist for the distinct subgenus of “inactive mutants”—those with putative (but implausible) utility as a contraceptive antigen⁶⁵—within the 10⁶⁰+ claimed PH20 polypeptides, which is neither described nor enabled. *See* §§ V.A.2, V.B.3.

E. Instituted PGR Challenges

The Board instituted PGR proceedings for fourteen challenged patents by finding that claims reading on a “modified PH20 polypeptide, comprising one or

⁶⁴ EX1003, ¶¶ 201-08.

⁶⁵ EX1003, ¶¶ 284.

more amino acid replacements in an unmodified PH20 polypeptide” more likely than not failed to satisfy § 112(a) for a lack of adequate written description and enablement. *See, e.g., Merck Sharp & Dohme LLC v. Halozyme, Inc.*, PGR2025-00046, Paper 18 (P.T.A.B. Oct. 10, 2025) (“*PGR-046*”). The challenged claims suffer from the same deficiencies as those identified by the Board in its PGR institution decisions. Thus, they are not entitled to the effective filing date of the ’731 Application, or any other earlier filing.

Claim 1 of the ’692 Patent, like claim 1 of the ’149 Patent, recites a modified PH20 polypeptide with a mutation at position 313 of SEQ ID NO: 3 and at least 91% sequence identity with SEQ ID NOs: 3, 7 and 32-66.⁶⁶ Although claim 1 of the ’692 Patent does not expressly recite hyaluronidase activity, the Board found that it does “encompass polypeptides with some hyaluronidase activity.” *PGR-046*, 14. Claim 17 of the ’149 Patent, which does not expressly recite “hyaluronidase activity,” is nearly identical in scope to claim 15 of the ’692 Patent, with only one word of difference (replacement v. modification) that is immaterial to the § 112 deficiencies, because a replacement is an example of a modification (below).⁶⁷

⁶⁶ EX1207, 317:19-44; EX1001, 311:41-64.

⁶⁷ EX1207, 318:41-49; EX1001, 311:21-28; *e.g.*, EX1026, 86:23-31.

'149 Claim 17	17. A modified PH20 polypeptide, comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 591-598, or a sequence of amino acids that exhibits at least 91% sequence identity to a sequence of amino acids set forth in any of SEQ ID NOs: 591-598 and that contains the amino acid replacement at residue 313 compared to corresponding positions in the amino acid sequence selected from the group consisting of SEQ ID NOs: 3 and 32-66.
'692 Claim 15	15. The modified PH20 polypeptide of claim 1, comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 591-598, or a sequence of amino acids that exhibits at least 91% sequence identity to a sequence of amino acids selected from the group consisting of SEQ ID NO: 591-598 and that contains an amino acid modification at residue 313 compared to corresponding positions in the amino acid sequence selected from the group consisting of SEQ ID NO: 3 and 32-66.

The Board concluded that the claims of the '692 patent—including claim 15—lacked written description and enablement in the '731 application . *PGR-046*, 22, 26, 32-33, 35, 37-38. For the same reasons—explained further below—the '731 Application lacks written description and enablement for '149 Patent claim 17.

V. The Challenged Claims Are Not Entitled to Benefit of or Priority to Earlier-Filed Applications

For claims to be entitled to § 120 benefit of or § 119(e) priority to the filing date of an earlier-filed application, they must be described in and enabled by the disclosures of those earlier-filed applications, as § 112 requires. *See Arthrex, Inc. v. Smith & Nephew, Inc.*, 35 F.4th 1328, 1343 (Fed. Cir. 2022) (citing *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1571 (Fed. Cir. 1997)); *Tronzo v. Biomet, Inc.*,

156 F.3d 1154, 1158 (Fed. Cir. 1998). If they are not, the claims' effective filing date can be no earlier than the filing date of the application that issued as the patent, and publication of the earlier-filed application can become invalidating prior art. *See, e.g., Indivior UK Ltd. v. Dr. Reddy's Labs. S.A.*, 18 F.4th 1323, 1330 (Fed. Cir. 2021); *Zenon Envtl., Inc. v. United States Filter Corp.*, 506 F.3d 1370, 1381-82 (Fed. Cir. 2007); *Arthrex*, 35 F.4th at 1342-44; *Reckitt Benckiser v. Ansell Healthcare*, IPR2017-00063, Paper 38, 5, 15-16 (P.T.A.B. Jan. 30, 2018).

That is the situation here. The '149 Patent claims the benefit of the '731 Application, which claims priority to and incorporates-by-reference the contents of two provisional applications (61/631,313, filed November 1, 2012 and 61/796,208, filed December 30, 2011). But (as explained below), the claims are not entitled to the filing dates of the '731 Application or the provisionals, as none of them provides written description and enablement support for those claims. Because the filing date of the claims is not prior to August 2, 2016, US-275, which published on November 14, 2013, anticipates each claim.⁶⁸

⁶⁸ The provisionals contain less disclosure than the '731 Application and are equivalently insufficient under § 112. EX1026, 1:3-11, 37:19-51:11, 140:15-150:26, 311:4-321:5, 6:25-26; EX1051; EX1052. The claims also lack § 112

A. The Claims Are Not Supported by the Written Description of Prior Applications

The written description analysis focuses on the four corners of the patent disclosure.⁶⁹ “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.”⁷⁰ If the claims define a genus using functional language, “the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the

support in the ’149 Patent’s disclosure, which is substantively identical to the ’731 Application (*see* EX1015).

⁶⁹ *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*).

⁷⁰ *Idenix Pharm., LLC v. Gilead Sciences, Inc.*, 941 F.3d 1149, 1163 (Fed. Cir. 2019); *see also Duke Univ. v. Sandoz Inc.*, 160 F.4th 1305, 1310 (Fed. Cir. 2025) (inventor must possess “full scope of the invention”).

functionally-defined genus.”⁷¹ “Otherwise, one has only a research plan, leaving it to others to explore the unknown contours of the claimed genus.”⁷²

“[A] genus can be sufficiently disclosed by ‘either a representative number of species falling within 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.’”⁷³ “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.”⁷⁴

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

⁷¹ *Ariad*, 598 F.3d at 1349.

⁷² *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300 (Fed. Cir. 2014).

⁷³ *Idenix*, 941 F.3d at 1164 (quoting *Ariad*, 598 F.3d at 1350); *see also Regents of Univ. of Minn. v. Gilead Sciences, Inc.*, 61 F.4th 1350, 1356-57 (Fed. Cir. 2023).

⁷⁴ *AbbVie*, 759 F.3d at 1299-1300.

satisfy § 112(a).⁷⁵ “[M]erely drawing a fence around the outer limits of a purported genus” is insufficient.⁷⁶

Four cases are especially probative here.

First, *Novozymes et al., v. DuPont Nutrition Biosciences et al.*, 723 F.3d 1336 (Fed. Cir. 2013) held claims directed to modified enzymes with one substitution, at least 90% sequence identity, and that exhibited “increased thermostability” lacked written description.⁷⁷ The Court rejected the premise that written description could be established by combining individual attributes of the enzymes reported in the specification, holding instead the disclosure must describe specific enzyme variants that possess those combinations of attributes.⁷⁸ The Court also held that written description cannot be established by a disclosure describing experiments that might discover additional species of mutated enzymes within the genus, but instead “actually making and testing individual variants or at least

⁷⁵ *Idenix*, 941 F.3d at 1164.

⁷⁶ *Ariad*, 598 F.3d at 1350-54.

⁷⁷ *Novozymes*, 723 F.3d at 1348.

⁷⁸ *Novozymes*, 723 F.3d at 1346, 1349 (“[T]he supporting disclosure of the 2000 application provides only generalized guidance listing several variables that might, in some combination, lead to a useful result.”).

identifying subclasses of variants that could be expected to possess the claimed properties....”⁷⁹ It also found insufficient the patent’s “roadmap” for discovering mutant enzymes with the desired functional property (thermostability).⁸⁰

Second, in *AbbVie*, the Federal Circuit found a disclosure of ~300 examples of a similar type of IL-12 antibodies was not representative of a genus of such antibodies of varying types.⁸¹ It also criticized a prophetic description as being “only a research plan, leaving it to others to explore the unknown contours of the claimed genus” using a “trial and error approach.”⁸²

Third, *Idenix* addressed method of treatment claims using a broad genera of compounds defined by “eighteen position-by-position formulas describing ‘principal embodiments’ of compounds that may treat HCV,” each with “more than a dozen options” at each position (totaling “more than 7,000 unique configurations”).⁸³ The court criticized the specification’s failure to indicate which of the thousands of compounds would be effective, finding that “provid[ing] lists

⁷⁹ *Novozymes*, 723 F.3d at 1350.

⁸⁰ *Id.*

⁸¹ *AbbVie*, 759 F.3d at 1300-01.

⁸² *Id.*

⁸³ *Idenix*, 941 F.3d at 1158-64.

or examples of supposedly effective nucleosides,” without “explain[ing] what makes them effective, or why” deprives a POSA “of any meaningful guidance into what compounds beyond the examples and formulas, if any, would provide the same result” because they “fail[] to provide sufficient blaze marks to direct a POSA to the specific subset of 2’-methyl-up nucleosides that are effective in treating HCV.”⁸⁴

Finally, the Board in *Boehringer Ingelheim Animal Health USA Inc. v. Kan. State Univ. Research Found.*, PGR2020-00076, Paper 42, 6 (P.T.A.B. Jan. 31, 2022) found unpatentable claims employing “90% sequence homology” language that captured a “broad genus of amino acid sequence homologues” but which (like these claims) imposed no restrictions where particular replacements could be made, thereby covering “at minimum, thousands of amino acid sequences.”⁸⁵ The Board found fatal 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 antigenic characteristics.⁸⁶ As it observed, the homology limitation “serves to merely draw a fence around the outer limits of a purported genus

⁸⁴ *Id.* at 1164.

⁸⁵ *Boehringer*, at 15-16.

⁸⁶ *Boehringer*, at 35; EX1026, 83:5-6.

[which] is not an adequate substitute for describing a variety of materials constituting the genus” for purposes of section 112(a).⁸⁷

The deficiencies of the challenged claims dwarf those in the aforementioned cases. They implicate much larger, more unpredictable, and more diverse sets of sequences, and the ’731 Application’s disclosure is far more limited. Because the ’731 Application neither discloses representative species of active modified PH20 polypeptides meeting the claim requirements, nor identifies structural features common to such modified PH20 polypeptides, it fails to demonstrate possession of the full scope of the challenged claims.

1. The Disclosure Does Not Describe the Genera Defined by Claims 1-17

Claims 1-9 claim genera of modified PH20 polypeptides exhibiting increased hyaluronidase activity within the claims’ sequence identity parameters. This requirement is express in the language of claims 1-16, and permitted by claim 17, which encompasses all active mutants in its sequence space. But the ’731 Application does not identify **which** of the $10^{60}+$ polypeptides within those claim parameters exhibit activity (or increased activity), much less demonstrates possession of all of them. As to claims 1-16, simply reciting a **desired**

⁸⁷ *Boehringer*, at 35-36.

hyaluronidase activity does not identify **which** members of the sequence space will exhibit those functional properties. As explained in the sections below:

- the claims define structurally heterogeneous genera of multiply-modified PH20s;
- examples of singly-modified PH20₁₋₄₄₇ in the disclosure are not representative of the heterogeneity of the claimed genera;
- the disclosure does not identify a common set of structural features that correlates to multiply-modified PH20s with activity (or increased activity);
- the disclosure's research plans do not describe any multiply-modified PH20s; and
- the claims capture combinations of modifications the disclosure instructs POSAs to not make.

And in response written description challenges to comparable “activity” claims in its related patents, Patentee statutorily disclaimed (rather than defended) those claims.⁸⁸

⁸⁸ *Supra* n.3.

(a) *The Claims Capture Structurally Diverse Enzymatically Active Modified PH20 Polypeptides*

The claims encompass multiply-modified PH20 polypeptides that are not only immense in number but are structurally diverse. The claim language permits:

- mutants with up to 20-41 substitutions, deletions, or additions (or combinations thereof), in addition to a required substitution at position 313;
- making sets of modifications anywhere within the PH20 sequence (*i.e.*, clustered in a narrow region, spaced apart in groups, or spread randomly throughout the sequence);
- substitutions that introduce physicochemically different residues, that can be made at surface or buried positions, and that can be arranged in any manner.⁸⁹

Sequence modifications permitted by the claim language can impair the ability of a mutated PH20 sequence to properly fold into and/or maintain the tertiary structure of PH20 required for activity.⁹⁰ For example, the claims permit introduction of a cluster of 5 hydrophobic residues at or near the protein surface, or substitutions resulting in random patterns of polar, charged, aliphatic, and aromatic

⁸⁹ EX1003, ¶¶ 180-83, 38-39; EX1026, 68:26-30, 53:1-3, 53:10-11, 46:19-23.

⁹⁰ EX1003, ¶¶ 197-98.

amino acids. Such changes can prevent formation of or alter secondary structures (α -helices, β -strands), alter loops that position them, alter or prevent formation of higher order motifs and/or domains (*e.g.*, Hyal-EGF), and/or impair functions of structures responsible for substrate binding or catalysis.⁹¹ Nothing in the '731 Application describes whether, or how, **combinations** of mutations will or will not result in a modified PH20 polypeptide with activity, much less increased activity.

Also claimed are multiply-modified PH20 polypeptides having up to 17 fewer (430) or 18 more (465) C-terminal amino acids than PH20₁₋₄₄₇: the only PH20 in which single mutations were tested. But data in applications incorporated-by-reference by the '731 Application show such truncations and additions unpredictably affect activity of wild-type PH20. *See* § V.A.1(c)(iii). The disclosure also contains **no examples** of single substitutions at positions beyond position 447.⁹²

⁹¹ §§ IV.A.1-IV.A.2; EX1003, ¶¶ 72-74, 78, 198, 210, 40.

⁹² EX1003, ¶¶ 151, 218; EX1026, Table 8.

(b) *Examples in the Disclosure Show Unpredictability and a Limited Investigation of Types of Mutations*

(i) Examples Show Unpredictable Effects from Even Single Mutations

The '731 Application reports results from testing a portion of a library of ~6,753 single-replacement PH20₁₋₄₄₇ mutants.⁹³ The mutants were produced by transfecting CHO cells with plasmids encoding mutagenized PH20₁₋₄₄₇ sequences where one of the 447 positions in the sequence “was changed to one of about 15 amino acid residues, such that each member contained a single amino change.”⁹⁴ Substitutions were only investigated in one length of PH20 (*i.e.*, PH20₁₋₄₄₇) and activities were only reported relative to the unmodified PH20₁₋₄₄₇ (SEQ ID NO: 3). Approximately 900 of the single mutations made were not classified, about 1,741 (~20%) of the possible single substitutions were never made, and no substitutions were made at positions beyond position 447.⁹⁵

⁹³ EX1026, 140:36-141:6, 220:27-28, 220:14-18; *see also* EX1003, ¶¶ 152-156.

⁹⁴ EX1026, 220:14-20; *see also* EX1003, ¶ 157.

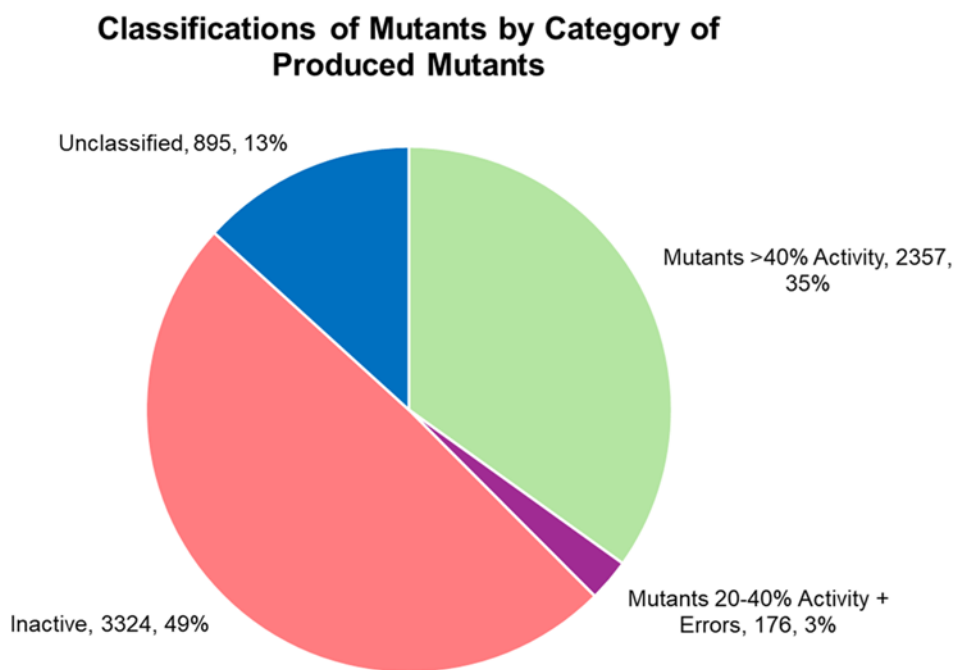
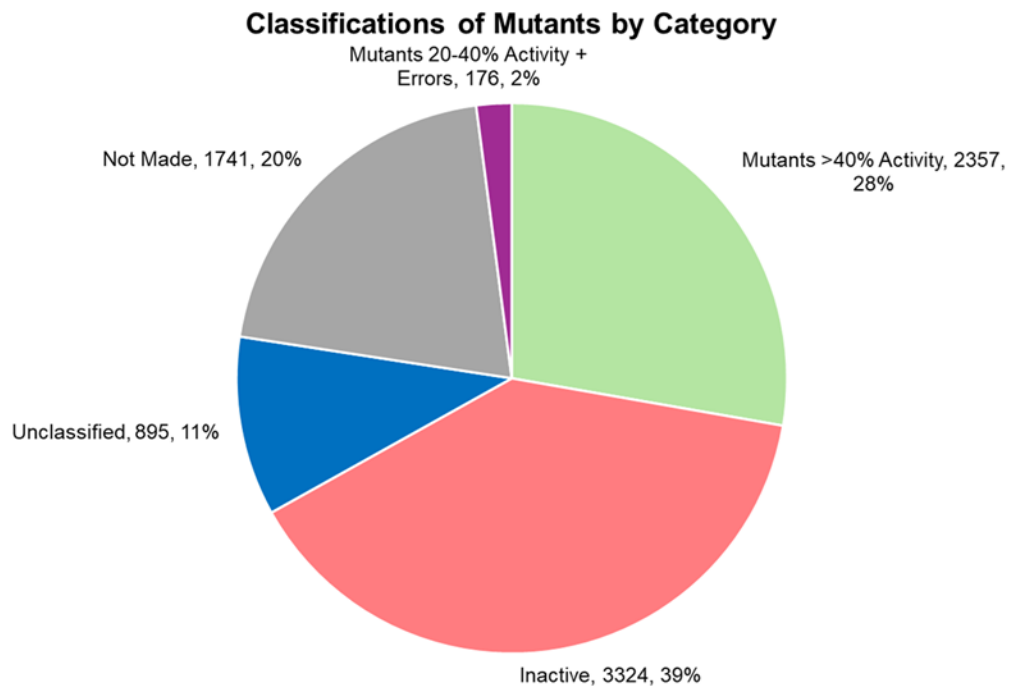
⁹⁵ EX1003, ¶¶ 151, 218.

Approximately ~5,917 such mutants were classified as “active” or “inactive” mutants.⁹⁶ More than half (~57%) of the tested mutants were classified as “inactive mutants” and ~30% had less activity than unmodified PH20₁₋₄₄₇ (20%-100%).⁹⁷ Thus, per the disclosure, ~87% of the 5,917 single-replacement PH20₁₋₄₄₇ polypeptides had ***decreased or no*** activity compared to unmodified PH20₁₋₄₄₇.

Activity vs. Unmodified PH20	Number	% of Tested (5,916)
Active Mutants (Table 9)		
>120%	532	9.0%
100%-120%	265	4.5%
40%-100%	1,562	26.4%
Inactive Mutants (Table 9)		
20-40%	127	2.1%
Inactive Mutants (Table 10)		
Number	3,330	56.3%
Double Counted Mutants		
Tables 9 & 10	50 (100)	1.7%

⁹⁶ EX1026, Tables 3, 5, 8-10; EX1003, ¶ 163. 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% hyaluronidase activity; (ii) Tables 5 and 10 list 3,368 and 3,380 PH20₁₋₄₄₇ “inactive mutants,” respectively, not accounting for errors.

⁹⁷ EX1003, ¶ 163; EX1135.



(ii) Unpredictable and Unexplained Effects of Single Substitutions

The empirical results reported in the '731 Application do not provide any guidance to a POSA about ***any particular combinations*** of substitutions to make to yield PH20 polypeptides with enzymatic activity or increased activity. Indeed, the data is not analyzed or interpreted in the '731 Application at all—it is simply presented.⁹⁸ The disclosure also does not describe the effect of any single substitution on the tertiary structure of PH20, much less provide a description that would permit a POSA to predict the effect of particular combinations of substitutions or other modifications.⁹⁹

The disclosure's data by itself also does not reveal trends or correlations even for single-replacement PH20₁₋₄₄₇ polypeptides.¹⁰⁰ For example, different substitutions at the same position in PH20₁₋₄₄₇ yielded active and inactive mutants, and ~900 mutants were not even classified.¹⁰¹

⁹⁸ EX1003, ¶¶ 175-176, 209-210, 214.

⁹⁹ EX1003, ¶¶ 114, 175-176, 209.

¹⁰⁰ EX1003, ¶¶ 173-175, 177.

¹⁰¹ EX1026, 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

POSAs recognized that changing multiple residues in PH20 polypeptides can cause unpredictable interactions within the protein's structure that can impact structure, stability, and function.¹⁰² The empirical test results for single substitution mutants do not identify to a POSA which of the 10⁶⁰-10¹¹³ PH20 mutants with 21-42 substitutions may have increased activity, or for that matter, exhibit lesser activity, are inactive, or cannot be secreted and properly folded.¹⁰³ The data shows that **most** single-substitutions were (for unexplained reasons) deleterious to production, secretion, stability, and/or activity of PH20.¹⁰⁴

No substitutions in PH20 wild-type sequences of different lengths were tested (§ V.A.1(c)(iii)). The '731 Application also reports that many single

¹⁰² EX1003, ¶ 177, 73-77.

¹⁰³ EX1003, ¶¶ 172, 210, 213-215.

¹⁰⁴ EX1003, ¶¶ 159-163, 175-176.

substitutions in PH20₁₋₄₄₇ at positions between 430 and 447 can render PH20 inactive.¹⁰⁵ Critically, it does not explain these unpredictable results.¹⁰⁶

TABLE 5: Inactive Mutants					
Corresponding Position	Replacement	Corresponding Position	Replacement	Corresponding Position	Replacement
430	A D E L M N S T V	431	P	432	C F I K L M P Y
434	H K P Q R W	437	T	438	Y
439	N R	440	Q	441	R
442	M N S	443	D		

The data's quality is also questionable: in addition to unexplained double-counting errors,¹⁰⁷ no control values or statistical assessments are provided for the primary assay.¹⁰⁸ The disclosure also does not reveal the measured hyaluronidase activities of 3,330 inactive mutants, or ~900 unclassified mutants.¹⁰⁹ Measured activities of 17 samples of unmodified PH20₁₋₄₄₇ are, however, reported in Example 5, and show unusually high variability (*i.e.*, ~40%) (below) in the assay, relative to the ~10% variability reported by US-457 for such assays.¹¹⁰

¹⁰⁵ EX1026, 136 (Table 5); EX1003, ¶¶ 231, 234.

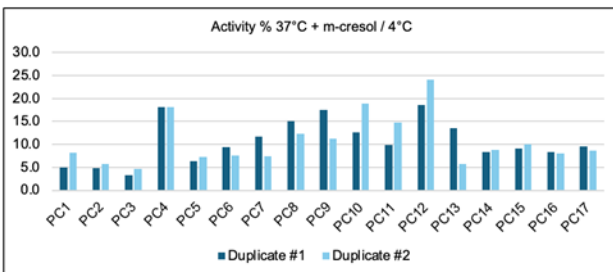
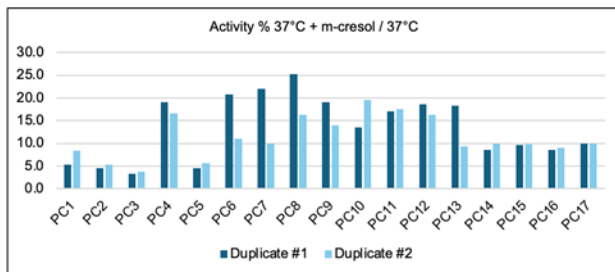
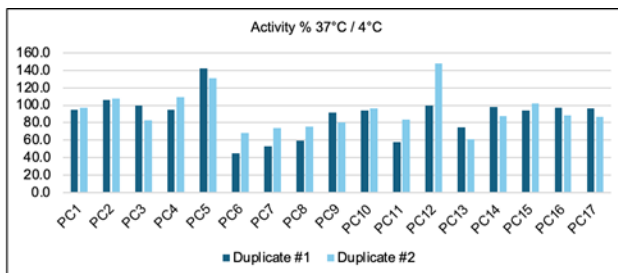
¹⁰⁶ EX1003, ¶¶ 98, 173.

¹⁰⁷ EX1003, ¶ 164.

¹⁰⁸ EX1003, ¶ 162.

¹⁰⁹ EX1003, ¶¶ 159-163.

¹¹⁰ EX1105, ¶ 271.



	Duplicate 1			Duplicate 2		
	% Activity at 37°C/4°C	% Activity at 37°C+m-cresol / 37°C	% Activity at 37°C + mcr/4°C	% Activity at 37°C/4°C	% Activity at 37°C+m-cresol / 37°C	% Activity at 37°C + mcr/4°C
High	142.02	25.24	18.56	148.23	19.45	24.07
Low	45.12	3.33	3.33	61.12	3.76	4.59
Range	96.91	21.91	15.23	87.11	15.70	19.48
Average	88.17	13.38	10.64	93.00	11.30	10.64
Mean	94.76	13.47	9.58	87.68	9.96	8.63

Assay Condition	Number of WT Measurements (n)	Mean WT Activity (μ)	Standard Deviation (σ)	Coefficient of Variation ($CV = \sigma/\mu$)
37 °C, No Preservative	17	3.756	1.488	40%
37 °C, + Preservative (m-cresol)	17	0.444	0.222	49%
4 °C, No Preservative	17	4.233	1.407	33%

The unusual variability of the hyaluronidase assay used to screen and classify single-mutants forecloses reliance on mutants with <40% activity, as well as the

~3,330 “inactive mutants” for which no measurements are provided; no conclusions can be made about the effects of such mutations on the folding, stability or activity of PH20s.¹¹¹

(c) *The '731 Application Does Not Describe Species Reflecting the Diversity of Multiply-Modified PH20s Being Claimed*

The '731 Application does not describe modified PH20 polypeptides reflecting the structural diversity of the enzymatically active, multiply-modified PH20s within the claims' sequence space, let alone the portion of them with increased activity. The claim language, read literally, also captures multiply-modified PH20s a POSA would have read as being excluded by the '731 Application's disclosure.

(i) Singly-Substituted PH20₁₋₄₄₇ Active Mutants Are Not Representative of Multiply-Modified PH20s

The '731 Application's disclosure of exemplified species of modified PH20s with activity or increased activity—all of which contains only **one** type of modification (a **single substitution**) in **one** truncated PH20 sequence (PH20₁₋₄₄₇)—does not reflect the structural diversity of the claimed genera of multiply-modified PH20s (§ V.A.1(a)).

¹¹¹ EX1003, ¶¶ 167-171; *see also* EX1026, 303:5-12 (positive control also varied); EX1148, 1235.

POSAs would not have expected enzymatically active PH20s with only one substitution to have a structure that is meaningfully different from the wild-type human PH20.¹¹² By contrast, POSAs would have expected that introducing multiple deletions, additions, and/or substitutions into the PH20 sequence could meaningfully alter portions of the PH20 tertiary structure.¹¹³ For example, deletions/additions can shift positioning of residues required for formation or positioning of secondary structures or higher order motifs in PH20s.¹¹⁴ Introducing combinations of substitutions can change or disrupt secondary structures and higher order structures even if they include one or more substitutions that individually did not impair folding or activity of a PH20.¹¹⁵ These more significant structural changes within the PH20 also can impair folding, stability, and activity of the PH20.¹¹⁶

Combinations of substitutions also can frequently cause effects not observed when those substitutions are made individually. For example, a first amino acid

¹¹² EX1003, ¶¶ 72, 97; EX1005, 16:4-36.

¹¹³ EX1003, ¶¶ 73-76, 210-213.

¹¹⁴ EX1003, ¶¶ 77-78, 213.

¹¹⁵ EX1003, ¶¶ 73-74, 78-80.

¹¹⁶ EX1003, ¶¶ 52, 58, 78, 90.

substitution may affect the neighbors of the replaced amino acid by (i) introducing a stabilizing interaction, (ii) removing a stabilizing interaction, and/or (iii) introducing a conflicting interaction (*e.g.*, adverse charge or hydrophobicity interactions).¹¹⁷ A second substitution in that region may reverse some or all of those interactions (or not), and a third substitution may do the same, and so on up to 21 rounds permitted by the narrowest claim (and 42 for the broadest). Many of these types of changes when combined can cause different effects than each change would cause by itself (including long-distance effects) that cannot be predicted from single substitutions in PH20.¹¹⁸

Further, POSAs knew that the ability of a protein to properly fold and remain folded is dictated by the combined effects of all of the residues in the protein (and interactions they are involved in).¹¹⁹ But making multiple changes to the protein's amino acid sequence will alter the net free energy of stabilization of a protein (which dictates whether it remains folded or unfolds) in ways that could not have been predicted by POSAs.¹²⁰ Despite this, the '731 Application provides no

¹¹⁷ EX1003, ¶¶ 72, 75, 97.

¹¹⁸ EX1003, ¶¶ 73-75, 78, 97, 210-212.

¹¹⁹ EX1003, ¶¶ 44, 47, 49-50; EX1131, 99:4-22.

¹²⁰ EX1003, ¶¶ 51-53.

information on structural effects of any of the single substitutions, much less sets of substitutions, or deletions/additions of amino acids.¹²¹

POSAs would thus not view single substitutions in active PH20₁₋₄₄₇ to reflect the structural and functional diversity of the enzymatically active PH20s having multiple changes, including those with numerous deletions, additions and/or sets of substitutions.¹²²

(ii) The '731 Application Discourages Multiply-Modified Active PH20s with Substitutions that Individually Render PH20₁₋₄₄₇ Inactive

The '731 Application instructs POSAs to not include in enzymatically active multiply-modified PH20 polypeptides substitutions that as single substitutions rendered PH20₁₋₄₄₇ inactive:

To retain hyaluronidase activity, modifications typically ***are not made*** at those positions that are less tolerant to change or required for hyaluronidase activity.¹²³

It identifies these changes as: (i) any substitution at 96 different positions in the PH20 sequence, and (ii) 313 specific substitutions in Tables 5 and 10.¹²⁴ The

¹²¹ EX1003, ¶¶ 114, 209, 214-219, 221-222.

¹²² EX1003, ¶¶ 97, 210-211, 219, 222.

¹²³ EX1026, 91:30-31 (emphases added).

¹²⁴ EX1026, 91:31-92:20.

disclosure does not limit this observation to single-replacement PH20₁₋₄₄₇ mutants. It also does not identify exceptions to this guidance, such as particular combinations of substitutions that both retained and abolished activity in PH20₁₋₄₄₇ as single substitutions.¹²⁵

A POSA thus would have understood from the '731 Application's disclosure that enzymatically active multiply-modified PH20 polypeptides (including those with increased activity) should not contain substitutions that, as single substitutions in PH20₁₋₄₄₇, resulted in "inactive mutants."¹²⁶ Logically, the '731 Application describes ***no examples*** of modified PH20s with such combinations. And despite this, the claim language does ***not*** explicitly exclude modified PH20 polypeptides having (i) one or more of the substitutions listed in Tables 3 or 9 ("active mutants"), plus (ii) one or more of the substitutions in Tables 5 and 10 ("inactive mutants").

(iii) No Multiply-Modified Active PH20s with Significant C-terminal Truncations

Despite explicitly claiming singly- and multiply-modified PH20s that terminate between positions 430-446 and 448-465, the '731 Application describes

¹²⁵ EX1003, ¶¶ 226, 229.

¹²⁶ EX1003, ¶¶ 224-225; EX1026, 91:30-92:20, 80:19-26.

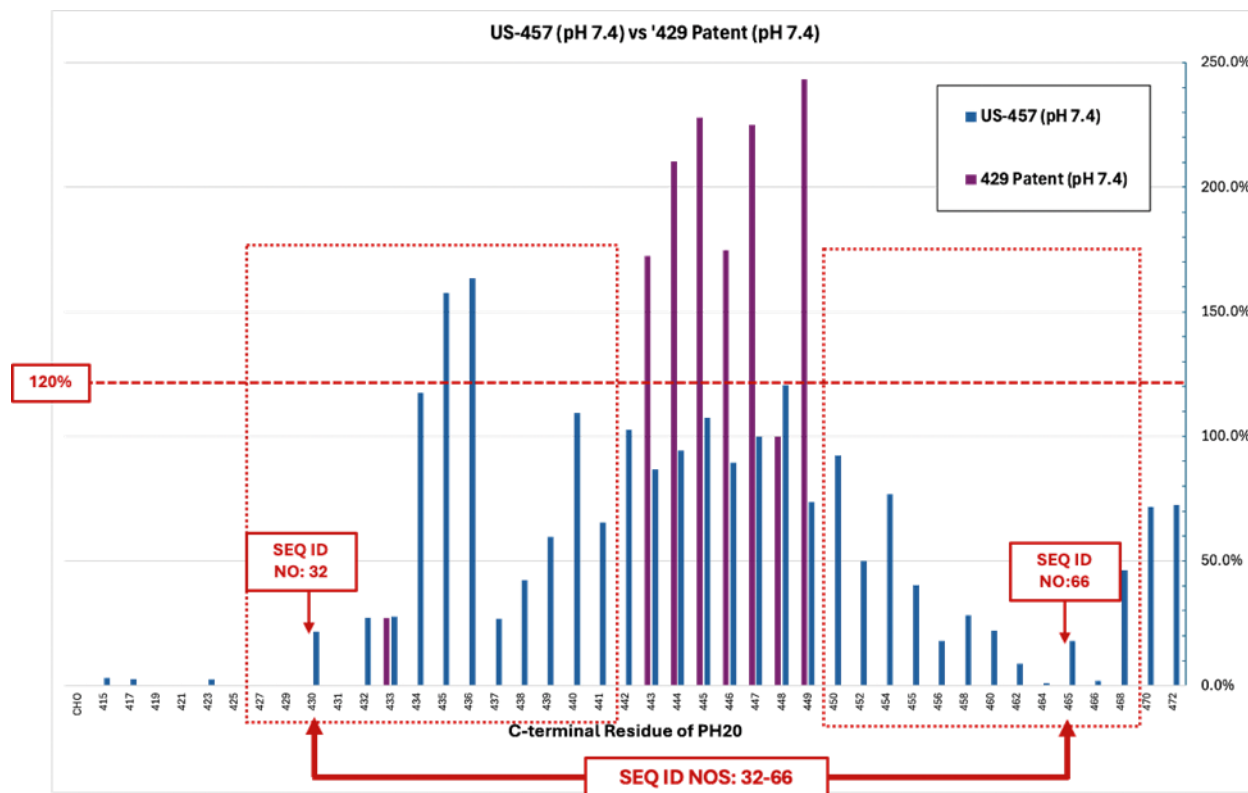
none.¹²⁷ But the activity of C-terminal truncation mutants terminating between positions 430 and 465 varies unpredictably, particularly those terminating between positions 430-442 and 449-465 (below).¹²⁸ For example, the PH20₁₋₄₃₆ mutant exhibits ~130% more activity than the PH20₁₋₄₃₇ mutant, with the latter having only one more residue. Despite this unpredictability, the disclosure describes no examples of modified PH20 polypeptides other than ones terminating at position 447, and no examples of any mutants with single substitutions above position 447.¹²⁹ There is also no explanation in the disclosure or the prior art for this variability, or any structural characterization of this region of the PH20 protein in the disclosure or the prior art.¹³⁰

¹²⁷ EX1003, ¶¶ 151, 211-212, 218, 240; EX1026, 84:21-25.

¹²⁸ See § V.A.1(a); EX1005, 87:52-88:24 (PH20₁₋₄₄₂ activity “decreased to approximately 10%”); EX1013, Fig. 2, 430-32 (“[l]ess than 10% activity was recovered when constructs terminated after amino acid 467 [432] or when using the full-length PH20 cDNA”); EX1003, ¶ 142-149.

¹²⁹ EX1003, ¶¶ 143-144.

¹³⁰ EX1003, ¶¶ 147-148, 151, 216.

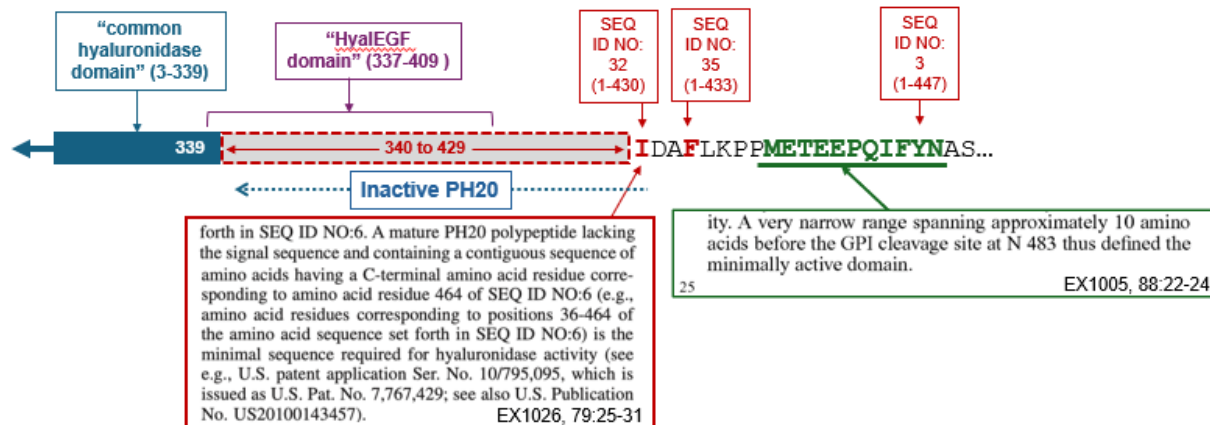


Compounding these deficiencies, the sequence identity language permits deletions to positions before position 430 and additions past position 465. But the disclosure portrays the sequence 1-429 as being necessary for enzymatically active PH20s, and inclusion of residues in the GPI anchor sequence causing PH20s to be insoluble.¹³¹

In 2007, Chao reported that the C-terminal region of human hyaluronidases contains a unique domain (“Hyal-EGF”) linked to a characteristic pattern of

¹³¹ EX1026, 79:25-31, 46:30-33, 81:22-82:31; EX1003, ¶¶ 230-231, 260-265; EX1005, 88:22-24, 6:65-7:7.

sequences, which runs from positions 337-409 in PH20.¹³² In 2009, Zhang showed the Hyal-EGF domain was necessary for hyaluronidase activity—truncations terminating at position 409 of Hyal-1 were inactive and not secreted.¹³³ While the '731 Application references a “common core hyaluronidase domain” (3-339 in PH20), it make no mention of Chao or Zhang or their findings, and does not explain how positions 3-339 relate to any feature in the tertiary structure of human PH20.¹³⁴ These regions are illustrated below.



The '731 Application does not explain how a POSA can navigate the unpredictability in activity of PH20s that deviate from the sole length of PH20 that is exemplified (1-447) when producing multiply-modified PH20s terminating

¹³² EX1006, 6912-13, 6916-18; EX1003, ¶¶ 126-128, 131.

¹³³ EX1010, 9438-39; EX1003, ¶ 134-136.

¹³⁴ EX1003, ¶ 139-140.

between position 430 and 465.¹³⁵ It provides no examples of singly- or multiply-modified PH20 polypeptides truncated to positions before 430, between 430-446, between 448-465, or above position 465, much less ones with increased activity,¹³⁶ even though the claims capture such mutants.¹³⁷

(iv) Disclosure Does Not Demonstrate Possession of Multiply-Modified Active PH20s

As explained above, the '731 Application reports no examples of **modified** PH20 polypeptides with **different lengths** (*i.e.*, SEQ ID NOS: 7, 32-66) or with **more than one substitution**.¹³⁸ Thus, despite claiming variants in PH20s having between 430 (SEQ ID NO:32) and 465 (SEQ ID NO: 66) residues, and having between 2 and up to 42 changes, all of the examples in the disclosure contain only a single substitution in a single length of PH20 (1-447) (illustrated below). Thus, like *Abbvie*, the disclosure demonstrates possession of only a limited number of species found in one corner of an immense genus of modified PH20 polypeptides being claimed.

¹³⁵ EX1003, ¶¶ 149-151.

¹³⁶ EX1003, ¶¶ 231, 234.

¹³⁷ EX1003, ¶¶ 232-233.

¹³⁸ EX1003, ¶ 231.

SEQ	Number of Changes																						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
3																							
7																							
32																							
33																							
34																							
35																							
36																							
37																							
38																							
39																							
40																							
41																							
42																							
43																							
44																							
45																							
46																							
47																							
48																							
49																							
50																							
51																							
52																							
53																							
54																							
55																							
56																							
57																							
58																							
59																							
60																							
61																							
62																							
63																							
64																							
65																							
66																							

(d) The Research Plan in the '731 Application Does Not Identify Any Multiply-Modified PH20 Polypeptides with Hyaluronidase Activity

The '731 Application does not describe **any** multiply-modified “active” PH20 polypeptides (including those with increased hyaluronidase activity).¹³⁹ Instead, it simply presents **the idea** that multiply-modified PH20 polypeptides can be made that **may** have hyaluronidase activity.¹⁴⁰

The '731 Application posits that “[a] modified PH20 polypeptide can have up to 150 amino acid replacements,” “[t]ypically” contains between 1 and 50

¹³⁹ EX1003, ¶¶ 212, 220-221, 234, 254.

¹⁴⁰ EX1003, ¶ 240.

amino acid replacements and “can include any one or more other modifications, in addition to at least one amino acid replacement as described herein.”¹⁴¹ It also contends a modified PH20 polypeptide with “a sequence of amino acids that exhibits” between 68% and 99% sequence identity with any of unmodified SEQ ID NOS: 74-855 “**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).”¹⁴²

None of these statements ***identify any particular*** multiply-modified PH20 polypeptides (*i.e.*, PH20 polypeptides with specific sets of 2 or more amino acid substitutions) that will properly fold and exhibit activity (or >100% activity). They simply draw boundaries around immense numbers of sequences, or list optional substitutions that may be considered for combination. Neither is an adequate description of ***particular species*** of chemical compounds (PH20 proteins).¹⁴³

¹⁴¹ EX1026, 54:8-14.

¹⁴² EX1026, 108:14-23 (emphasis added).

¹⁴³ EX1003, ¶¶ 222-223; *Ariad*, 598 F.3d at 1349-50; *AbbVie*, 759 F.3d at 1299-1300.

The '731 Application does not describe **any** multiply-modified, enzymatically active PH20 polypeptides that were made and tested.¹⁴⁴ It provides only a prophetic research plan requiring “iterative” production of libraries of mutants, followed by screening that **might discover** such PH20 polypeptides, stating they “**can be** modified or further modified” and “**can be** identified.”¹⁴⁵ This research plan does not identify **which** multiply-modified PH20 polypeptides can be made (e.g., which fold and are secreted), which **are** active mutants, and which active mutants have **increased activity** compared to wild-type PH20.¹⁴⁶ An alternative version of this “iterative” methodology suggests 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.”¹⁴⁷ But Tables 5 and 10 report at least one substitution at each of 405 positions between positions

¹⁴⁴ EX1003, ¶¶ 212, 220-221, 234, 254.

¹⁴⁵ EX1026, 150:1-9 (emphases added); *see also id.* at 47:12-17, 141:30-33; EX1003, ¶¶ 240-243, 244-246.

¹⁴⁶ EX1003, ¶¶ 250-254; EX1026, 140:15-16; *see generally id.*, 140:36-141:29, 141:36-143:34, 144:16-149:37.

¹⁴⁷ EX1026, 150:10-26; EX1003, ¶¶ 246, 248-249.

1 and 444 of PH20₁₋₄₄₇ resulted in an inactive mutant.¹⁴⁸ This guidance to “target” locations “near” ~90% of the amino acids in PH20₁₋₄₄₇ effectively “targets” **every residue**.¹⁴⁹

These prophetic research plans, based entirely on unfocused, iterative “make-and-test” experiments, do not identify to a POSA which of the 10⁶⁰+ multiply-modified PH20 polypeptides within the claims’ sequence space **are** active.¹⁵⁰ Instead, they require a POSA to perform repeated cycles of mutagenesis, screening and selection until 10⁶⁰+ modified PH20 polypeptides are made and tested.¹⁵¹ That in no way demonstrates possession of the **full scope** of “active mutant” modified PH20 polypeptides or those with increased activity.

(e) The '731 Application Does Not Identify a Structure-Function Relationship for Multiply-Modified, PH20 Polypeptides with Activity or Increased Activity

The '731 Application does not identify the structural significance of any of the ~2,500 mutations that yielded single residue “active mutant” PH20₁₋₄₄₇

¹⁴⁸ EX1003, ¶ 249.

¹⁴⁹ *Id.*

¹⁵⁰ EX1003, ¶¶ 251, 253-254.

¹⁵¹ EX1003, ¶¶ 199-200, 202-204, 214-216; EX1026, 144:2-6, 143:35-144:14, 147:36-148:2, 148:9-12, 148:23-32.

polypeptides (or the ~800 mutations that exhibited >100% activity).¹⁵² Its data is also **incapable** of providing such structural insights for the ~3,400 inactive mutants and ~900 unclassified mutants.¹⁵³ For example, it does not identify the effect of any substitution on any domain structure, structural motif(s), or secondary structure at the site of the substitution, nor does it identify how any such (possible) structural change(s) is/are responsible for the measured change in hyaluronidase activity.¹⁵⁴ Instead, it simply lists **single** replacements that yielded “active mutants.”¹⁵⁵ Notably, the ’731 Application does not identify any **sets** of substitutions in a single PH20 polypeptide that correlate to changes in structural domains or motifs that positively influence hyaluronidase activity, much less **predictably** increase activity.¹⁵⁶ And the disclosure’s examples of “active mutant” single-replacement PH20₁₋₄₄₇ mutants **by themselves** do not identify any “structure-function” relationship between “active mutants” and the set of single-replacement modified PH20₁₋₄₄₇ polypeptides, much less for mutant PH20 polypeptides of

¹⁵² EX1003, ¶¶ 208-219.

¹⁵³ EX1003, ¶¶ 215, 165-166; *supra* § V.A.1(c)(iv).

¹⁵⁴ EX1003, ¶¶ 209, 222, 227, 110-118.

¹⁵⁵ EX1026, 251:2-20; EX1003, ¶¶ 214.

¹⁵⁶ EX1003, ¶¶ 220-223.

varying lengths with between 21 and 42 substitutions.¹⁵⁷ Each is a unique sequence with a unique measured result.

The '731 Application ***does not contend*** a particular substitution that makes PH20₁₋₄₄₇ an “active mutant” will make any other modified PH20 polypeptide with that replacement plus 20-41 additional substitutions an active mutant.¹⁵⁸ Such an assertion would have no scientific credibility—the activity of a protein such as PH20 is dictated by its overall structure, which can be influenced unpredictably by different combinations of changes to its amino acid sequence.¹⁵⁹ Thus, the '731 Application does not portray its compilation of empirical test results as identifying a structure-function relationship for multiply-modified “active mutants” within the claims’ sequence space of 10⁶⁰-10¹¹³ polypeptides.¹⁶⁰

The '731 Application does not identify any particular structural features in the tertiary structure of native human PH20 as being “common structural features” of modified PH20 polypeptides with increased activity, and the human PH20

¹⁵⁷ EX1003, ¶¶ 208-219.

¹⁵⁸ EX1003, ¶¶ 97, 211-212.

¹⁵⁹ EX1003, ¶¶ 73-78, 198, 218.

¹⁶⁰ See, e.g., EX1026, 90:32-93:3, 108:24-109:27.

structure was not published until 2024.¹⁶¹ It omits any discussion of the PH20 Hyal-EGF domain or its necessity for activity, and does not describe the active site relative to other features of the tertiary structure of mammalian hyaluronidases.¹⁶² It also does not correlate any regions of the PH20 sequence to any such structural motifs.¹⁶³ And it nowhere mentions using a PH20 homology model to select combinations of changes to make to yield PH20s with activity (or increased activity).¹⁶⁴

The '731 Application thus does not identify to a POSA the ***structural features*** shared by the claimed multiply-modified PH20 polypeptides having hyaluronidase activity (or increased activity) within the scope of the claims.¹⁶⁵

¹⁶¹ EX1003, ¶¶ 102, 216-217; EX1126, 1067.

¹⁶² EX1008, 824, 829; EX1006, 6913.

¹⁶³ EX1003, ¶ 216, 222-223, 191-193.

¹⁶⁴ EX1003, ¶¶ 209, 216-217.

¹⁶⁵ EX1003, ¶¶ 217, 223; *Boston Sci. Corp. v Johnson & Johnson*, 647 F.3d 1353, 1366-67 (Fed. Cir. 2011).

(f) The Claims Capture Multiply-Modified PH20 Polypeptides that the '731 Application Excludes from the Class of Enzymatically Active PH20 Proteins

The '731 Application instructs that certain changes are to be avoided in active mutant PH20 polypeptides (*i.e.*, substitutions listed in Tables 5/10 or C-terminal truncations before position 429).¹⁶⁶ It also provides no guidance on incorporating substitutions in an inactive mutant having one of the substitutions in Tables 5 or 10 that would fully restore—or increase—enzymatic activity.¹⁶⁷ Yet the claims purport to capture such active mutants in multiply-modified PH20 polypeptides having changes the disclosure says to omit from “active mutants” (if any exist).¹⁶⁸

The claims thus independently violate the written description requirement pursuant to *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.

¹⁶⁶ EX1026, 91:30-92:20; EX1003, ¶¶ 224-225, 230-235.

¹⁶⁷ EX1003, ¶ 226-229.

¹⁶⁸ EX1003, ¶ 229.

2. Lack of an Express Activity Limitation Does Not Save Claim 17

Within claim 17's vast sequence space of $10^{107}+$ modified PH20 polypeptides are an unknowable number of active multiply-modified polypeptides. Some number of these polypeptides may exhibit increased activity compared to wildtype PH20.¹⁶⁹ Although Patentee may contend claim 17's lack of an express activity limitation means that claim 17 encompasses both "active" and "inactive" mutants, this broader reading of claim 17 still is not supported by the written description for the same reasons as claims 1-16. *Supra* §§ V.A.1; IV.E.

Analogous § 112 problems exist for the distinct subgenus of "inactive mutants" that Patentee may contend are useful as contraceptive antigens. The '731 Application does not indicate which (if any) of the $10^{107}+$ PH20 polypeptides in the sequence space have antigenic utility—the common disclosure does not provide examples of **any** antigenic mutant polypeptides.¹⁷⁰ The '731 Application does not identify **which** multiply-modified PH20 polypeptides can be even made, or their characteristics.¹⁷¹ The experimental protocol incorrectly equates the **absence** of

¹⁶⁹ EX1003, ¶¶ 181.

¹⁷⁰ EX1003, ¶¶ 282-88.

¹⁷¹ EX1003, ¶¶ 221-224, 239-241, 254-56; EX1026, 140:15-16; *see generally id.*, 140:36-141:29, 141:36-143:34, 144:16-149:37.

hyaluronidase activity in the supernatant from each transfected cell with an “inactive mutant.”¹⁷² This does not establish the mutant was made: no activity in the assay would be observed if the cell did not secrete the mutant or if the secreted mutant did not fold, and the disclosure does not explain what caused each inactivity classification.¹⁷³ It is thus impossible to determine from the disclosure which of its ~3,330 inactive or ~900 unclassified mutants were (i) actually expressed, properly folded and enzymatically inactive, (ii) not successfully produced by or secreted from the transfected cells, or (iii) secreted but did not fold.¹⁷⁴

3. Dependent Claims 10-16 Lack Written Description

Claims 10-16 depend from claim 1 and recite further modifications (*e.g.*, glycosylation, polymer conjugation, heterologous signal sequence) to the modified PH20 polypeptides (claims 10-14), inclusion of the modified PH20 polypeptide in a chimeric polypeptide (claim 15), or a pharmaceutical composition comprising the

¹⁷² EX1003, ¶¶ 158-162.

¹⁷³ EX1003, ¶¶ 161; EX1026, 251:21-272:1 (Table 9), 272:23-282:2 (Table 10).

¹⁷⁴ EX1003, ¶¶ 160-62.

modified PH20 polypeptides (claim 16). They lack written description for the same reasons explained in § V.A.1.¹⁷⁵

B. The Claims Are Not Enabled by the '731 Application

“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.”¹⁷⁶ “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.”¹⁷⁷ “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.”¹⁷⁸

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

¹⁷⁵ *Idenix*, 941 F.3d at 1155, 1165; *Boehringer*, at 40-41.

¹⁷⁶ *Amgen Inc. v. Sanofi*, 598 U.S. 594, 610 (emphases added).

¹⁷⁷ *Idenix*, 941 F.3d at 1159.

¹⁷⁸ *Wyeth & Cordis Corp. v. Abbott. Labs*, 720 F.3d 1380, 1383-84 (Fed. Cir. 2013).

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.”¹⁷⁹

As here, 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.”¹⁸⁰

“It is well established that the enablement requirement of § 112 incorporates the utility requirement of § 101.”¹⁸¹ A claimed invention must be **presently useful**—stating a hypothesis and proposing testing to determine its accuracy is insufficient.¹⁸² If a claim encompasses significant numbers of inoperative

¹⁷⁹ *Idenix*, 941 F.3d at 1156 (citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)).

¹⁸⁰ *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).

¹⁸¹ *In re Fisher*, 421 F.3d 1365, 1379 (Fed. Cir. 2005).

¹⁸² *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).

embodiments, and a POSA must engage in undue experimentation to identify the operative ones, that renders the claims non-enabled.¹⁸³

Here, the '731 Application utterly fails to enable the claimed genus of active modified PH20 polypeptides. Using the disclosure and knowledge in the prior art, the POSA would have to make and test 10⁶⁰+ polypeptides within the claims' sequence space to determine which exhibit activity or increased activity. Such testing would also be necessary to weed out mutants exhibiting lesser activity (in the case of claims 1-16), folded but "inactive mutants," and, those that cannot stably fold or be produced.¹⁸⁴ But the scale of that experimentation is beyond undue—it is impossible.

1. Claims 1-9 and 17 Are Not Enabled

The challenged claims are a textbook example of a non-enabled genus under the Supreme Court's decision in *Amgen*. The Federal Circuit's framework for assessing undue experimentation using the factors in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) compels the same conclusion.

¹⁸³ *Crown Operations Intern. Ltd v. Solutia Inc.*, 389 F.3d 1367, 1380, FN8 (Fed. Cir. 2002); *Atlas Powder Co. v. E.I. du Pont De Nemours Co.*, 750 F.2d 1569, 1577 (Fed. Cir. 1984).

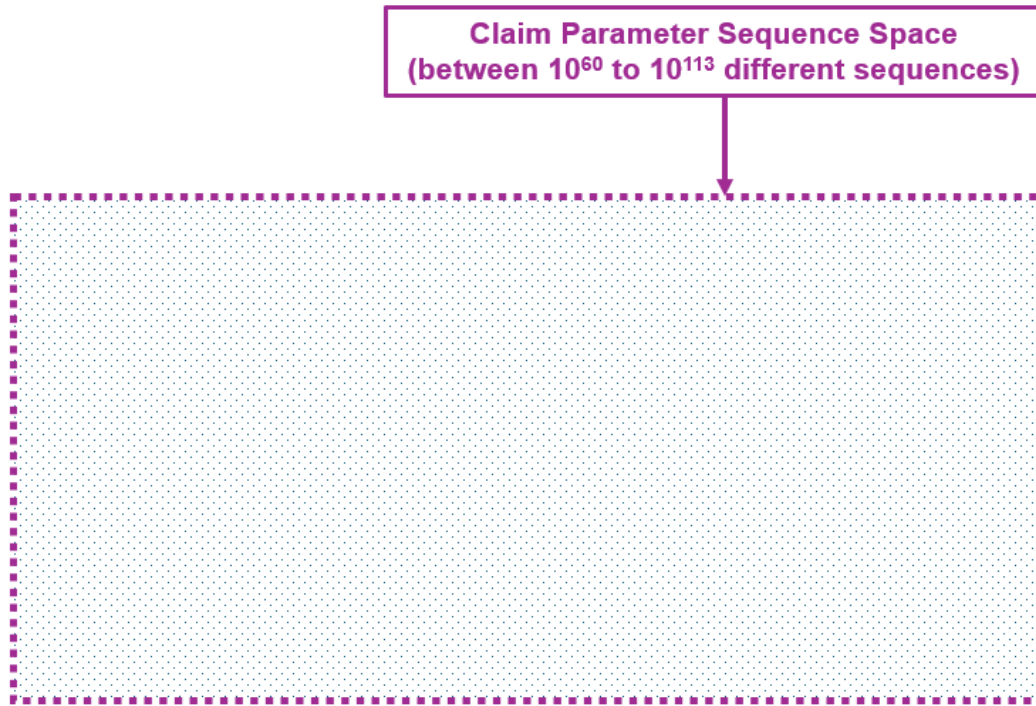
¹⁸⁴ EX1003, ¶¶ 172, 194-197.

(a) Extreme Scope of the Claims

As explained in § IV.D.1, the claim parameters define sequence spaces that capture 10^{60} - 10^{113+} distinct sequences with (i) a required substitution at position 313 and (ii) up to 20 or 41 additional modifications (replacements, deletions, or additions) at any other position within 36 reference PH20 sequences having between 430 (SEQ ID NO: 32) and 474 (SEQ ID NO: 7) residues. The growth in these sequence spaces from each additional mutation permitted in a PH20 is illustrated below. Taking the smallest claimed sequence space (claim 8), it requires a position 313 replacement and use of SEQ ID NO: 35 (433 residues). For each of 19 possible position 313 mutations, the growth in the sequence space with each additional permitted modification up to 20 total is shown below:

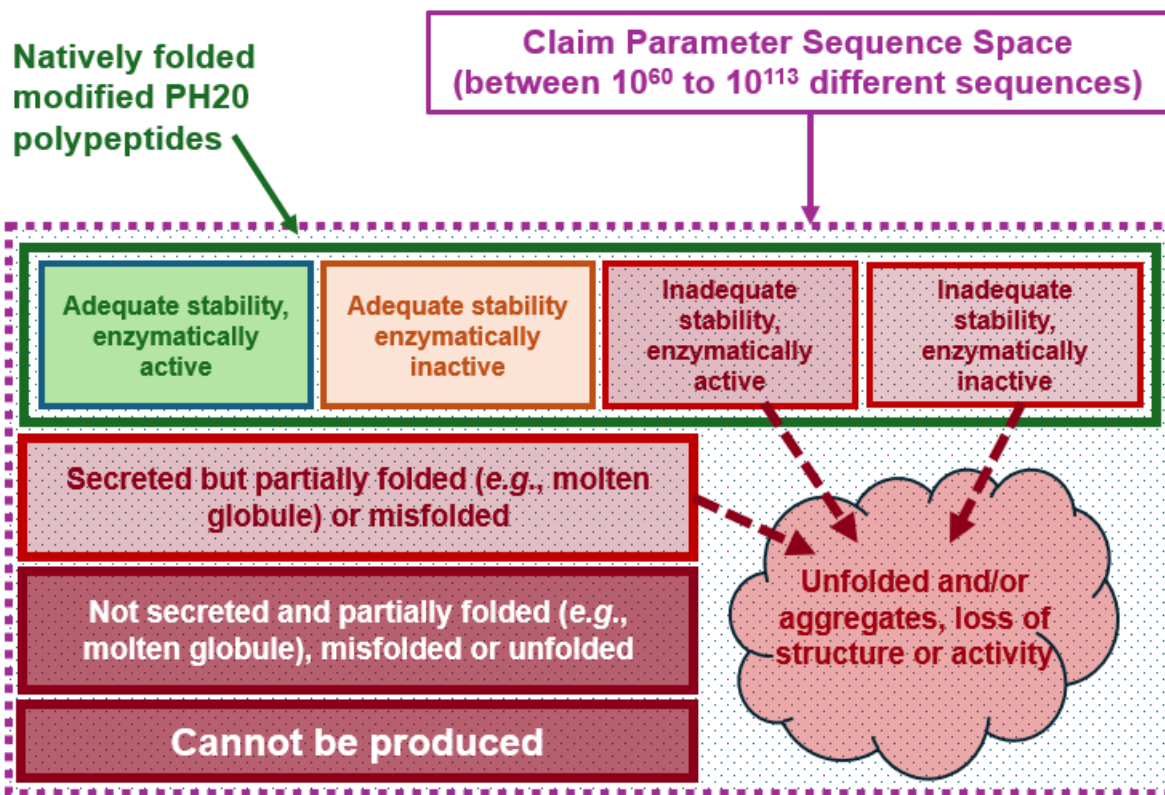
Additional Mutations	Sequences	#	% of Total
1	432	4.32E+02	0.00%
2	93,096	9.31E+04	0.00%
3	13,343,760	1.33E+07	0.00%
4	1,431,118,260	1.43E+09	0.00%
5	122,503,723,056	1.23E+11	0.00%
6	8,718,181,624,152	8.72E+12	0.00%
7	530,563,624,555,536	5.31E+14	0.00%
8	28,186,192,554,512,800	2.82E+16	0.00%
9	1,327,882,849,234,830,000	1.33E+18	0.00%
10	56,169,444,522,633,200,000	5.62E+19	0.00%
11	2,154,864,144,413,750,000,000	2.15E+21	0.00%
12	75,599,817,066,515,600,000,000	7.56E+22	0.00%
13	2,442,455,628,302,810,000,000,000	2.44E+24	0.00%
14	73,099,207,732,777,000,000,000,000	7.31E+25	0.00%
15	2,037,031,255,486,720,000,000,000,000	2.04E+27	0.00%
16	53,090,127,096,122,600,000,000,000,000	5.31E+28	0.00%
17	1,299,146,639,528,650,000,000,000,000,000	1.30E+30	0.00%
18	29,952,547,522,466,000,000,000,000,000,000	3.00E+31	0.00%
19	652,650,246,015,840,000,000,000,000,000,000	6.53E+32	0.25%
20	13,477,227,580,227,100,000,000,000,000,000,000	1.35E+34	100.00%

The sequence space is simplistically illustrated below:



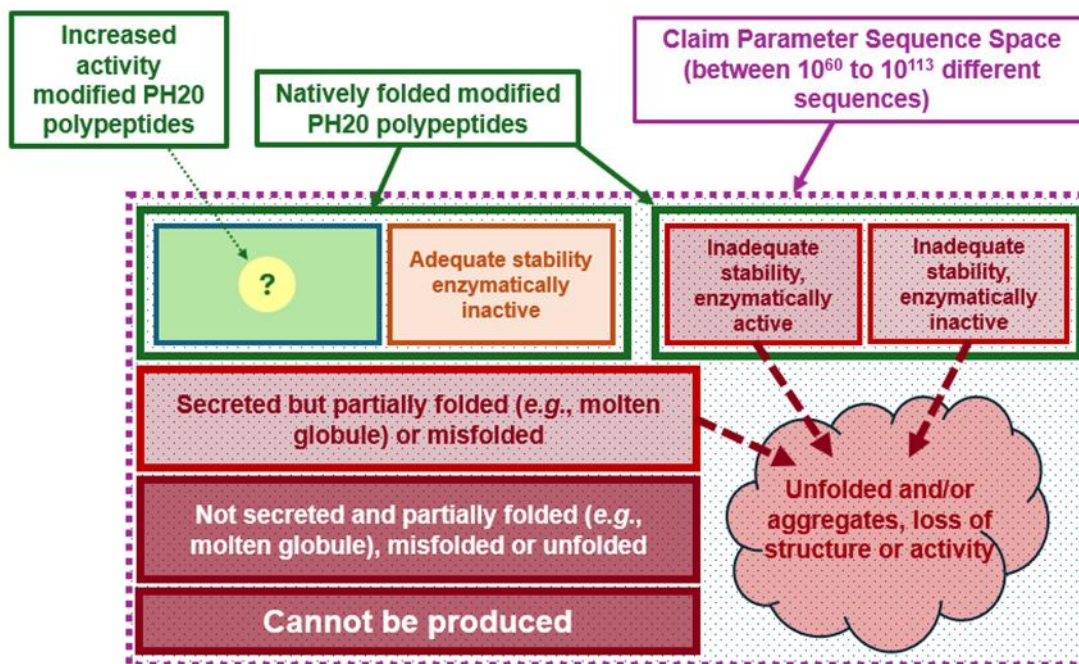
The modified PH20s within that sequence space will exist in a variety of forms, including forms that: (i) never leave the cell because they cannot be produced or secreted, (ii) are secreted but partially folded or misfolded, (iii) are properly folded but unstable. Many of those in the last two categories exist as unfolded and/or in aggregates (below).¹⁸⁵

¹⁸⁵ EX1003, ¶¶ 172, 195-197; *see also* EX1087 (Vembar), 944.



Multiply-modified PH20 polypeptides with increased activity (claims 1-16) and those that are properly folded and either active or inactive (claim 17) constitute an unidentified and unknowable portion of the sequence space containing properly folded PH20s (below). Determining what constitutes that portion of the sequence space requires an impossible scale of experimentation.¹⁸⁶

¹⁸⁶ EX1131 (Petsko Dep.), 63:19-64:17; EX1003, ¶¶ 196-197.



Claims that capture massive and structurally diverse sets of proteins such as those here have routinely been found non-enabled. For example, the claims in *Amgen* covered “millions” of different, untested antibodies,¹⁸⁷ while in *Idenix*, the Court found that a POSA would “understand that ‘billions and billions’ of compounds literally meet the structural limitations of the claim.”¹⁸⁸ In both cases (as here), the enormous claim scope was contrasted to limited working examples in the patent, the unpredictability in the field of technology, and the immense quantity of experimentation required to practice the claims’ full scope (*Wands* Factors 1, 3, 4, and 7). As in *Idenix*, it is improper to rely on the knowledge and efforts of a

¹⁸⁷ 598 U.S. at 603.

¹⁸⁸ 941 F.3d at 1157.

POSA to try to “fill the gaps in the specification” regarding which of the “many, many thousands” of possible compounds should be selected for screening, and which in this case is impossible.¹⁸⁹

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

Relative to the scope of the claims, the '731 Application provides an extremely narrow set of working examples: ~2,500 PH20₁₋₄₄₇ single-substitution “active mutants,” and ~800 with increased activity, which represents ~13.5% of the single-mutants classified in the '731 Application, and ~9% of the total possible (8,493) single-mutant PH20s.¹⁹⁰ As a percentage of the claimed sequence spaces, it is effectively 0%.

More generally, the examples provide no insights into the effects of combining 5, 10, 15, or 20+ substitutions in one PH20 polypeptide.¹⁹¹ Similarly, **none** of the exemplified PH20 polypeptides is based on a PH20 polypeptide truncated before position 447 or extending beyond that position, even though activities of such truncation mutants vary extensively.¹⁹²

¹⁸⁹ *Id.* at 1159.

¹⁹⁰ EX1003, ¶¶ 163, 208.

¹⁹¹ EX1003, ¶¶ 209-214, 239.

¹⁹² EX1003, ¶¶ 151, 218, 231-234.

The disclosure's only explicit guidance for producing multiply-modified PH20 polypeptides is a prophetic and "iterative" "make and test" process for **discovering** active modified PH20 polypeptides. *See* § V.A.1(d). But this research plan requires a POSA to engage in undue experimentation to practice the full scope of the claims.

First, the disclosed method requires performing iterative rounds of **randomized** mutations (up to 41 rounds per starting molecule under the broadest claims) to **discover** which of the 10^{60} - $10^{113}+$ possible modified PH20 polypeptides in the claims' sequence space might possess hyaluronidase activity.¹⁹³

Second, the disclosure provides no meaningful guidance or information that a POSA could use to implement the prophetic procedure it discloses for making and discovering modified PH20 polypeptides with hyaluronidase activity (or increased activity) relative to PH20₁₋₄₄₇:

¹⁹³ EX1003, ¶¶ 241-243, 252-254; *see also* EX1018, 382 ("[C]ombinatorial 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.

- (i) it does not identify **any** specific combination of two or more replacements within any PH20 polypeptide that yield mutants with activity or increased activity;
- (ii) it provides no data from testing **any** PH20 polypeptide with two or more substitutions; and
- (iii) it does not identify the regions or residues in PH20 polypeptides that are “associated with activity and/or stability of the molecule” or “critical residues that are involved in the structural folding or other activities of the molecule” particularly when two or more replacements have been made.¹⁹⁴

Instead, the disclosure requires the POSA to iteratively repeat its prophetic mutagenesis research plan to make and screen 10⁶⁰+ multiply-modified PH20 polypeptides to discover which are active, and which will exhibit increased activity.¹⁹⁵

Regardless of whether individual rounds of “iterative” production and screening of PH20 mutants might be considered “routine,” the aggregate scale of experimentation required to practice the full scope of the claims goes far beyond

¹⁹⁴ EX1026, 150:10-18; EX1003, ¶¶ 246-249.

¹⁹⁵ EX1003, ¶¶ 253-254; *see also id.* at ¶ 240.

undue—it is impossible.¹⁹⁶ For example, screening technologies in the 2011-2012 timeframe could not screen enzyme libraries with more than $\sim 10^9$ mutants, a small fraction of the sequence spaces of the claims (*e.g.*, $\sim 10^{60}$ to $\sim 10^{113}$) (below).¹⁹⁷

Additional Mutations	Sequences	#
1	432	4.32E+02
2	93,096	9.31E+04
3	13,343,760	1.33E+07
4	1,431,118,260	1.43E+09
5	122,503,723,056	1.23E+11
6	8,718,181,624,152	8.72E+12
7	530,563,624,555,536	5.31E+14
8	28,186,192,554,512,800	2.82E+16
9	1,327,882,849,234,830,000	1.33E+18
10	56,169,444,522,633,200,000	5.62E+19
11	2,154,864,144,413,750,000,000	2.15E+21
12	75,599,817,066,515,600,000,000	7.56E+22
13	2,442,455,628,302,810,000,000,000	2.44E+24
14	73,099,207,732,777,000,000,000,000	7.31E+25
15	2,037,031,255,486,720,000,000,000,000	2.04E+27
16	53,090,127,096,122,600,000,000,000,000	5.31E+28
17	1,299,146,639,528,650,000,000,000,000,000	1.30E+30
18	29,952,547,522,466,000,000,000,000,000,000	3.00E+31
19	652,650,246,015,840,000,000,000,000,000,000	6.53E+32
20	13,477,227,580,227,100,000,000,000,000,000,000	1.35E+34

Limits of Screening Technologies in 2011-2012

The disclosure's prophetic and iterative directed evolution techniques thus could not be used by a POSA to identify the sequences of multiply-modified PH20s that properly fold, and exhibit inactivity, activity, or increased activity until they are made, discovered and characterized.¹⁹⁸

¹⁹⁶ EX1003, ¶¶ 71, 238-240.

¹⁹⁷ EX1003, ¶¶ 67, 70-71; EX1147, 2990-93, Table 1; EX1141, 409; EX1018 (Chica), 378.

¹⁹⁸ EX1003, ¶¶ 253-254, 256.

Patentee may contend a POSA could make individual active or increased activity multiply-modified PH20s by selecting particular combinations of single-substitutions that yielded PH20₁₋₄₄₇ mutants that retained activity. But even if a POSA were to exclude changes at essential or highly conserved positions identified in the prior art,¹⁹⁹ and only make 5 substitutions in each potential mutant, the POSA would still need to perform an impossible scale of assessments of such potential substitution mutants (*i.e.*, $\sim 10^{60}+$) and would have no guidance about mutants that incorporate deletions or additions in PH20 variants terminating at positions other than position 447. The POSA thus could not reasonably predict which of those $10^{60}+$ combinations of substitutions would properly fold and preserve activity, much less predict which exhibit increased activity.²⁰⁰

These “***iterative, trial-and-error process[es]***” are indistinguishable from those consistently found to not enable broad genus claims to modified proteins and other therapeutically active compounds.²⁰¹

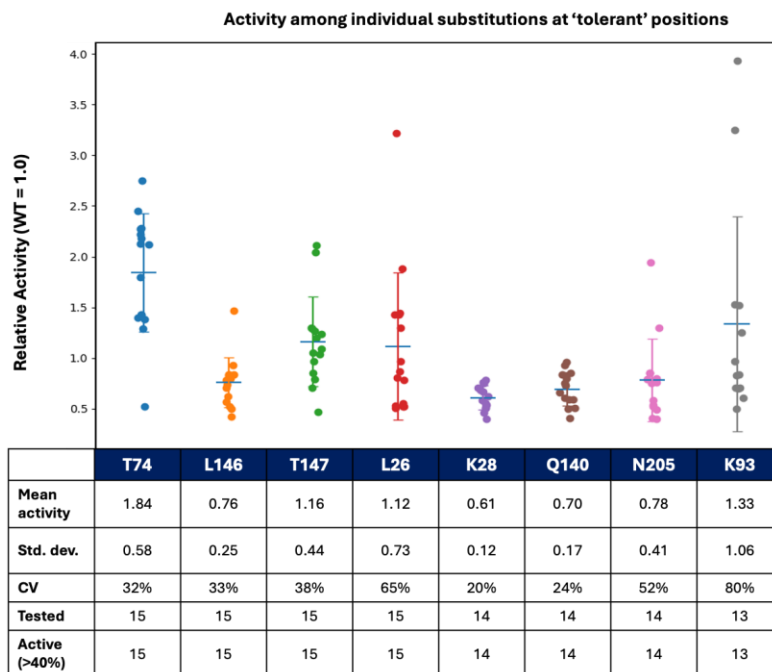
¹⁹⁹ EX1026, 80:19-35; EX1006, 6916 (Fig. 3).

²⁰⁰ EX1003, ¶¶ 209-214; *see also id.* at ¶¶ 76, 78-79.

²⁰¹ *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.

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

Like any protein, the activity of PH20 can be unpredictably influenced by even a single change to its amino acid sequence.²⁰² The data in the '731 Application concerning single substitutions shows these unpredictable effects on activity of PH20s. For example, ~86.5% of tested single mutants reduced activity below 100%.²⁰³ In addition, even at positions where many substitutions retained activity, the amount of that activity varied unpredictably.²⁰⁴



²⁰² EX1003, ¶¶ 173-177; EX1209 (Petsko Textbook), 160 (Figure 4-53).

²⁰³ See § V.A.1(c)(iv).

²⁰⁴ EX1003, ¶¶ 173-174.

Introducing **multiple** modifications (especially within a particular region of the protein) greatly increases this unpredictability. Sets of changes can prevent a modified PH20 from efficiently folding into its native state, or unpredictably affect its stability if it does properly fold.²⁰⁵ Multiple modifications can alter or transform secondary structures, alter positioning of secondary structures or higher order motifs, or otherwise alter features within the tertiary structure of PH20 that are important to its catalytic and substrate binding functions.²⁰⁶ Mutations can also cause long-distance effects, and can alter activity even without causing significant changes in the tertiary structure of the PH20.²⁰⁷ Combinations thus can introduce an immense number of simultaneous influences on a PH20's structure, the effects of which are unpredictable.²⁰⁸

The cumulative effects of multiple changes would have rapidly exceeded the capacity of computer-based protein engineering techniques to reasonably predict changes to the protein's structure in the 2011-2012 timeframe.²⁰⁹ For example,

²⁰⁵ EX1131, 99:4-22.

²⁰⁶ EX1003, ¶¶ 73-80, 95-96, 198-199, 236-237.

²⁰⁷ EX1003, ¶¶ 76, 178.

²⁰⁸ EX1003, ¶¶ 73-78, 212-213.

²⁰⁹ EX1003, ¶ 104-108; EX1027, 6-11, Figure 6.

PH20 models based on the experimentally determined structure of a homologous protein (*e.g.*, Hyal-1) become unreliable after a few changes to the wild-type amino acid sequence and in areas of the model with insufficient quality, and the sole published PH20 homology model was known to be inaccurate by 2007.²¹⁰ Also, while homology models can assess effects of a single substitution on the local structure of a protein, they cannot detect steric changes below the resolution of the model, non-steric effects (*e.g.*, long-distance charge or van der Waals effects), nor can they predict particular effects on activity.²¹¹ And the disclosure nowhere proposes the use of homology models to guide selections of combinations of changes to a PH20, much less show how to make such selections to yield active (or increased activity) forms of multiply-modified PH20s.²¹²

²¹⁰ EX1003, ¶¶ 104-106, 108, 133; EX1012, 4, 8-9; EX1006, 6913 (*ab initio* models did not accurately describe C-terminal region); *see also* EX1008, 828-832; EX1009, 230-234, 236-237.

²¹¹ EX1003, ¶¶ 105-106.

²¹² EX1003, ¶¶ 109, 216.

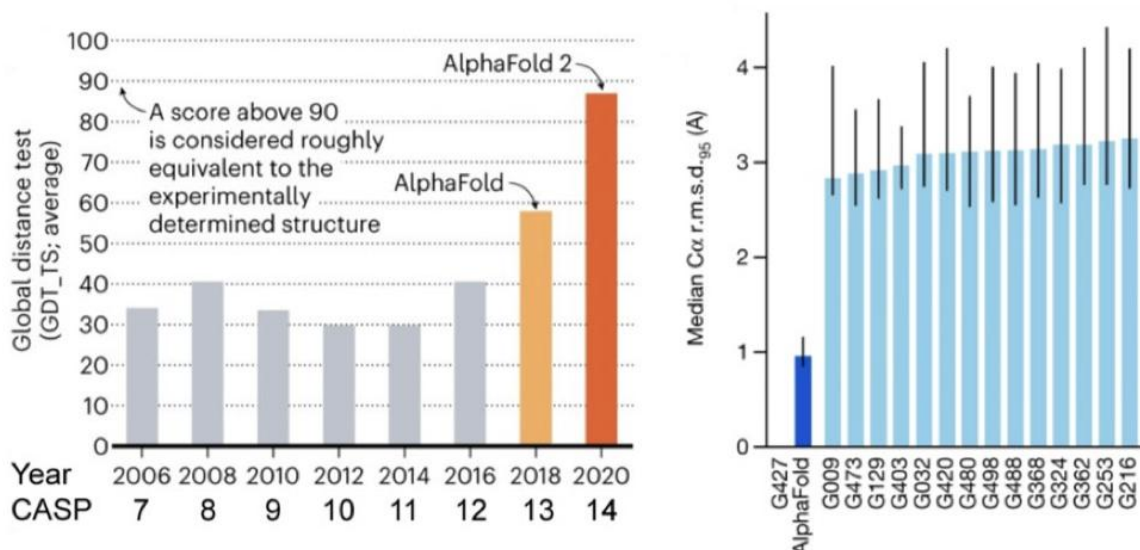


Figure 6. Left: progress of the CASP performance over the years for the best models and the most difficult targets.³⁸ Right: performance of AlphaFold2 relative to the top 15 entries by other groups in CASP14. Data are the median coordinate error and the 95% confidence interval of the median, estimated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

For all of these reasons, POSAs in the 2011-2012 timeframe could **not** have predicted the effects of making more than a few concurrent amino acid replacements within a PH20 polypeptide.²¹³ Predicting the effects of 10, 15 or 20+ modifications in the 2011-2012 on the ability of a PH20 to properly fold, remain stably folded or on its overall activity was impossible.

Consequently, a POSA could not have used rational design techniques or computational tools available in the 2011-2012 timeframe to identify which multiply-modified PH20 polypeptides in the claimed sequence spaces will exhibit

²¹³ EX1003, ¶ 108; EX1027, 6-11, Figure 6.

activity or increased activity.²¹⁴ And using such techniques to identify even a handful of active mutant PH20 polypeptides with more than 1 substitution would have taken an extreme amount of time and effort (*i.e.*, billions of days for even a small subset of the sequence space).²¹⁵

(d) Other Wands Factors and Conclusion

The remaining *Wands* factors either support the conclusion that practicing the full scope of the claims would require undue experimentation or are neutral.

For example, while a POSA was highly skilled, the field of protein engineering was unpredictable and tools did not exist that permitted accurate modeling of the range of multiply-changed PH20 polypeptides being claimed.²¹⁶ Likewise, while there was significant public knowledge about hyaluronidases, there was no experimentally-determined structure of the PH20 protein.²¹⁷ Also, the public literature generally reported on ***loss of activity*** from mutations in

²¹⁴ EX1003, ¶¶ 64, 108, 254-255.

²¹⁵ EX1003, ¶¶ 64, 240, 254-255.

²¹⁶ EX1003, ¶¶ 105-108, 218; EX1027, 6-11, Fig. 6.

²¹⁷ EX1003, ¶¶ 102, 120-122, 126-132.

hyaluronidases, and did not predictably teach how to introduce changes that maintained or **enhanced** stability or activity of such proteins.²¹⁸

Practicing the full scope of the claims thus would have required undue experimentation, which renders those claims non-enabled.

2. Claims 10-16 Are Not Enabled

Claims 10-16 recite further modifications (*e.g.*, glycosylation, polymer conjugation, heterologous signal sequence) to the modified PH20 polypeptides (claims 10-14), inclusion of the modified PH20 polypeptide in a chimeric polypeptide (claim 15), or a pharmaceutical composition comprising the modified PH20 polypeptides (claim 16). These claims are not enabled for the same reasons as claims 1-9 and 17.²¹⁹

3. Even if Claim 17 Encompasses Inactive Mutants, It Is Not Enabled

Although claim 17 does not require increased hyaluronidase activity, it **encompasses** modified PH20 polypeptides having activity (and increased activity), as the Board has previously found. *Supra* § IV.E. Claim 17 encompasses an immense sequence space of $10^{107}+$ sequences, which includes polypeptides containing up to 40 possible amino acid substitutions. *Supra* § IV.D.1.

²¹⁸ EX1011, 812-814; EX1010, 9437-9439.

²¹⁹ *See, e.g., Idenix*, 941 F.3d at 1155, 1165.

Determining which of the claimed sequences yield active or inactive properly-folded polypeptides is an immense task (*supra* § V.B.1(a)), for which the '731 Application provides limited guidance directed only to singly-substituted PH20₁₋₄₄₇ polypeptides (*supra* § V.B.1(b)). Practicing the full scope of the multiply-modified proteins claimed would have required undue experimentation. *Supra* § V.B.1(c)-V.B.1(d).

Should patentee argue that enabling claim 17 does not require determining hyaluronidase activity, claim 17 is still not enabled. The disclosure's only proposed utility for "inactive mutants" is as "antigens in contraception vaccines."²²⁰ But a polypeptide must be produced and properly folded to be an antigen, and the '731 Application does not even identify **any** properly-folded and inactive multiply-modified PH20 polypeptides that were made.²²¹

If even a fraction of a percent of the 10¹⁰⁷+ multiply-modified PH20 polypeptides within the claims' sequence space cannot be produced or did not

²²⁰ EX1001, 86:20-22 ("Also provided are modified PH20 polypeptides that are inactive, **and** that can be used, for example, as antigens in contraception vaccines."); EX1003, ¶¶ 281-289; EX1060, 1711.

²²¹ *Supra* § V.A.2; EX1003, ¶¶ 288, 211-20, 229-30; EX1026, 140:15-16; *see generally id.*, 140:36-141:29, 141:36-143:34, 144:16-149:37.

properly fold, they represent a massive absolute number of inoperative and non-useful embodiments.²²² The impact of multiple concurrent substitutions, including on secretion and folding, was unknown, and highly unpredictable.²²³ Performing the scale of testing necessary to identify such inoperative species within the scope of the claims independently demonstrates a lack of enablement.²²⁴

The disclosure thus presents only a “research proposal” to discover active mutants with multiple modifications, and allegedly-useful properly-folded and inactive mutants, and requires use of a labor and resource-intensive process to sort them from inoperative mutants having no utility.²²⁵ To the extent certain “inactive” mutants have any alleged “contraceptive” utility—which is unsupported by the literature—yet further undue experimentation would be required to identify and

²²² EX1003, ¶¶ 197, 199, 215.

²²³ EX1003, ¶¶ 92-98.

²²⁴ EX1003, ¶¶ 207, 254-255; *Atlas Powder Co.*, 750 F.2d at 1576-77; *Pharm. Res., Inc. v. Roxane Labs., Inc.*, 253 F. App’x. 26, 30 (Fed. Cir. 2007).

²²⁵ *See Janssen Pharmaceutica N.V. v. Teva Pharms. USA, Inc.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009).

utilize them for this purpose.²²⁶ Thus, claim 17 is not enabled by the '731

Application even if found to encompass inactive mutants.

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

The original claims of the '731 Application do not demonstrate written description or enablement of the multiply-modified PH20 polypeptides being claimed. Those original claims recited 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). Certain dependent claims listed single positions (claim 12) or replacements (claims 13-16) in those polypeptides. None of the original claims are supported by an adequate written description or enabled by the disclosure, for the reasons set forth in §§ V.A-V.C.

VI. US-275 Anticipates Every Claim of the '149 Patent

US-275 (EX1004) was published on November 14, 2013, years before the application that issued as the '149 Patent was filed (March 19, 2020). *See* § 0. Thus, US-275 is prior art to the challenged claims under 35 U.S.C. § 102(a)(1) and is not subject to any of the 35 U.S.C. § 102(b) exceptions.

²²⁶ EX1003, ¶¶ 286-88; EX1019, 330-333; EX1020, 178-181; *see also* EX1112, 544-546; EX1023, 1133

US-275 has a substantively identical disclosure as the '731 Application.²²⁷ It describes production and testing of single amino acid substitutions in SEQ ID NO: 3 (*i.e.*, PH20₁₋₄₄₇).²²⁸ US-275 also describes methods and uses of modified PH20 polypeptides that derive from the ability of such modified PH20 polypeptides to degrade hyaluronan, including their use in combination with other therapeutic agents.²²⁹ For example, US-275 explains that enzymatically active modified PH20 polypeptides can be used to increase the delivery and/or bioavailability of subcutaneously administered therapeutic agents.²³⁰ With regard to active mutants, US-275 specifically highlights the class of ~530 single amino acid substitutions of PH20₁₋₄₄₇ (which includes M313K PH20₁₋₄₄₇) that exhibit ***at least 120%*** of the activity of unmodified PH20₁₋₄₄₇ (SEQ ID NO: 3).²³¹

²²⁷ See EX1068, ¶ 20; EX1003, ¶ 267.

²²⁸ EX1004, [0603]-[0631]; *see also* EX1003, ¶ 280.

²²⁹ *E.g.*, EX1004, [0005], [0042]-[0045], [0545].

²³⁰ EX1004, [0044], [0545].

²³¹ *See, e.g.*, EX1004, [0626] (“For example, about 536 mutants exhibit 120% or greater than 120% of the hyaluronidase activity of wildtype PH20...”); [0626] (Table 9), pp. 120-138; [0011] (“In some instances, among the PH20

The modified PH20 polypeptide M313K PH20₁₋₄₄₇ is a polypeptide having a single amino acid replacement of methionine (M) to lysine (K) as position 313 of SEQ ID NO: 3.²³² Because M313K PH20₁₋₄₄₇ has only a single amino acid replacement relative to SEQ ID NO: 3, it has >91% and >95% sequence identity to SEQ ID NO: 3 (446/447 = 99.8% sequence identity), and 100% sequence identity to SEQ ID NO: 594.²³³ The substitution of M to K at position 313 of SEQ ID NO: 3 “confer(s) [] increased hyaluronidase activity” compared to wildtype PH20₁₋₄₄₇ (SEQ ID NO: 3), as its activity is reported in Example 4 as a 2.85-fold increase (*i.e.*, 285%), which is greater than a 120% increase.²³⁴ US-275 recites every element of, and therefore anticipates, claims 1-3, 5-7, and 9.

US-275 anticipates claim 8 because M313K PH20₁₋₄₄₇ is 96.5% identical to SEQ ID NO: 35 (PH20₁₋₄₃₃) with 15 changes (1.00-15/433=0.965), including the

polypeptides provided herein, the modified PH20 polypeptide exhibits at least 120%, 130%...”); *see also* EX1003, ¶ 266.

²³² EX1004, [0606] (Table 8), p. 113; [0626] (Table 9), p. 133 (identifying M313K as having 285% relative activity); [0642] (Table 11), p. 147; [0642] (Table 12), p. 152.

²³³ EX1004, [0622]-[0626].

²³⁴ EX1003, ¶¶ 268-270.

substitution at position 313 and the addition of 14 residues to the C-terminus of SEQ ID NO: 35 (position 433).²³⁵

US-275 anticipates claim 10 because it discloses that modified PH20 polypeptides, including M313K PH20₁₋₄₄₇, can be modified by glycosylation, sialation, albumination, farnesylation, carboxylation, hydroxylation, or phosphorylation.²³⁶ The M313K PH20₁₋₄₄₇ mutant was produced in CHO cells, which is known to glycosylate the PH20₁₋₄₄₇ sequence.²³⁷

US-275 anticipates claim 11. US-275 reports that modified PH20 polypeptides being described “can be glycosylated, such as by containing at least an N-acetylglucosamine moiety linked to each of at least three asparagine (N) residues” that “correspond to amino acid residues 200, 333 and 358 of SEQ ID NO:3,” which are unaltered in M313K PH20₁₋₄₄₇.²³⁸ It further discloses that the three asparagine (N) residues can correspond to amino acid residues 200, 333 and

²³⁵ EX1003, ¶ 271; EX1004, [0626] (Table 9), p. 133.

²³⁶ EX1004, [0015], [0033], [0115], [0118], [0318], [0383]; EX1003, ¶ 273.

²³⁷ EX1004, [0607]-[0608]; EX1003, ¶ 273.

²³⁸ EX1004, [0015], [0033]; EX1003, ¶ 274.

358 of SEQ ID NO: 3.²³⁹ Because M313K PH20₁₋₄₄₇ is produced in CHO cells, each of those positions will be glycosylated.²⁴⁰

US-275 anticipates claims 12-13 because it teaches attaching a polymer, such as dextran or PEG, to modified PH20 polypeptides, including M313K PH20₁₋₄₄₇.²⁴¹

US-275 anticipates claims 14 because it discloses that modified PH20 polypeptides, including M313K PH20₁₋₄₄₇, “can be joined to a polypeptide-encoding nucleic acid molecule ... for example heterologous signal sequences, designed to facilitate protein secretion.”²⁴²

US-275 anticipates claims 15 because it discloses that modified PH20 polypeptides, including M313K PH20₁₋₄₄₇, “can be in a PH20 polypeptide that is a ... chimeric polypeptide.”²⁴³

²³⁹ EX1004, [0015], [0033].

²⁴⁰ EX1004, [0015], [0033], [0607]-[0608]; EX1003, ¶ 274.

²⁴¹ EX1004, [0015], [0033], [0192], [0261], [0326]-[0332], [0421]-[0434], claim 22; EX1003, ¶ 275.

²⁴² EX1004, [0371]; *see also id.*, [0384]; EX1003, ¶ 276.

²⁴³ EX1004, [0261]; EX1003, ¶ 277.

US-275 anticipates claim 16 because it discloses that pharmaceutical compositions can contain active modified PH20 polypeptides (such as M313K PH20₁₋₄₄₇).²⁴⁴ The claim imposes no requirements of said pharmaceutical compositions—any can satisfy its requirements. As such, US-275 teaches pharmaceutical compositions of M313K PH20₁₋₄₄₇.

The M313K PH20₁₋₄₄₇ mutant anticipates claim 17 because this mutant corresponds exactly SEQ ID NO: 594, which is recited in claim 17.²⁴⁵

M313A	591	1.34
M313E		0.63
M313G	592	0.56
M313H	593	1.23
M313K	594	2.85
S312L		0.38
M313L		1.05
M313P	595	1.11
M313R	596	2.30
M313S		0.88
M313T	597	0.67
M313V		0.99
M313Y	598	1.12

Finally, US-275 anticipates claim 4. Claim 4 depends from claim 1-3, and requires (i) an M313K replacement, (ii) 91% sequence identity to SEQ ID NO: 35 (PH20₁₋₄₃₃), and (iii) that the M313K replacement “confers increased hyaluronidase

²⁴⁴ EX1003, ¶ 278; EX1004, [0036], [0040], [0045], [0434]-[0544].

²⁴⁵ EX1003, ¶ 279; EX1004, [0626] (Table 9), p. 133.

activity” when compared to unmodified SEQ ID NO: 35. US-275 establishes each of these requirements for M313K PH20₁₋₄₄₇.²⁴⁶

M313K PH20₁₋₄₄₇, is 96.5% identical to SEQ ID NO: 35 (PH20₁₋₄₃₃) with 15 changes, including the substitution position 313 and addition of 14 residues to the C-terminus of SEQ ID NO: 35.²⁴⁷ Further, US-275 explicitly establishes (or, at a minimum, demonstrates necessarily and inevitably) that M313K PH20₁₋₄₄₇ has increased activity compared to SEQ ID NO: 35’s PH20₁₋₄₃₃. US-275’s Example 4 discloses that M313K PH20₁₋₄₄₇ exhibited 2.85-fold (*i.e.*, 285%) compared to the PH20₁₋₄₄₇ (SEQ ID NO: 3).²⁴⁸ US-457,²⁴⁹ which is incorporated-by-reference into US-275,²⁵⁰ establishes that SEQ ID NO: 3 has increased activity compared to unmodified SEQ ID NO: 35 (PH20₁₋₄₃₃).²⁵¹ The table below compares

²⁴⁶ EX1003, ¶ 272.

²⁴⁷ EX1003, ¶ 272.

²⁴⁸ EX1003, ¶ 272; EX1004, [0626] (Table 9), p. 133.

²⁴⁹ EX1105, US2010/0143457 (“US-457”).

²⁵⁰ EX1004, [0232], [0238], [0248], [0341].

²⁵¹ *See Arbutus Biopharma Corp. v. ModernaTX, Inc.*, 65 F.4th 656, 662–63 (Fed. Cir. 2023) (quoting *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000) (“When a reference or material from various

hyaluronidase activity at pH 7.4 (1) disclosed in US-457 for SPAM1-IDAF (SEQ ID NO: 84), which has the same sequence as SEQ ID NO: 35 of US-275 and the '149 Patent, (2) disclosed in US-457 for SPAM1-QIFY (SEQ ID NO: 70), which has the same sequence as SEQ ID NO: 3 of US-275 and the '149 Patent, and (3) disclosed in US-275 for M313K PH20₁₋₄₄₇.²⁵²

Mutant	pH 7.4 Activity Units/ml	Activity Normalized to PH20 ₁₋₄₄₇
PH20 ₁₋₄₃₃	0.5625	27.7%
PH20 ₁₋₄₄₇	2.03175	100%
M313K PH20 ₁₋₄₄₇	-	285%

Thus, as shown above, US-275's M313K PH20₁₋₄₄₇ has increased activity (over 10-fold) compared to SEQ ID NO: 35. This data establishes, and a POSA would have readily understood, that the M313K replacement confers increased activity reported relative to unmodified PH20₁₋₄₄₇ and PH20₁₋₄₃₃.²⁵³ US-275's M313K PH20₁₋₄₄₇ therefore anticipates claim 4.

documents is incorporated, they are effectively part of the host document as if they were explicitly contained therein.”) (internal quotations omitted)).

²⁵² EX1105, [0362] Table 6, p. 48; EX1003, ¶ 272.

²⁵³ EX1003, ¶ 272. If Patentee contends claim 4 requires that *all* observed increase in hyaluronidase activity relative to unmodified SEQ ID NO: 35 be attributable *solely* to the position 313 replacement, there is no § 112 support

All claims are therefore anticipated by US-275.

VII. Conclusion

For the foregoing reasons, the challenged claims are unpatentable.

Dated: March 23, 2026

Respectfully Submitted,

/Jeffrey P. Kushan/

Jeffrey P. Kushan

Reg. No. 43,401

Sidley Austin LLP

1501 K Street, N.W.

Washington, D.C. 20005

jkushan@sidley.com

(202) 736-8914

Attorney for Petitioner

for the claims at least because the disclosure reports only single-substitution mutants of PH20₁₋₄₄₇, and does not show possession of any other truncated forms of PH20 with amino acid replacements at any position (including PH20₁₋₄₃₃ with a position 313 replacement) or provide any means for predicting the effect a position 313 replacement would have in such other truncated forms. EX1003, ¶¶ 230-235.

EXHIBIT LIST

<u>EXHIBIT #</u>	<u>REFERENCE NAME</u>
1001	U.S. Patent No. 11,041,149
1002	File History of U.S. Patent No. 11,041,149
1003	Declaration of Dr. James Naismith
1004	United States Patent Publication No. 2013/0302275
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," Biochemistry, 46:6911-6920 (2007)
1007	WO 2010/077297, published 8 July 2010
1008	Stern et al., "Hyaluronidases: Their Genomics, Structures, and Mechanisms of Action," Chem. Rev. 106:818-839 (2006)
1009	Jedzrejas et al., "Structures of Vertebrate Hyaluronidases and Their Unique Enzymatic Mechanism of Hydrolysis," Proteins: Structure, Function and Bioinformatics, 61:227-238 (2005)
1010	Zhang et al., "Hyaluronidase Activity of Human Hyal1 Requires Active Site Acidic and Tyrosine Residues," J. Biol. Chem., 284(14):9433-9442 (2009)
1011	Arming et al., "In vitro mutagenesis of PH-20 hyaluronidase from human sperm," Eur. J. Biochem., 247:810-814 (1997)
1012	Bordoli et al., "Protein structure homology modeling using SWISSMODEL workspace," Nature Protocols, 4(1):1-13 (2008)
1013	Frost, "Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration," Expert Opinion on Drug Delivery, 4(4):427-440 (2007)
1014	Branden & Tooze, "Introduction to Protein Structure," Second Ed., Chapters 1-6, 11-12, 17-18 (1999)

<u>EXHIBIT #</u>	<u>REFERENCE NAME</u>
1015	Table Associating Citations from the '149 Patent (EX1001) to Corresponding Citations in the '731 Application (EX1026) and US-275 (EX1004)
1016	Steipe, "Consensus-Based Engineering of Protein Stability: From Intrabodies to Thermostable Enzymes," Methods in Enzymology, 388:176-186 (2004)
1017	Green, "Computer Graphics, Homology Modeling, and Bioinformatics," Protein Eng'g & Design, 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," Curr. Opin. Biotechnol., (4):378-384 (2005)
1019	Hardy et al., "Assessment of contraceptive vaccines based on recombinant mouse sperm protein PH20," Reprod., 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," Am. J. Reprod. Immunol., (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," J. Biol. Chem., 277(33):30310-4 (2002)
1022	Primakoff et al., "Reversible Contraceptive Effect of PH-20 Immunization in Male Guinea Pigs," Biol Reprod., 56(5):1142-6 (1997)
1023	Tung et al., "Mechanism of Infertility in Male Guinea Pigs Immunized with Sperm PH-20," Biol. Reprod., 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," BioDrugs, 32(1):83-89 (2018)
1025	[Reserved]
1026	U.S. Patent Application No. 13/694,731

<u>EXHIBIT #</u>	<u>REFERENCE NAME</u>
1027	2024 Chemistry Nobel Prize Background
1028	Bordier, "Phase separation of integral membrane proteins in Triton X-114 solution." J. Bio. Chem. 256 (4):1604-1607 (1981)
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 & Moulton, "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	[Reserved]
1036	Hayden, "Chemistry: Designer Debacle," Nature, 453:275-278 (2008)
1037-1038	[Reserved]
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)
1043-1044	[Reserved]

<u>EXHIBIT #</u>	<u>REFERENCE NAME</u>
1045	Redline Comparison of the '731 Application and '149 Patent 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)
1048	Hayden, "Key Protein-Design Papers Challenged," Nature, 461:859 (2009)
1049-1050	[Reserved]
1051	U.S. Patent Application No. 61/631,313
1052	U.S. Patent Application No. 61/796,208
1053-1058	[Reserved]
1059	Leisola & Turunen, "Protein Engineering: Opportunities and Challenges," Appl. Microbiol. Biotechnol. 75:1225-1232 (2007)
1060	[Reserved]
1061	Rosengren et al., "Clinical Immunogenicity of rHuPH20, a Hyaluronidase Enabling Subcutaneous Drug Administration," AAPS J. 5:1144-56 (2015)
1062-1065	[Reserved]
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	[Reserved]
1068	Declaration of Jeffrey P. Kushan
1069-1078	[Reserved]

<u>EXHIBIT #</u>	<u>REFERENCE NAME</u>
1079	Hunnicuttt et al., “Sperm Surface Protein PH-20 Is Bifunctional: One Activity Is a Hyaluronidase and a Second, Distinct Activity Is Required in Secondary Sperm-Zona Binding,” Biol. Reprod., 55(1):80-86 (1996)
1080	Bookbinder et al., “A Recombinant Human Enzyme for Enhanced Interstitial Transport of Therapeutics,” J. Controlled Release, 114:230-241 (2006)
1081	Goldberg, “Protein degradation and protection against misfolded or damaged proteins,” Nature, 426:895-899 (2003)
1082-1086	[Reserved]
1087	Vembar & Brodsky, “One Step at a Time: Endoplasmic Reticulum-Associated Degradation,” Nature, 9:944-958 (2008)
1088-1104	[Reserved]
1105	United States Patent Publication No. 2010/0143457
1106-1111	[Reserved]
1112	Primakoff, P., et al., “Fully effective contraception in male and female guinea pigs immunized with the sperm protein PH-20,” Nature 335:543-546 (October 6, 1988)
1113-1125	[Reserved]
1126	Im, S. et al., “Cryo-EM Structure of Human Hyaluronidase PH20,” Proteins: Structure, Function, and Bioinformatics 93:10671073 (2025)
1127-1129	[Reserved]
1130	Melanie Ann Simpson, Ph.D. Deposition Transcript
1131	Gregory Petsko, Ph.D. Deposition Transcript
1132-1134	[Reserved]
1135	Dr. Naismith Analysis Spreadsheet
1136	Dobson, “Principles of protein folding, misfolding and aggregation” Semin. Cell. Dev. Biol. 15(1):3-16 (2004)

<u>EXHIBIT #</u>	<u>REFERENCE NAME</u>
1137	Dobson, “Protein folding and misfolding” Nature. 18;426(6968):884-90 (2003)
1138	Dobson, “Experimental investigation of protein folding and misfolding” Methods 34(1):4-14 (2004)
1139	Chiti & Dobson, “Protein Misfolding, Functional Amyloid, and Human Disease” Annu. Rev. Biochem. 75:333–66 (2006)
1140	Dobson, “Protein misfolding, evolution and Disease” Trends Biochem. Sci. (9):329-32 (1999)
1141	Goldsmith & Tawfik, “Directed enzyme evolution: beyond the low-hanging fruit” Curr. Opin. Struct. Biol. 22(4):406-12 (2012)
1142-43	[Reserved]
1144	Ochoa-Leyva et al., “Protein Design through Systematic Catalytic Loop Exchange in the (beta/alpha) ₈ Fold” J. Mol. Biol. 387(4):949-64 (2009)
1145	[Reserved]
1146	Pal et al., “Comprehensive and Quantitative Mapping of Energy Landscapes for Protein-Protein Interactions by Rapid Combinatorial Scanning” J. Biol. Chem. 4;281(31):22378-22385 (2006)
1147	van Rossum et al., “Reporter-based screening and selection of enzymes” FEBS J. 280:2979-96 (2013)
1148	Reed et al., “Use of Coefficient of Variation in Assessing Variability of Quantitative Assays” Clin. Diagn. Lab Immunol. 9(6):1235-9 (2002)
1149	Ten Have et al., “Cloning and characterization of the cDNA encoding the PH20 protein in the European red fox Vulpes” Reprod. Fertil. Dev. 10(2):165-72 (1998)
1150	Chowpongpan et al., “Cloning and characterization of the bovine testicular PH-20 hyaluronidase core domain” Biotechnol. Lett. 26(15):1247-52 (2004)

<u>EXHIBIT #</u>	<u>REFERENCE NAME</u>
1151	Fowler et al., “High-resolution mapping of protein sequence function relationships” Nature Methods 7, 741–746 (2010)
1152	Ringe & Petsko, “Q&A: What are pharmacological chaperones and why are they interesting?” J. Biol. 8:80 (2009)
1153-1154	[Reserved]
1155	Calloni et al., “Investigating the Effects of Mutations on Protein Aggregation in the Cell” J. Biol. Chem. 10607-13 (2005)
1156	Chiti et al., “Studies of aggregation of mutant proteins in vitro provided insights into genetics of amyloid diseases” PNAS 99:16419-26 (2002)
1157	Chiti et al., “Rationalization of the effects of mutations on peptide and protein aggregation rates” Nature, 424:805-808 (2003)
1158	Wang et al., “Immunogenicity of protein aggregates-Concerns and Realities” Int. J. Pharmaceutics 431:1-11, (2012)
1159	[Reserved]
1160	Poelwijk, Frank J., et al., “Empirical fitness landscapes reveal accessible evolutionary paths” Nature 445.7126 (2007): 383-386
1161-1188	[Reserved]
1189	Martin-Deleon, P., “Epididymal SPAM1 and its Impact on Sperm Function,” Molecular and Cellular Endocrinology 250:114-121 (2006)
1190-1205	[Reserved]
1206	U.S. Food and Drug Administration, Medical Review: Hylenex, App. No. 21-859 (2005)
1207	US Patent No. 12,091,692
1208	Redline of the '731 App. and US-275 Publication
1209	Petsko & Ringe, Protein Structure and Function, New Science Press (2004)

<u>EXHIBIT #</u>	<u>REFERENCE NAME</u>
1210	Nelson & Cox, Lehninger Principles of Biochemistry, W.H. Freeman, 4th ed. (2005)
1211	Halozyme Therapeutics, Inc., Hylenex Label, U.S. Food and Drug Administration: AccessData (2005)
-	Declaration of Gregory A. Petsko, PGR2025-00003 (U.S. Patent No. 11,952,600), EX2070 (Sept. 22, 2025)

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 13,900 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: March 23, 2026

Respectfully Submitted,

/Jeffrey P. Kushan/

Jeffrey P. Kushan

Reg. No. 43,401

Sidley Austin LLP

1501 K Street, N.W.

Washington, D.C. 20005

jkushan@sidley.com

(202) 736-8914

Attorney for Petitioner

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on this 23rd day of March, 2026, I caused to be served a true and correct copy of the foregoing and any accompanying exhibits by FedEx on the following counsel:

Morgan, Lewis & Bockius LLP 2222 Market Street Philadelphia, PA 19103 United States	Mark Snyder Senior Vice President, General Counsel, CCO & Secretary Halozyme Therapeutics 12390 El Camino Real San Diego, CA 92130 United States
Robert Smyth Morgan, Lewis & Bockius LLP 1111 Pennsylvania Avenue, NW Washington, DC 20004-2541 United States	Eldora Ellison Sterne, Kessler, Goldstein & Fox PLLC 1101 K Street NW, 10th Floor Washington, DC 20005 United States

Dated: March 23, 2026

Respectfully Submitted,

/Jeffrey P. Kushan/

Jeffrey P. Kushan
Reg. No. 43,401
Sidley Austin LLP
1501 K Street, N.W.
Washington, D.C. 20005
jkushan@sidley.com
(202) 736-8914
Attorney for Petitioner