

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyme Inc.,
Patentee.

Case No. PGR2025-00046
U.S. Patent No. 12,091,692

PETITION FOR POST GRANT REVIEW

TABLE OF CONTENTS

I.	Introduction.....	1
II.	Compliance with PGR Requirements.....	4
	A. Certification of Standing	4
	B. Mandatory Notices	6
	1. <i>Real Party-in-Interest</i>	6
	2. <i>Related Proceedings</i>	7
	3. <i>Counsel and Service Information</i>	7
III.	Grounds	7
IV.	Background on the '692 Patent	8
	A. Field of the Patent.....	8
	1. <i>Protein Structures</i>	9
	2. <i>Hyaluronidase Enzymes</i>	11
	3. <i>Protein Engineering</i>	13
	B. Person of Ordinary Skill in the Art.....	15
	C. Prosecution History.....	16
	D. The Challenged Claims.....	17
	1. <i>The Claims Encompass a Staggering Number of Modified PH20 Polypeptides</i>	18
	2. <i>The Claims Encompass M313K PH20₁₋₄₄₇</i>	21
	3. <i>The Claims Encompass or Require “Active Mutants”</i>	22
V.	All Challenged Claims Are Unpatentable Under § 112 and None Are Entitled to Benefit to Any Pre-March 13, 2013 Application	28
	A. All Claims Lack Written Description.....	29
	1. <i>Claims 1-2, 5, 7-16, and 22-25 Lack Written Description</i>	35
	(a) <i>The Claims Capture Massive and Diverse Sets of Enzymatically Active PH20 Polypeptides</i>	35

- (b) Mutations the Common Disclosure Says to Avoid in Enzymatically Active PH20 Polypeptides.....36
 - (i) No Multiply-Modified “Active Mutant” PH20 Polypeptides with Substitutions that Render PH20₁₋₄₄₇ Inactive.....37
 - (ii) No Multiply-Modified “Active Mutant” PH20 Polypeptides with Significant C-terminal Truncations.....38
- (c) Empirical Test Results Do Not Identify Multiply-Modified Enzymatically Active PH20 Polypeptides.....42
 - (i) Single-Replacement Results Not Probative of Multiple-Replacement Mutants.....42
 - (ii) Purported Stability Data Is Not Reliable or Probative.....46
- (d) The Common Disclosure’s Research Plan Does Not Identify Any Multiply-Mutated Enzymatically Active PH20 Polypeptides49
- (e) The Common Disclosure Does Not Identify a Structure-Function Relationship for Multiply-Modified, Enzymatically Active PH20 Polypeptides.....52
- (f) The Common Disclosure Does Not Describe a Representative Number of Multiply-Modified Enzymatically Active PH20 Polypeptides.....54
- 2. *Dependent Claims 3-4, 6, 17-22, and 26-40 Lack Written Description*.....59
 - (a) Claims 3, 6, 27, 28.....59
 - (b) Claim 4.....60
 - (c) Claims 17-22, 26-3662
 - (a) Claims 37-40.....63
- 3. *Certain Claims Lack Written Description Under the Logic of Gentry Gallery*65
- B. All Challenged Claims Are Not Enabled65**
 - 1. *Claims 1-2, 5, 7-16, and 22-25 Are Not Enabled*68

- (a) Extreme Scope of the Claims68
 - (b) Limited Working Examples and Only a Research Plan for Discovering Active Mutant PH20 Polypeptides 71
 - (c) Making Multiple Changes to PH20 Polypeptides Was Unpredictable.....75
 - (d) Other Wands Factors and Conclusion77
 - 2. *Dependent Claims 3-4, 6, 17-22, and 26-40 Are Not Enabled.* 78
 - (a) Claims 3, 6, 27, 2878
 - (b) Claim 4.....79
 - (c) Claims 17-22, 26-3679
 - (a) Claims 37-40.....80
- C. Inactive PH20 Polypeptides Are Not Useful and Do Not Remedy the § 112(a) Deficiencies of the Claims.....81**
- D. The Original Claims of the '731 Application Do Not Cure the Written Description and Enablement Deficiencies88**
- VI. Challenged Claims 1-2, 4-5, 7-26, and 29-40 Are Unpatentable Under § 10389**
 - A. The Prior Art89**
 - B. Because M313K PH20₁₋₄₄₇ Is Obvious, Claims 1-2, 5, 7-16, and 22-25 Are Unpatentable90**
 - 1. *Patentee's '429 Patent Motivates a Skilled Artisan to Make Single Amino Acid Substitutions in Non-Essential Regions of PH20₁₋₄₄₇* 91
 - 2. *Chao Provides Information Useful for Engineering the Changes to PH20₁₋₄₄₇ that the '429 Patent Suggests* 93
 - 3. *A Skilled Artisan Would Have Identified Position 313 as Being in a Non-Essential Region of PH20₁₋₄₄₇ in 2011*..... 97
 - 4. *A Skilled Artisan Would Have Viewed Lysine as an Obvious Single Amino Acid Substitution for Methionine at Position 313 of PH20₁₋₄₄₇* 99
 - 5. *A Skilled Artisan Would Have Reasonably Expected the M313K PH20₁₋₄₄₇ to Be Enzymatically Active* 102

- (a) Patentee Cannot Contradict Its Past Representations to the PTO 102
 - (b) Skilled Artisans Would Reasonably Expect the M313K Substitution to be Tolerated in PH20₁₋₄₄₇ 103
 - (c) A PH20 Structural Model Confirms that PH20₁₋₄₄₇ Would Tolerate Lysine at Position 313 104
- 6. *M313K PH20₁₋₄₄₇ Would Have Reasonably Been Expected to Be an Active Mutant* 110
- C. Dependent Claims 4, 17-22, 26, and 29-40 Are Obvious 111**
 - 1. *Claim 4* 111
 - 2. *Claims 17-19* 111
 - 3. *Claims 20-22, 26* 112
 - 4. *Claims 29-40* 113
- D. There Is No Nexus Between the Claims and Any Evidence of Putative Secondary Indicia 115**
- VII. The Board Should Not Exercise Its Discretion Under § 324(a) or § 325(d) 116**
- VIII. Conclusion 117**

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>In re '318 Patent Infringement Litigation</i> , 583 F.3d 1317 (Fed. Cir. 2009)	67, 84, 86, 88
<i>AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.</i> , 759 F.3d 1285 (Fed. Cir. 2014)	29, 30, 32
<i>ABS Glob., Inc. v. Inguran</i> , 914 F.3d 1054 (7th Cir. 2019)	82
<i>Amgen Inc. v. Sanofi</i> , 598 U.S. 594 (2023).....	<i>passim</i>
<i>Apple Inc. v. Fintiv, Inc.</i> , Case IPR2020-00019, Paper 11 (P.T.A.B. Mar. 20, 2020)	117
<i>Ariad Pharms., Inc. v. Eli Lilly & Co.</i> , 598 F.3d 1336 (Fed. Cir. 2010) (<i>en banc</i>)	29, 30, 31, 89
<i>Atlas Powder Co. v. E.I.Dupont De Nemours</i> , 750 F.2d 1569 (Fed. Cir. 1984)	67, 87
<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)	67, 74, 78
<i>Boehringer Ingelheim Animal Health USA Inc. v. Kan. State Univ. Rsch. Found.</i> , Case PGR2020-00076, Paper 42 (P.T.A.B. Jan. 31, 2022)	33, 34, 36, 63
<i>Collegium Pharm., Inc. v. Purdue Pharma L.P.</i> , Case PGR2018-00048, 2021 WL 6340198 (P.T.A.B. Nov. 19, 2021), <i>aff'd</i> , 86 F.4th 1338 (Fed. Cir. 2023)	5
<i>Corona Cord Tire Co., v. Dovan Chemical Corp.</i> , 276 U.S. 358 (1928).....	30

<i>Crown Operations Intern. Ltd v. Solutia Inc.</i> , 389 F.3d 1367 (Fed. Cir. 2002)	67
<i>In re Entresto</i> , 125 F.4th 1090 (Fed. Cir. 2025)	32
<i>Fiers v. Revel</i> , 984 F.2d 1164 (Fed. Cir. 1993)	89, 92
<i>In re Fisher</i> , 421 F.3d 1365 (Fed. Cir. 2005)	67
<i>Fujikawa v. Wattanasin</i> , 93 F.3d 1559 (Fed. Cir. 1996)	31
<i>Gentry Gallery, Inc. v. Berkline Corp.</i> , 134 F.3d 1473 (Fed. Cir. 1998)	65
<i>Idenix Pharm., LLC v. Gilead Scis., Inc.</i> , 941 F.3d 1149 (Fed. Cir. 2019)	<i>passim</i>
<i>Inguran, LLC v. Premium Genetics (UK) Ltd.</i> , Case PGR2015-00017, Paper 8 (P.T.A.B. Dec. 22, 2015)	5
<i>Intex Recreation Corp. v. Team Worldwide Corp.</i> , Case PGR2019-00015, 2020 WL 2071543 (P.T.A.B. Apr. 29, 2020)	5
<i>In re Kirk</i> , 376 F.2d (C.C.P.A. 1967)	67
<i>Lockwood v. Am. Airlines, Inc.</i> , 107 F. 3d 1565 (Fed. Cir. 1997)	31
<i>Pharm. Res., Inc. v. Roxane Labs., Inc.</i> , 253 F. App'x. 26 (Fed. Cir. 2007)	87
<i>Rasmusson v. SmithKline Beecham Corp.</i> , 413 F.3d 1318 (Fed. Cir. 2005)	86
<i>Regents of Univ. of Minn. v. Gilead Sciences., Inc.</i> , 61 F. 4th 1350 (Fed. Cir. 2023)	31

US Endodontics, LLC v. Gold Standard Instruments, LLC,
 Case PGR2015-00019, Paper 17 (P.T.A.B. Jan. 29, 2016).....5

In re Wands,
 858 F.2d 731 (Fed. Cir. 1988)66, 68, 71, 77

Wyeth & Cordis Corp. v. Abbott Labs,
 720 F.3d 1380 (Fed. Cir. 2013)66, 74

Statutes

35 U.S.C. § 1038, 89

35 U.S.C. § 112*passim*

35 U.S.C. § 1202, 5

Other

Memorandum from Coke Morgan Stewart, Acting Director of the
 United States Patent and Trademark Office Memorandum (March
 26, 2025),
<https://www.uspto.gov/sites/default/files/documents/InterimProcesses-PTABWorkloadMgmt-20250326.pdf>117

I. Introduction

Petitioner Merck Sharp & Dohme LLC (“Merck”) requests post grant review of U.S. Patent No. 12,091,692 (“’692 Patent”).

Claims 1-40 of the ’692 Patent define modified human PH20 polypeptides that (i) *must have* one amino acid substitution at position 313, and (ii) *may have* between 20 and 41 additional substitutions at *any* of 430+ positions, and to *any* of 19 other amino acids. These parameters capture between 10^{60} and 10^{113} distinct PH20 polypeptides, a scale that is unfathomable—the collective weight of one molecule of each polypeptide in the smallest set exceeds the weight of the Earth, and simply making and testing each set per the patent’s methodology would require lifetimes of “making and testing” experiments.

Within this massive set of modified PH20 polypeptides are undisclosed and unknown numbers of (i) enzymatically *active* multiply-modified PH20 mutants—the only mutants with an established utility, (ii) enzymatically *inactive* modified PH20 polypeptides that retain the PH20 protein structure—mutants the patent implausibly contends are useful in contraceptive vaccines, and (iii) modified PH20 polypeptides that, due to the additional 1-41 changes they incorporate, cannot be produced or will not fold into a PH20 protein—mutants with no utility.

The claims are unpatentable for three independent reasons. The first two are linked to their extreme breadth—measured against the common disclosure of the

'692 Patent and its ultimate parent '731 Application,¹ each utterly fails the written description and enablement requirements of § 112(a). That also precludes the claims from having a valid § 120 benefit claim to the '731 Application, the only non-provisional application filed before March 16, 2013, thus making the '692 Patent PGR eligible.

Regarding written description, the common disclosure makes no effort to identify (and never contends there is) a common structure shared by the subgenus of enzymatically active multiply-modified PH20 polypeptides within each claim's scope. The disclosed examples also are not representative of this "active mutant" subgenus: each has only *one* amino acid substitution in *one* PH20 sequence (1-447), while the claims encompass PH20 proteins with myriad *undescribed* combinations of 5, 10, 15, or 20+ substitutions anywhere within PH20 sequences of varying length, and even capture combinations the disclosure says to avoid in enzymatically active PH20 mutants. Both points are true for the other two types of PH20 polypeptides within the claims' scope—those with implausible or no utility. Because the disclosure fails to demonstrate possession of *any* of these distinct subsets of modified PH20 polypeptides, the claims are unpatentable.

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

Regarding enablement, equally fatal problems exist: the disclosure identifies *no* enzymatically active modified PH20 polypeptide with 2 or more substitutions, much less affirmatively guides the selection of *which* of the $10^{60}+$ combinations of substitutions yield such enzymes. The only process it discloses for identifying these multiply-substituted active mutants is a prophetic “trial-and-error” one that must be repeated innumerable times until $10^{60}+$ unique proteins are made and tested. That is far more than undue experimentation—it is impossible. Indeed, the Supreme Court found claims non-enabled due to the necessity of performing analogous “trial and error discovery” to discover a much smaller genus of claimed proteins.² This same amount of undue experimentation is required to identify the enzymatically inactive mutants with purported contraceptive utility—if any exist—that make up this distinct subgenus of modified PH20 polypeptides, and to weed out the modified PH20 polypeptides within the scope of the claims that cannot be made or do not fold—inoperative species with no utility. The claims are unpatentable because the common disclosure does not enable their “full scope.”

Finally, claims 1-2, 4-5, 7-26, and 29-40 are unpatentable because each captures one obvious PH20₁₋₄₄₇ mutant that replaces the methionine at position 313 with lysine (M313K PH20₁₋₄₄₇), or its use in compositions or methods. But

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

Patentee's prior '429 Patent (EX1005) directs artisans to make single amino acid substitutions in non-essential regions of PH20₁₋₄₄₇ (and expressly claimed them). Skilled artisans implementing that guidance in 2011 would have found Chao (EX1006)—an intervening publication ignored in the common disclosure—and from their collective teachings would have (i) readily identified position 313 as being in a non-essential region of PH20 and (ii) found it obvious to change methionine at position 313 to lysine. They also would have reasonably expected this singly-substituted mutant to retain its enzymatic activity because that is what Patentee said in its '429 Patent: “[t]hose of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity.”³ Because numerous claims capture this obvious mutant and obvious compositions and methods that use it, they are unpatentable.

The Board should institute trial.

II. Compliance with PGR Requirements

A. Certification of Standing

This Petition is filed within 9 months of the '692 Patent's issuance.

Petitioner certifies it is not barred or estopped from requesting this PGR.

³ EX1005, 16:17-22.

Petitioner and its privies have not filed a civil action challenging the validity of any claim of the '692 Patent.

The '692 Patent is eligible for post-grant review because at least one of its claims is not entitled to an effective filing date prior to March 16, 2013.

A patent is PGR eligible if it issued from an application filed after March 16, 2013 “if the patent contains ... at least one claim that was not disclosed in compliance with the written description and enablement requirements of § 112(a) in the earlier application for which the benefit of an earlier filing date prior to March 16, 2013 was sought.” *See Inguran, LLC v. Premium Genetics (UK) Ltd.*, Case PGR2015-00017, Paper 8 at 16-17 (P.T.A.B. Dec. 22, 2015); *US Endodontics, LLC v. Gold Standard Instruments, LLC*, PGR2015-00019, Paper 17 at 8 (P.T.A.B. Jan. 29, 2016); *Collegium Pharm., Inc. v. Purdue Pharma L.P.*, 2021 WL 6340198, at *14-18 (P.T.A.B. Nov. 19, 2021) (same) *aff'd Purdue Pharma L.P. v. Collegium Pharm., Inc.*, 86 F.4th 1338, 1346 (Fed. Cir. 2023); *Intex Recreation Corp. v. Team Worldwide Corp.*, 2020 WL 2071543, at *26 (P.T.A.B. Apr. 29, 2020) (same).

Only one application to which the '692 Patent claims benefit under 35 U.S.C. § 120 and/or § 121—U.S. Application No. 13/694,731 (the '731 Application)—was filed before March 16, 2013. That application, issued as U.S. Patent No. 9,447,401 (EX1025), claims priority to two provisional applications

(61/631,313, filed November 1, 2012 and 61/796,208, filed December 30, 2011) and WO 01/3087 (“WO087”). The ’731 Application, however, alters several passages of the provisional disclosures, adds new examples and tested mutants, and makes other changes.⁴

The ’731 Application (including subject matter incorporated by reference) does not provide written description support for and does not enable any claim of the ’692 Patent (§§ V.A, V.B). The same is true for the ’692 Patent, whose disclosure relative to the claims is generally the same as the ’731 Application.⁵ The ’692 Patent is PGR eligible as at least one of its claims does not comply with § 112(a) based on the ’731 Application filed before March 16, 2013.

B. Mandatory Notices

1. Real Party-in-Interest

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

⁴ EX1026, 153:15-163:26, 324-34, 19:25-26, 28; EX1051; EX1052.

⁵ “Common disclosure” refers to the shared disclosure of the ’692 Patent and the ’731 Application (EX1026). Citations are to the ’692 Patent; EX1015 correlates citations to the ’731 Application. The disclosures are highly similar but not identical. *See* EX1068, ¶ 6.

2. Related Proceedings

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

On April 24, 2025, Patentee 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 '692 Patent.

3. Counsel and Service Information

Lead Counsel 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	Backup Counsel Leif Peterson Pro Hac Vice forthcoming Sidley Austin LLP 1 S Dearborn Street Chicago, IL 60603 leif.peterson@sidley.com (312) 853-7190	Backup Counsel 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
--	--	---

Petitioner consents to service via e-mail at the email addresses listed above and at HalozyymePGRs@sidley.com.

III. Grounds

The grounds advanced in this Petition are:

- (a) Claims 1-40 are unpatentable under 35 U.S.C. § 112 as lacking adequate written description.
- (b) Claims 1-40 are unpatentable under 35 U.S.C. § 112 as not being enabled.

- (c) Claims 1-2, 4-5, 7-26, and 29-40 are unpatentable as obvious under 35 U.S.C. § 103 based on the '429 Patent (EX1005), Chao (EX1006), and knowledge held by a person of ordinary skill in the art.

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

"PH20" refers to the human PH20 hyaluronidase protein. 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), and "AxxxB" is used to identify the position of a substitution (*e.g.*, "M313K").

IV. Background on the '692 Patent

A. Field of the Patent

The '692 Patent concerns the human PH20 hyaluronidase enzyme and making structurally altered forms of that protein that retain enzymatic activity.⁷

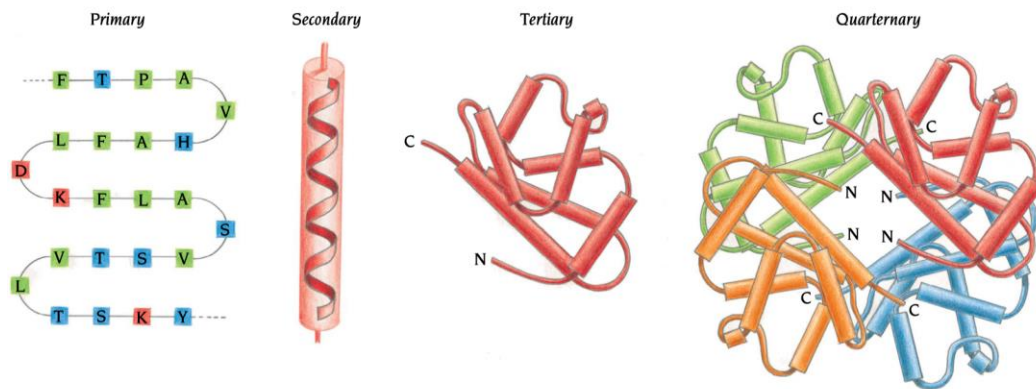
The information below would have been known to a skilled artisan prior to 2013.

⁶ EX1003, ¶ 15.

⁷ EX1001, 2:37-40.

1. Protein Structures

Proteins are comprised of sequences of amino acids. A protein's activity, however, derives from its unique, three-dimensional shape—its structure.⁸ That is dictated by specific and often characteristic patterns of amino acids in its sequence, which induce formation and maintenance of various secondary structures, structural motifs, and compact domains that define the protein's overall structure (tertiary structure).⁹



Secondary structures, such as α -helices or β -strands, are formed and stabilized by different but characteristic patterns of amino acids (below).¹⁰

⁸ EX1003, ¶¶ 36; EX1014, 3-4; EX1032, 125-127, 130-131, 136-137.

⁹ EX1014, 3-4, 24-32, Figure 1.1; EX1039, 136-37 (Figure 3-11); EX1003, ¶¶ 36-40.

¹⁰ EX1039, 134; EX1014, 14-22, Figures 2.2, 2.5, Table 2.1; EX1047, 2031-32; EX1003, ¶¶ 40-43.

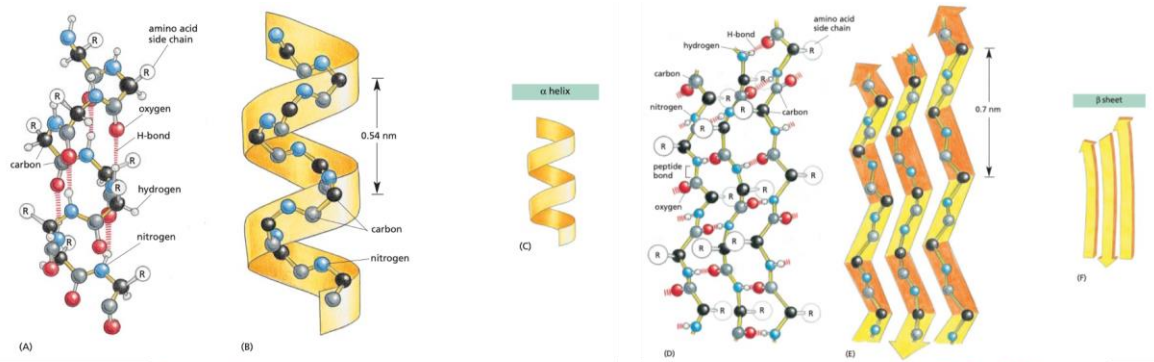


Figure 3-7 The regular conformation of the polypeptide backbone in the α helix and the β sheet. <GTAG> <TGCT>
 (A, B, and C) The α helix. The N-H of every peptide bond is hydrogen-bonded to the C=O of a neighboring peptide bond located four peptide bonds away in the same chain. Note that all of the N-H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

Intervening sequences between those characteristic sequences are important too; they direct and facilitate positioning and arrangement of the various secondary structures into structural motifs and the protein's tertiary structure.¹¹

Changes to a protein's amino acid sequence can affect the folding, formation and stability of these various structures that define the protein's overall shape. For example, changing even a single residue known to be critical to the protein's structure or activity can render a protein inactive.¹²

Making many concurrent changes to a protein's sequence can cause myriad effects on the protein's structure, especially when they are in or affect the same

¹¹ EX1003, ¶¶ 44-46; EX1014, 21-22.

¹² EX1003, ¶¶ 54, 154; EX1004, ¶¶ 20, 25.

region(s) of the protein.¹³ For example, it can disrupt the characteristic patterns, spacing and/or types of amino acids required to induce formation and stability of secondary structures, and disrupt folding and positioning of the secondary structures and structural motifs into the protein's tertiary structure.¹⁴ Multiple changes in different regions of the amino acid sequence also cause unfavorable spatial interactions that destabilize or impair or prevent folding.¹⁵ Consequently, in 2011, predicting the effects of the myriad interactions that may be disrupted by multiple concurrent substitutions was beyond the capacity of skilled artisans and available computational tools.¹⁶

2. Hyaluronidase Enzymes

PH20 is one of five structurally similar human hyaluronidases and is homologous—evolutionarily related to—hyaluronidases in many species.¹⁷ PH20

¹³ EX1003, ¶ 163.

¹⁴ EX1003, ¶¶ 55-56, 151; EX1047, 6349; EX1046, 2034; *see also* EX1040, 14412-13; EX1041, 21149-50; EX1042, 1-3.

¹⁵ EX1003, ¶¶ 55, 57-59.

¹⁶ EX1003, ¶¶ 50, 163, 201, 240; EX1004, ¶¶ 166-168; EX1027 at 8-11.

¹⁷ EX1007, 10:18-30; EX1006, 6911, 6916 (Figure 3); EX1003, ¶¶ 33, 77.

breaks down hyaluronan (“HA”) by selectively hydrolyzing glycosidic linkages.¹⁸

PH20 exists naturally as a GPI anchored protein; deletion of its GPI-anchoring sequence yields a soluble, neutral active enzyme.¹⁹

Many essential residues in PH20 had been identified before 2011. Several are in the shared catalytic site of the protein;²⁰ mutating certain residues in or near that site can abolish enzymatic activity.²¹ Conserved cysteine residues that stabilize the protein structure are also essential,²² as are certain conserved asparagine residues involved in glycosylation.²³

In 2007, Chao reported an experimentally determined structure of the human HYAL1 hyaluronidase, and used an alignment of the five human hyaluronidases to

¹⁸ EX1003, ¶ 77; EX1008, 819.

¹⁹ EX1005, 2:40-61, 87:52-88:24; EX1013, 430-32, Figure 2; EX1003, ¶¶ 92, 207; EX1029, 546, Figure 1.

²⁰ EX1006, 6914-16, Figure 3; EX1007, 35:28-36:10; EX1011, 810-14; EX1008, 824-25; EX1009, 6912-17.

²¹ EX1011, 812-14; EX1010, 9435-39, Table 1.

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

²³ EX1005, 7:9-27; EX1007, 36:12-20; EX1010, 9433, 9435-40.

illustrate shared secondary structures and conserved residues in these proteins.²⁴

Among its findings was that human hyaluronidases contain a unique structure—the Hyal-EGF domain.²⁵ Using its sequence analysis, an earlier structure of bee venom hyaluronidase, and a computer model of the protein structures, Chao identified residues in the catalytic site that interact with HA.²⁶

3. Protein Engineering

There are two general approaches used to engineer changes into proteins.²⁷ In “rational design,” skilled artisans employed computational tools—sequence alignments and protein structure models—to study the protein and then select where and what changes to introduce.²⁸ For example, a “multiple-sequence

²⁴ EX1006, 6914-18.

²⁵ EX1006, 6912-13, 6916-18; EX1010, 9439-40; EX1003, ¶¶ 84-88; EX1004, ¶¶ 97-99.

²⁶ EX1006, 6912-13, 6916-18, Figures 2C, 4A; EX1033, 1028-29, 1035; EX1010, 9434, 9436, Figure 1.

²⁷ EX1003, ¶ 47.

²⁸ EX1016, 181-82; EX1017, 223, 236; EX1003, ¶¶ 48-50.

alignment” (“MSA”)²⁹ produced by aligning known sequences of homologous, naturally occurring proteins identifies positions with no or little amino acid variation (“conserved” / “essential” residues) and positions where different amino acids occur (“non-conserved” / “non-essential” residues).³⁰ A structural model using the protein’s sequence but based on a known structure of a homologous protein enabled assessment of interactions between amino acids at a particular positions.³¹ Using rational design techniques, a skilled artisan could assess, with varying effort, effects of changing one or a few amino acids, but could not use those techniques to predict the effects of many concurrent changes, given the escalating complexity of numerous, interrelated interactions (which exponentially increase with the number of changes) and the limits of protein modeling tools.³²

²⁹ EX1017, 224-27; EX1016, 181-86 (Figure 1); EX1003, ¶¶ 48-50; EX1004, ¶¶ 22-23, 29.

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

³¹ EX1017, 228-30; EX1031, 461, 463, 469-71; EX1014, 351-52; EX1032, 265-66; EX1004, ¶ 37; *also id.* 33-36; EX1003, ¶¶ 235-37.

³² EX1003, ¶¶ 50, 163; EX1004, ¶¶ 166-168.

“Directed evolution” techniques arose due to the limits of rational design.³³ 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.³⁴ Importantly, until a desired mutant is made, found, and tested, whether it exists and its sequence are unknown.³⁵ Sophisticated assays that rapidly and precisely identify mutants with desired properties are critical, given the scale of experimentation this approach requires.³⁶ The ’692 Patent embodies this approach.³⁷

B. Person of Ordinary Skill in the Art

While the ’692 Patent claims priority to provisional applications dating to December 30, 2011 and benefit to the ’731 Application filed December 28, 2012, none of those earlier-filed applications when each was filed supported the claims as required by § 112(a). *See* §§ II.A, V.A, V.B. Conversely, the obviousness

³³ EX1003, ¶ 51; EX1059, 1225-26; EX1018, 378.

³⁴ EX1003, ¶ 51; EX1059, 1225-26; EX1018, 378.

³⁵ EX1003, ¶ 194.

³⁶ EX1003, ¶¶ 52-53.

³⁷ EX1003, ¶¶ 146, 183, 193, 197.

grounds rely on prior art published before and knowledge/perspectives of a skilled artisan before December 2011.

A person of ordinary skill in the art would have had an undergraduate degree, a Ph.D., and post-doctoral experience in scientific fields relevant to study of protein structure and function (*e.g.*, chemistry, biochemistry, biology, biophysics). From training and experience, the person would have been familiar with factors influencing protein structure, folding and activity, production of modified proteins using recombinant DNA techniques, and use of biological assays to characterize protein function, as well with techniques used to analyze protein structure (*i.e.*, sequence searching and alignments, protein modeling software, etc.).³⁸

C. Prosecution History

No issues relevant to the present grounds were raised during examination. In the sole Office action, indefiniteness rejections were imposed,³⁹ which Patentee

³⁸ EX1003, ¶ 13.

³⁹ EX1002, 631.

overcame with claim amendments.⁴⁰ Non-statutory double patenting rejections were overcome with a terminal disclaimer.⁴¹

D. The Challenged Claims

The claim terms are either expressly defined in the common disclosure or are used with their common and ordinary meaning.⁴² Consequently, no term requires an express construction to assess the grounds in this Petition.

A clear understanding of the *breadth* of the claims, however, is important—each captures a massive number of structurally distinct modified PH20 polypeptides meeting sequence identity parameters in each claim, including enzymatically active PH20 mutants that are neither adequately described in nor enabled by the common disclosure of the '731 Application and the '692 Patent.

⁴⁰ EX1002, 703-707.

⁴¹ EX1002, 632-48, 708, 743.

⁴² EX1001, 44:13-14 (“PH20 refers to a type of hyaluronidase that occurs in sperm and is neutral-active”); *id.* at 44:30-34 (“Reference to PH20 includes precursor PH20 polypeptides and mature PH20 polypeptides [], truncated forms thereof that have activity” and “species variants...”); *id.* at 43:61-44:6.

1. The Claims Encompass a Staggering Number of Modified PH20 Polypeptides

The claims define an incredibly broad and diverse genus of “modified PH20 polypeptides,” which the common disclosure defines as “a PH20 polypeptide that contains at least one amino acid modification, such as at least one amino acid replacement ... in its sequence of amino acids compared to a reference unmodified PH20 polypeptide.”⁴³

Per claim 1, each modified PH20 polypeptide:

- **must** contain **one** amino acid replacement at position 313; and
- **may** contain **additional** modifications, 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 restrict these parameters:

- (i) claims 2 and 24-25 require at least 95% sequence identity;
- (ii) claims 8-16 and 22-25 narrow the comparator sequences (*e.g.*, omitting SEQ ID NO: 7, requiring SEQ ID NOs: 35 or 32, or listing one or more of SEQ ID NOs: 591-598),

⁴³ EX1001, 46:63-47:1.

- (iii) claims 5, 7, 10, 13-14, 16, and 23-25 require the position 313 substitution to be to one or more specific amino acids (*e.g.*, K), and
- (iv) claims 3-4, 6, and 27-28 add functional requirements (*e.g.*, increased “stability,” increased activity, or solubility).

The specification explains that “sequence identity can be determined by standard alignment algorithm programs ...”⁴⁴ and provides an example, explaining a polypeptide that is “‘at least 90% identical to’ refers to percent identities from 90 to 100% relative to the reference polypeptide” where “no more than 10% (*i.e.*, 10 out of 100) of amino acids [] in the test polypeptide [] differs from that of the reference polypeptides.”⁴⁵

It further explains that “differences can be represented as point mutations randomly distributed over the entire length of an amino acid sequence” and that “[d]ifferences are defined as [] amino acid substitutions, insertions or deletions.”⁴⁶ Also, “amino acids selected to replace the target positions on the particular protein being optimized can be either all of the remaining 19 amino acids, or a more restricted group containing only selected amino acids” (*e.g.*, 10-18 of the 19

⁴⁴ EX1001, 58:29-31.

⁴⁵ EX1001, 58:64-59:6.

⁴⁶ EX1001, 59:7-15; *see also id.* at 3:22-23, 46:1-5, 14-16.

alternative amino acids).⁴⁷ The claims do not restrict (other than position 313) *where* substitutions can occur within the modified PH20 sequence, or *which* of 19 other amino acids can be substituted at those positions.

The claims' sequence identity parameters capture immense numbers of modified PH20 polypeptides, each with a unique amino acid sequence (below).⁴⁸

⁴⁷ EX1001, 135:52-59; *see also id.* at 141:2-4.

⁴⁸ EX1003, ¶¶ 129-131; EX1004, ¶¶ 174-178, Appendix F.

<i>Claims</i>	<i>Max PH20 length</i>	<i>Sequence Identity %</i>	<i># Changes</i>	<i>Pos. 313 Choices</i>	<i># of Distinct Polypeptides</i>
1, 3, 17-21, 26, 29-40	474	91	42	19	1.20×10^{113}
2, 4, 6, 27, 28	474	95	23	19	9.85×10^{66}
5	474	91	42	8	5.05×10^{112}
7	474	91	42	1	6.32×10^{111}
8, 22	465	91	41	19	2.68×10^{110}
9	465	95	23	19	6.39×10^{66}
10, 16	465	91	41	1	1.41×10^{109}
11	433	91	41	19	1.35×10^{109}
12	430	91	41	19	1.01×10^{109}
13	433	91	41	1	7.10×10^{107}
14	430	91	41	1	5.30×10^{107}
15	447	91	40	19	2.65×10^{107}
23	447	91	40	1	1.40×10^{106}
24	430	95	21	8	3.52×10^{60}
25	433	95	21	8	4.06×10^{60}

2. The Claims Encompass M313K PH20₁₋₄₄₇

Claims 1-40 capture a modified PH20₁₋₄₄₇ polypeptide that changes one amino acid: methionine at position 313 to lysine (K) (“M313K”). This single-replacement PH20₁₋₄₄₇ mutant is: (i) 99.7% identical to SEQ ID NO: 3 (1 change,

447 residues), (ii) 96.5% identical to SEQ ID NO: 35 (15 changes, 433 residues), and (iii) 95.9% identical to SEQ ID NO: 32 (18 changes, 430 residues).⁴⁹

3. The Claims Encompass or Require “Active Mutants”

The common disclosure describes two mutually exclusive categories of “modified PH20 polypeptides” (*i.e.*, “active mutants” vs. “inactive mutants”):

- “*Active mutants*” are modified PH20 polypeptides “whereby the polypeptides exhibit at least 40% of the hyaluronidase activity of the corresponding PH20 polypeptide not containing the amino acid modification (*e.g.*, amino acid replacement).”⁵⁰
- “*Inactive mutants*” are modified PH20 polypeptides that “generally exhibit less than 20% ... of the hyaluronidase activity of a wildtype or reference PH20 polypeptide, such as the polypeptide set forth in SEQ ID NO: 3 or 7.”⁵¹

⁴⁹ EX1003, ¶ 145.

⁵⁰ EX1001, 73:61-66; *see also id.* at 77:43-47; *id.* at 77:40-43.

⁵¹ EX1001, 117:34-45. *See also id.* at 266:55-60 (mutants with <20% activity “were rescreened to confirm that the dead mutants are inactive” in Table 10).

It then classifies mutants into tables of “active” or “inactive” mutants using the >40% threshold (Tables 3 and 9) or <20% threshold (Tables 5 and 10).⁵² No examples of an “active mutant” modified PH20 polypeptide have two or more specific substitutions,⁵³ 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 distinct utilities with mutually exclusive properties. “Active mutants” have a variety of therapeutic uses *because they possess hyaluronidase activity.*”⁵⁴

⁵² EX1001, 232:27-29 (“Active mutants were selected whereby *at least one duplicate sample* exhibited greater than 40% of wildtype activity ...”); *id.* at 232:35-39 (Table 9 “...sets forth the *average hyaluronidase activity* of tested duplicates...”); *id.* at 79:7-80:17, 232:28-30, 118:39-67, 268:6-9 (“reconfirmed inactive mutants are set forth in Table 10.”); EX1003 ¶¶ 101, 103-04, 111, 116.

⁵³ *E.g.*, EX1003, ¶¶ 148, 182.

⁵⁴ EX1001, 179:48-54; *see also id.* at 2:54-57, 71:47-61, 179:48-193:7, 156:2-4. EX1003, ¶ 117.

However, the common disclosure identifies only one utility for “inactive mutants”:
“antigens in contraception vaccines” (*see* § V.C).⁵⁵

Each claim either encompasses or is limited to “active mutant” modified PH20 polypeptides meeting the sequence identity parameters of the claims.

First, dependent claims 5, 7, 10, 13-14, and 23-25 require modified PH20 polypeptides that include a position 313 mutation (*e.g.*, M313K) that yielded PH20₁₋₄₄₇ polypeptides with >40% activity.⁵⁶ Each is read correctly as being limited to “active mutants.”

⁵⁵ EX1001, 74:3-5 (“Also provided are modified PH20 polypeptides that are inactive, *and* that can be used, for example, as antigens in contraception vaccines.”); *see also id.* at 193:8-9, 71:7-9, 193:7-26 (for “contraception” “the modified PH20 polypeptides can be inactive enzymes, such as any described in Sections C.2.”); EX1003, ¶ 118; EX1001, 156:3-16; EX1060, 1711.

⁵⁶ EX1001, 85 (Table 3), 256 (Table 9), 99:12-24; EX1003, ¶¶ 135-38.

TABLE 8-continued

PH20 Variants	
mut	cod
M313A	GCT
M313C	TGT
M313D	GAT
M313E	GAG
M313F	TTT
M313G	GGG
M313H	CAT
M313K	AAG
M313L	CTT
M313P	CCT
M313R	CGT
M313S	TCG
M313T	ACT
M313V	GTT
M313Y	TAT

EX1001, 217-219

TABLE 9-continued

ACTIVE MUTANTS		
mutant	SEQ ID NO	AvgNorm Act.
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

EX1001, 256

Second, dependent claims 3, 6, and 27-28 require modified PH20 polypeptides with “increased resistance or stability” or “increased hyaluronidase activity” relative to an unmodified PH20.⁵⁷ All require modified PH20s with hyaluronidase activity (*i.e.*, “[a]s used herein, ‘increased stability’ ... means the modified PH20 ... exhibits greater hyaluronidase activity ...”, “[a]s used herein, ‘increased activity’ means that, when tested under the same conditions, the modified PH20 hyaluronidase exhibits greater hyaluronidase activity...”).⁵⁸

Third, dependent claims 28 and 30-40 define pharmaceutical compositions or methods that require use of PH20 with hyaluronidase activity:

⁵⁷ EX1001, 50:64-51:3, 132:52-133:4, 178:36-39, 311:18-312:44.

⁵⁸ EX1001, 50:64-51:12; *also id.* 50:25-33; 50:33-54.

- claim 28 requires use of an “active” chimeric polypeptide of claim 27;
- claims 30-33 require combinations with “a therapeutically active agent,” which the disclosure indicates are compositions that “can contain a further therapeutically active agent”;⁵⁹
- claims 34-36 specify methods for treating “a hyaluronan-associated disease or condition” associated with “accumulation or overproduction of hyaluronan,” which require a PH20 that degrades hyaluronan (*i.e.*, has hyaluronidase activity);⁶⁰ and
- claims 37-40 claim methods to “increase delivery of a therapeutic agent,” which require use of a PH20 that can degrade HA and thereby cause “spreading” or “diffusion” of the other agent.⁶¹

The common disclosure’s description of multiply-modified PH20 polypeptides and producing them also indicate they are “active mutants.” For example, it defines a “modified PH20 polypeptide” as “a PH20 polypeptide that

⁵⁹ EX1001, 31:65-66.

⁶⁰ EX1001, 37:27-46 (“conditions in which hyaluronan plays a role or is associated with etiology of the disease due to, for example, accumulation or overproduction of hyaluronan”).

⁶¹ EX1001, 2:53-3:4, 71:36-61, 179:48-54, 180:50-62; EX1003, ¶ 174-75.

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 PH20 polypeptides with multiple changes, which selects “active mutants” with one substitution, randomly introduces another, and then screens to find “double mutants” that *retained* hyaluronidase activity.⁶³ It also tracks the claims, which require one substitution and permit others.

Patentee may contend certain claims encompass both “active” and “inactive” mutants, but that only compounds their § 112 problems. First, every claim still encompasses (and must describe and enable) the subgenus of “active mutants” (*e.g.*, claim 1 contains the genus of “active mutants” defined in claim 6).⁶⁴ Second, analogous § 112 problems exist for the distinct subgenus of “inactive mutants”—those with putative utility as a contraceptive antigen—within the 10⁶⁰⁺ claimed PH20 polypeptides, which is neither described nor enabled. *See* § V.C.

⁶² EX1001, 46:63-47:11; *see also id.* at 46:19-23, 74:19-22, 75:14-21, 79:15-80:17; EX1003, ¶ 139.

⁶³ EX1001, 140:36-47; *see also id.* at 41:3-10.

⁶⁴ EX1003, ¶¶ 143-44.

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

Claims 1-40 are unpatentable because each claims an immense genus of modified PH20 polypeptides that lack written description in and were not enabled by the common disclosure.

Per § IV.D.1, the claim parameters capture between 10^{60} and 10^{113} distinct PH20 polypeptides. To practice the claims' full scope of "active" (or for that matter "inactive") multiply-modified PH20 mutants requires a skilled artisan to make-and-test at least $\sim 10^{60}$ mutants.⁶⁵ Simply producing one molecule of each mutant in the smallest set—required to know if each is active, inactive or exhibits increased stability—would consume an aggregate mass ($\sim 3.15 \times 10^{38}$ kg) that exceeds the mass of the Earth ($\sim 6 \times 10^{24}$ kg).⁶⁶ Testing every polypeptide within the claims' scope in search of "active mutants" is impossible—literally.

Relative to that broad scope, the '692 Patent and the '731 Application provide only a meager disclosure: *singly*-modified PH20 polypeptides and a prophetic, make-and-test research plan to discover multiply-modified ones that retain activity. It nowhere demonstrates possession of the vast remainder of

⁶⁵ EX1003, ¶¶ 194-95.

⁶⁶ EX1003, ¶¶ 132, 200; *see also, e.g.*, EX1039, 136-37 (10^{390} forms of a polypeptide possible from 300 residue sequence).

enzymatically active multiply-modified polypeptides within each claim's scope, nor does it enable a skilled artisan to practice that full-range of active mutants without undue experimentation.

A. All Claims Lack Written Description

The written description analysis focuses on the four corners of the patent disclosure.⁶⁷ “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.”⁶⁸

If the claims define a genus, the written description must “show that one has truly invented a genus ...,” “[o]therwise, one has only a research plan, leaving it to others to explore the unknown contours of the claimed genus.”⁶⁹

⁶⁷ *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*).

⁶⁸ *Idenix Pharm., LLC v. Gilead Scis., Inc.*, 941 F.3d 1149, 1163 (Fed. Cir. 2019) (internal quotation marks omitted).

⁶⁹ *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300 (Fed. Cir. 2014).

“[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.”⁷⁰ Also, the species in the claimed genus must share a common quality or attribute.⁷¹

“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.”⁷²

Claims to genera of chemical compounds require “a precise definition, such as by structure, formula, chemical name, physical properties, or other properties, of species falling within the genus sufficient to distinguish the genus from other materials.”⁷³ “[M]erely drawing a fence around the outer limits of a purported

⁷⁰ *Idenix*, 941 F.3d at 1164.

⁷¹ *Corona Cord Tire Co., v. Dovan Chemical Corp.*, 276 U.S. 358, 385 (1928), citing *Incarescent Lamp Patent*, 159 U.S. 465, 475 (1895).

⁷² *AbbVie*, 759 F.3d at 1299-1300.

⁷³ *Ariad*, 598 F.3d at 1350.

genus” does not “demonstrate[] that the applicant has an invented species sufficient to support a claim to a genus...”⁷⁴ As the Federal Circuit has explained:

... just because a moiety is listed as one possible choice for one position does not mean there is *ipsis verbis* support for every species or sub-genus that chooses that moiety. Were this the case, a “laundry list” disclosure of every possible moiety for every possible position would constitute a written description of every species in the genus. This cannot be because such a disclosure would not “reasonably lead” those skilled in the art to any particular species.⁷⁵

This is true for any genus of chemical compounds, although broad genus claims defined with “functional language” create an “especially acute” problem.⁷⁶

Written description deficiencies also cannot be remedied by contending that subject matter not described would have been obvious from the disclosure.⁷⁷

Simply put, a disclosure that fails to “provide sufficient blaze marks to direct a

⁷⁴ *Ariad*, 598 F.3d at 1349-1350.

⁷⁵ *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571 (Fed. Cir. 1996); *accord Regents of Univ. of Minn. v. Gilead Sciences, Inc.*, 61 F. 4th 1350, 1357 (Fed. Cir. 2023).

⁷⁶ *Ariad*, 598 F.3d at 1349.

⁷⁷ *Lockwood v. Am. Airlines, Inc.*, 107 F. 3d 1565, 1571-2 (Fed. Cir. 1997).

POSA to the specific subset” of a genus with the claimed function or characteristic does not satisfy § 112(a).⁷⁸

Three cases are especially probative here.

In *AbbVie*, a disclosure of 300 examples was found to not be representative of a genus of particular IL-12 antibodies because “[a]lthough the number of the described species appears high quantitatively, the described species are all of the similar type and do not qualitatively represent other types of antibodies encompassed by the genus.”⁷⁹ The prophetic description of other non-exemplified species also was found insufficient as it was “only a research plan, leaving it to others to explore the unknown contours of the claimed genus” and a “trial and error approach.”⁸⁰

⁷⁸ *Idenix*, 941 F.3d at 1164. *In re Entresto*, 125 F.4th 1090, 1097-99 (Fed. Cir. 2025) found sufficient written description of a pharmaceutical composition of two known active ingredients even though it did not disclose that they formed a particular complex. Unlike *Entresto*, there is no disclosure of the vast majority of mutant species within the claimed genera here.

⁷⁹ *AbbVie*, 59 F.3d at 1300-1301.

⁸⁰ *Id.*

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 and “more than 7,000 unique configurations.”⁸¹ The specification’s failure to indicate which of the thousands of compounds would be effective was the problem: “provid[ing] lists or examples of supposedly effective nucleosides,” without “explain[ing] what makes them effective, or why” deprives a skilled artisan “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.”⁸²

Finally, *Boehringer Ingelheim Animal Health USA Inc. v. Kan. State Univ. Rsch. Found.*, PGR2020-00076, Paper 42, 6 (P.T.A.B. Jan. 31, 2022) concerned claims employing “90% sequence homology” language that captured “broad genus of amino acid sequence homologues” but which (like claim 1 here) imposed no restrictions where particular replacements could be made, thereby causing the

⁸¹ *Idenix*, 941 F.3d at 1158-64.

⁸² *Id.* at 1164.

claim “to cover, at minimum, thousands of amino acid sequences.”⁸³ Citing dependent claim 12, the Board found fatal to claim 1 the specification’s failure to “explain what, if any, structural features exist (*e.g.*, remain) in sequences that vary by as much as 10% that allow them to retain the antigenic characteristics referenced in the Specification” (*i.e.*, the same property required of “inactive mutant” contraceptive PH20 polypeptides here).⁸⁴ And (as here), the homology limitation “serves to merely draw a fence around the outer limits of a purported genus [which] is not an adequate substitute for describing a variety of materials constituting the genus” for purposes of section 112(a).⁸⁵

The deficiencies of the present claims dwarf those in these three cases. They capture much larger, less predictable, and more diverse sub-genera, and the common disclosure is far more limited. Because the common disclosure neither discloses a representative number of species of active modified PH20 polypeptides meeting the claim requirements, nor identifies sufficient structural features common to such modified PH20 polypeptides, it fails to demonstrate possession of the full scope of the claims.

⁸³ *Boehringer*, at 16. The claims included methods of using proteins. *Id.* at 6.

⁸⁴ *Boehringer*, at 35; EX1001, 71:7-9.

⁸⁵ *Boehringer*, at 35-36.

1. Claims 1-2, 5, 7-16, and 22-25 Lack Written Description

The claims encompass all PH20 polypeptides that are enzymatically active and that meet the sequence identity parameters in the claims. But the specification does not identify which of the 10^{60+} species in the claims' scope are those polypeptides, much less demonstrate possession of all of them. This renders those claims unpatentable for lack of written description, which remains true whether the claims capture enzymatically inactive modified PH20 polypeptides or polypeptides that cannot be produced or will not fold (which also are not adequately described). *See* § V.C.

(a) *The Claims Capture Massive and Diverse Sets of Enzymatically Active PH20 Polypeptides*

Claims 1-2, 5, 7-16, and 22-25 define genera of modified PH20 polypeptides that are not only immense in number but are structurally and functionally diverse. They include mutants with between 2-21 substitutions for the narrowest claims (*e.g.* claims 24 and 25) to 2-42 for the broadest (claim 1). The optional sets of substitutions can be anywhere in the sequence (*i.e.*, clustered in a narrow region, spaced apart in groups, or spread randomly throughout the sequence), to any of 19 other amino acids, and arranged in any manner.⁸⁶ The claims thus capture a mutant with 5 substituted hydrophobic residues clustered in a small region, and one with

⁸⁶ EX1003, ¶ 128; EX1001, 59:7-14, 46:1-5, 46:14-16, 40:25-31.

42 substitutions that mix polar, charged, aliphatic, and aromatic amino acids in any manner.⁸⁷

The claims also encompass substitutions within C-terminally truncated forms of PH20 terminating between residues 430 to 474, which, via the claims' sequence identity language, capture PH20 polypeptides terminating before position 430. For example, claims referencing SEQ ID NO: 32 permit between 21 and 42 changes (any mixture of deletions and substitutions) within PH20s terminating at position 416 or below that include a position 313 substitution.⁸⁸ See § V.A.1(b)(ii).

(b) Mutations the Common Disclosure Says to Avoid in Enzymatically Active PH20 Polypeptides

The claims' unconstrained sequence identity language captures not only modified PH20 polypeptides with innumerable combinations of substitutions but also those with structural features a skilled artisan would understand the disclosure to be saying to avoid when making "active mutants." Multiply-modified PH20 polypeptides with these different structural features raise questions regarding whether any will possess hyaluronidase activity, but at a minimum would be viewed by a skilled artisan as being structurally distinct types of enzymatically

⁸⁷ EX1003, ¶¶ 128-29.

⁸⁸ EX1003, ¶¶ 168-71.

active PH20 polypeptides as compared to singly-substituted PH20₁₋₄₄₇ polypeptides.

Instead of navigating this confusing landscape, the patent simply instructs the skilled artisan “to generate a modified PH20 polypeptide containing any one or more of the described mutation, and test each for a property or activity as described herein.”⁸⁹ The common disclosure does not describe PH20 polypeptides reflecting the structural diversity of the “active mutants” subgenus within the claims’ scope.

(i) No Multiply-Modified “Active Mutant” PH20 Polypeptides with Substitutions that Render PH20₁₋₄₄₇ Inactive

The common disclosure indicates that enzymatically active modified PH20 polypeptides should not incorporate amino acid substitutions that as single substitutions rendered PH20₁₋₄₄₇ inactive, stating:

To retain hyaluronidase activity, modifications typically ***are not made*** at those positions that are less tolerant to change or required for hyaluronidase activity.⁹⁰

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

⁸⁹ EX1001, 76:47-52; EX1003, ¶ 204.

⁹⁰ EX1001, 78:27-29.

and 10.⁹¹ It does not limit this observation to single-replacement PH20₁₋₄₄₇ mutants, or suggest that any of these substitutions that render PH20₁₋₄₄₇ inactive should be included in enzymatically active, multiply-modified PH20 polypeptides (much less identify specific combinations of substitutions including them).⁹²

By stating that the substitutions listed in Tables 5 and 10 should not be included in enzymatically active multiply-modified PH20 polypeptides, the common disclosure clearly conveys to the skilled artisan that active multiply-modified PH20 polypeptides do not and should not contain these substitutions.⁹³ The claim language however captures “active mutants” that include one or more of the substitutions in Tables 5 and 10.

(ii) No Multiply-Modified “Active Mutant” PH20 Polypeptides with Significant C-terminal Truncations

The common disclosure does not describe “active mutant” PH20 polypeptides truncated before position 447, particularly multiply-modified PH20 mutants terminating significantly before that position.⁹⁴

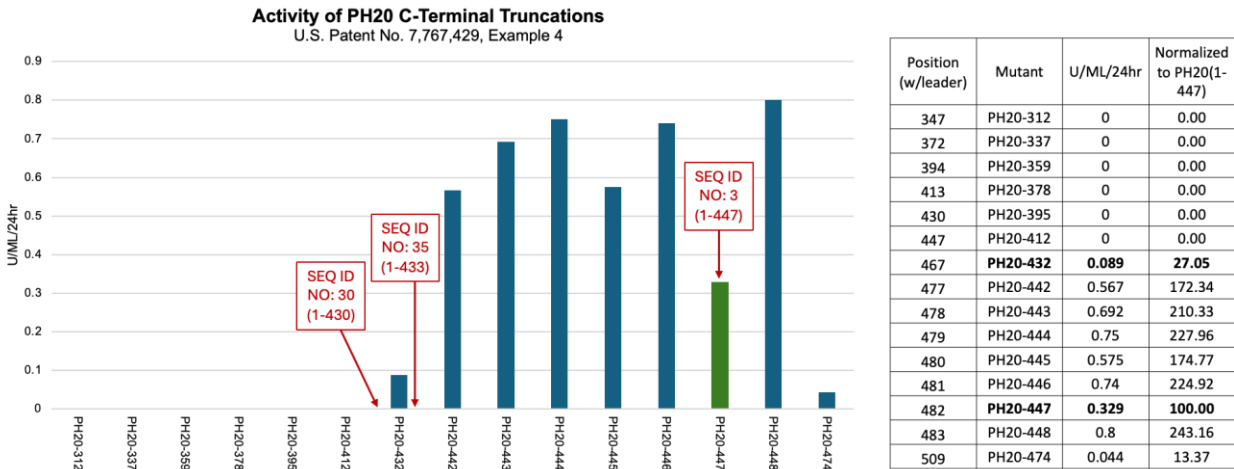
⁹¹ EX1001, 78:29-79:2.

⁹² EX1003, ¶¶ 156, 166-67, 173.

⁹³ EX1003, ¶¶ 153-56, 167; EX1001, 78:27-79:2, 68:60-69:3.

⁹⁴ EX1003, ¶¶ 97, 100, 171-73; EX1001, 72:23-29.

Patentee's '429 Patent reports that wild-type PH20 polypeptides terminating at or below position 442 have *significantly reduced or no* hyaluronidase activity, with those terminating below position 432 lacking hyaluronidase activity and those between positions 432 and 448 showing widely varying activity (below):⁹⁵



⁹⁵ EX1005, 87:52-88:24 (PH20₁₋₄₄₂ activity “decreased to approximately 10%”); EX1013, Figure 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, ¶ 94.

Patentee's '429 Patent also reports "a very narrow range spanning ... [437-447] ... defined the minimally active domain" of human PH20, and this "minimally active" human PH20 domain contains at least residues 1-429.⁹⁶

The common disclosure reiterates these findings, stating that PH20 polypeptides must extend to at least position 429 to exhibit hyaluronidase activity:

A mature PH20 polypeptide ... containing a contiguous sequence of amino acids having a C-terminal amino acid residue corresponding to amino acid residue **464** of SEQ ID NO: 6 [position **429** without signal] ... *is the minimal sequence required for hyaluronidase activity.*⁹⁷

In 2007, Chao reported that the C-terminal region of human hyaluronidases contains a unique domain ("Hyal-EGF") linked to a characteristic pattern of sequences, which runs from positions 337-409 in PH20.⁹⁸ In 2009, Zhang showed the Hyal-EGF domain was necessary for hyaluronidase activity.⁹⁹

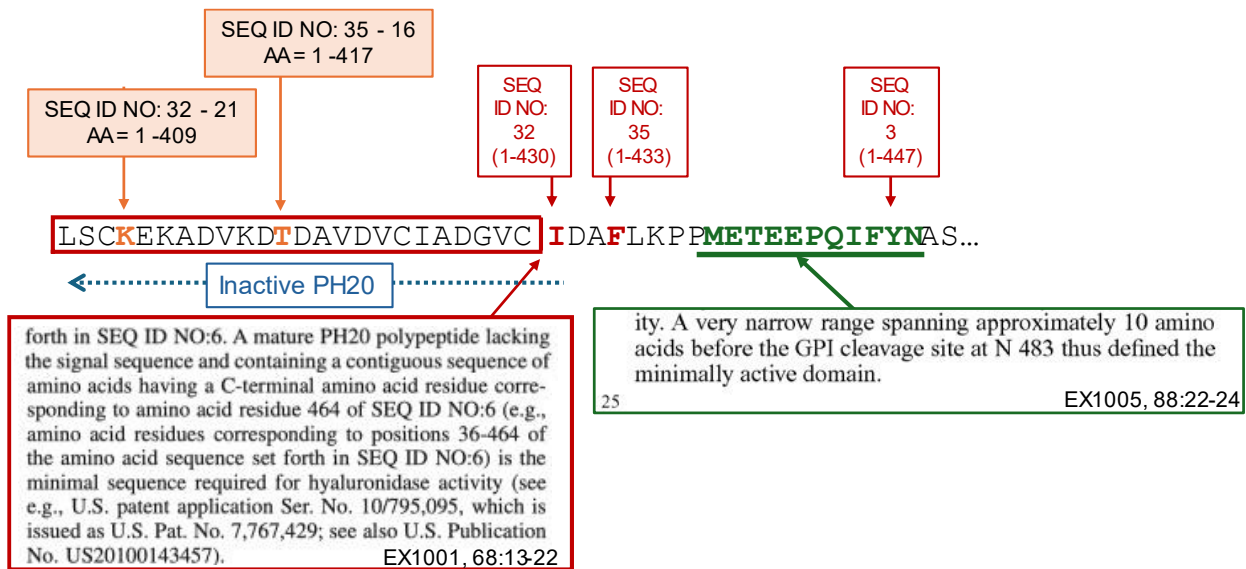
⁹⁶ EX1005, 6:65-7:7 ("... sHASEGP from amino acids 36 to Cys 464 [429] ... comprise the minimally active human sHASEGP hyaluronidase domain"); EX1003, ¶ 93.

⁹⁷ EX1001, 68:13-22 (emphases added); *also* EX1003, ¶¶ 96, 157.

⁹⁸ EX1006, 6912-13, 6916-18; EX1004, ¶¶ 97-99; EX1003, ¶ 95.

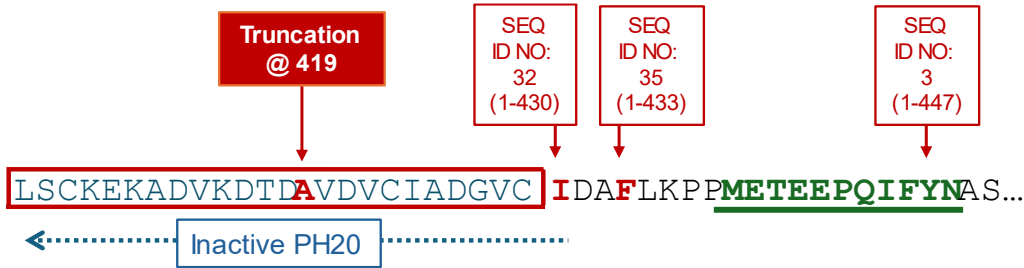
⁹⁹ EX1010, 9438; EX1003, ¶ 89.

An illustration of the C-terminus of PH20 (below) shows: (i) positions where SEQ ID NOS: **3** (447), **32** (430) and **35** (433) terminate, (ii) the “minimally active domain” at 437-447, (iii) residues before position 429, and (iv) that PH20 polypeptides with 21 or 16 deletions from SEQ ID NOS: 32 and 35, respectively, terminate before position 429.



From this, a skilled artisan would have believed a PH20 polypeptide terminating at position 419 would be inactive based on the common disclosure and information published before 2011.¹⁰⁰

¹⁰⁰ EX1003, ¶¶ 95-97, 169-72.



The common disclosure provides no examples of (or guidance concerning) enzymatically active multiply-substituted PH20 mutants truncated to positions 419.¹⁰¹ The claims nonetheless capture such mutants.

(c) *Empirical Test Results Do Not Identify Multiply-Modified Enzymatically Active PH20 Polypeptides*

The empirical results in the common disclosure do not provide any guidance to a skilled artisan about the structural features of enzymatically active, multiply-modified PH20 polypeptides.

(i) Single-Replacement Results Not Probative of Multiple-Replacement Mutants

The common disclosure reports results from testing a portion of a library of ~6,753 single-replacement PH20₁₋₄₄₇ polypeptide sequences.¹⁰² The mutants were produced using a library of CHO cells transfected with a plasmid encoding mutagenized PH20₁₋₄₄₇ sequences where one of 447 positions in the sequence “was

¹⁰¹ EX1003, ¶¶ 95-98, 100.

¹⁰² EX1001, 133:5-16, 200:22-24, 200:1-7.

changed to one of about 15 amino acid residues, such that each member contained a single amino change.”¹⁰³ Results for ~5,917 of the mutants are reported.¹⁰⁴

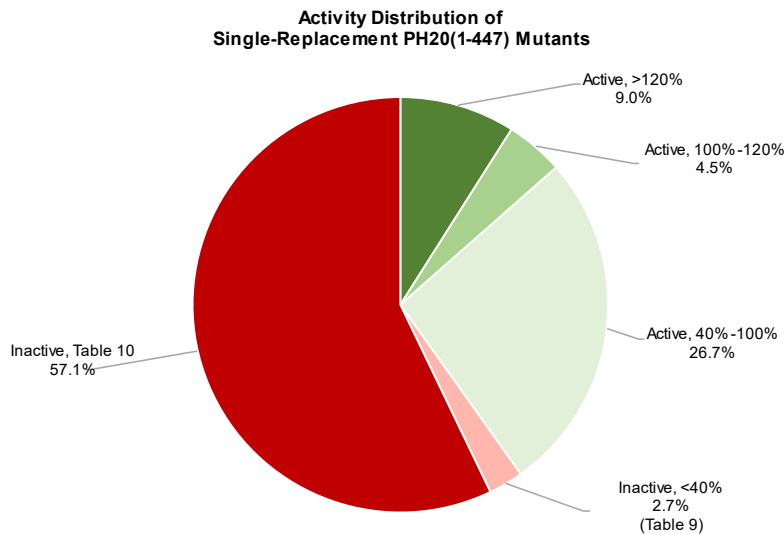
The common disclosure classifies more than half (~57%) of the tested mutants as “inactive mutants” and ~30% as having less activity than unmodified PH20₁₋₄₄₇ (20%-100%).¹⁰⁵ In other words, it portrays ~87% of the 5,917 single-replacement PH20₁₋₄₄₇ polypeptides that were made and tested as having *less* activity than unmodified PH20₁₋₄₄₇.

¹⁰³ EX1001, 200:1-10.

¹⁰⁴ EX1003, ¶¶ 111-12, 114. Inconsistent numbers and classifications of mutants are not explained: (i) Table 3 lists 2,516 single-replacement PH20₁₋₄₄₇ mutants as “active mutants,” but Table 9 identifies 2,536 total mutants and 2,376 that in one assay exhibited >40% hyaluronidase activity; (ii) Tables 5 and 10 list 3,368 and 3,380 PH20₁₋₄₄₇ “inactive mutants,” respectively.

¹⁰⁵ EX1003, ¶ 110, 114-15.

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



Notably, the data is not analyzed in the common disclosure—it is simply presented. No attempt is made to assess the impact of any single substitution on the protein’s structure, much less extrapolate these results to PH20 polypeptides with multiple substitutions.¹⁰⁶

¹⁰⁶ EX1003, ¶ 115.

The data's quality is also questionable: no control values or statistical assessments are provided for these activity results.¹⁰⁷ The common disclosure also does not report hyaluronidase activity values measured for 3,380 inactive mutants or the 836 unclassified single substitution PH20₁₋₄₄₇ mutants that were made and tested. *See* § V.C.

Further, the data reveal no trends or correlations even for single-replacement PH20₁₋₄₄₇ polypeptides. For example, different substitutions at the same position in PH20₁₋₄₄₇ yielded both active and inactive mutants, along with unreported effects for >800 mutants.¹⁰⁸

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

Changing multiple residues in PH20 polypeptides can cause unpredictable interactions within the protein's structure and resulting function that do not occur

¹⁰⁷ EX1003, ¶¶ 107, 115.

¹⁰⁸ EX1001, Table 8, 9, 10.

in single-substitution mutants.¹⁰⁹ The empirical test results for single substitution mutants do not identify to a skilled artisan which of the 10^{60+} PH20 mutants with a 313 substitution and 1-41 additional substitutions are enzymatically active (or for that matter, are inactive or cannot be made and are useless).¹¹⁰ Instead, all it shows is that *most* single-substitutions impaired or eliminated hyaluronidase activity.

(ii) Purported Stability Data Is Not Reliable or Probative

The common disclosure reports results of testing ~409 single-replacement PH20₁₋₄₄₇ polypeptides in “stability” assays.¹¹¹ Table 11 reports hyaluronidase activities of the mutants at 4° C and 37° C, and with a “phenolic preservative” (m-cresol).¹¹² Table 12 reports relative hyaluronidase activities of those mutants.¹¹³

The “stability” data provides no meaningful insights.¹¹⁴ Unsurprisingly, many single-replacement PH20₁₋₄₄₇ polypeptides showed more activity at 37° C

¹⁰⁹ EX1003, ¶¶ 54-58, 240.

¹¹⁰ EX1003, ¶¶ 147, 149, 204.

¹¹¹ EX1001, Tables 11-12.

¹¹² EX1001, 280:5-286:32 (Table 11).

¹¹³ EX1001, 286:33-297:38 (Table 12).

¹¹⁴ EX1003, ¶ 76.

(the temperature where human PH20 naturally exists) than at 4° C.¹¹⁵ Testing with m-cresol showed only a few mutants resisted that type of denaturation.¹¹⁶ With one exception, the measured activity data cannot be attributed to improved stability of PH20.¹¹⁷ The data are also largely meaningless—many measured activity values are within the activity ranges reported for the positive control.¹¹⁸

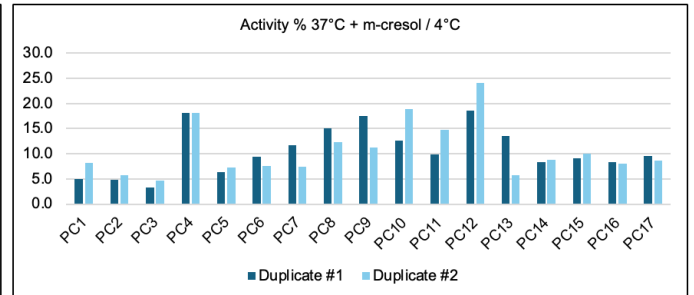
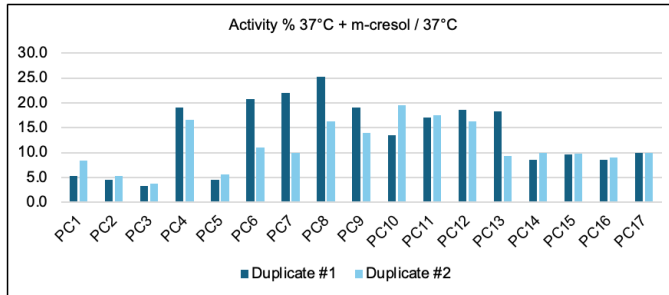
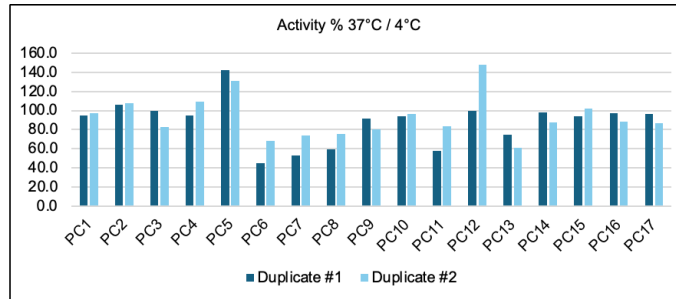
Positive Control ("PC") (OHO)	Duplicate #1			Duplicate #2			KEY										
	% Activity at 37°C/4°C	% Activity at 37°C+m-cresol / 37°C	% Activity at 37°C + mcr/4°C	% Activity at 37°C/4°C	% Activity at 37°C+m-cresol / 37°C	% Activity at 37°C+mcr/4 °C											
PC1	94.998	5.230	4.970	96.871	8.456	8.190	<table border="1"> <tr><th>KEY</th></tr> <tr><th>Coloration of Percent (%) Activity Values</th></tr> <tr><td>n/a</td></tr> <tr><td>>120</td></tr> <tr><td>between 100 and 120</td></tr> <tr><td>between 80 and 100</td></tr> <tr><td>between 40 and 80</td></tr> <tr><td>between 20 and 40</td></tr> <tr><td>between 10 and 20</td></tr> <tr><td>between 0 and < 10</td></tr> </table>	KEY	Coloration of Percent (%) Activity Values	n/a	>120	between 100 and 120	between 80 and 100	between 40 and 80	between 20 and 40	between 10 and 20	between 0 and < 10
KEY																	
Coloration of Percent (%) Activity Values																	
n/a																	
>120																	
between 100 and 120																	
between 80 and 100																	
between 40 and 80																	
between 20 and 40																	
between 10 and 20																	
between 0 and < 10																	
PC2	105.798	4.480	4.740	108.066	5.246	5.670											
PC3	100.000	3.330	3.330	82.778	3.759	4.590											
PC4	94.762	19.070	18.070	109.539	16.529	18.110											
PC5	142.024	4.480	6.360	130.947	5.595	7.330											
PC6	45.115	20.770	9.370	68.017	11.035	7.510											
PC7	53.324	21.950	11.710	74.253	9.960	7.400											
PC8	59.581	25.240	15.040	75.872	16.231	12.310											
PC9	91.844	19.050	17.500	80.371	13.977	11.230											
PC10	93.828	13.470	12.630	96.630	19.454	18.800											
PC11	57.773	17.040	9.850	83.536	17.573	14.680											
PC12	100.000	18.560	18.560	148.226	16.239	24.070											
PC13	74.325	18.290	13.600	61.119	9.286	5.680											
PC14	98.132	8.480	8.320	87.677	10.006	8.770											
PC15	93.817	9.620	9.020	102.223	9.745	9.960											
PC16	96.922	8.560	8.300	87.993	9.064	7.980											
PC17	96.648	9.910	9.580	86.891	9.938	8.630											

¹¹⁵ EX1003, ¶ 73; EX1001, 176:25-34.

¹¹⁶ EX1003, ¶ 69.

¹¹⁷ EX1003, ¶ 69.

¹¹⁸ EX1003, ¶ 71, Appendix A-7, A-8; EX1001, 297 (Table 12).



	Duplicate #1			Duplicate #2		
	% Activity at 37°C/4°C	% Activity at 37°C + m-cresol	% Activity at 37°C + mcr/4°C	% Activity at 37°C/4°C	% Activity at 37°C+m-cresol	% 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

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

¹¹⁹ EX1003, ¶¶ 70-72; see also EX1001, 297:44-53 (positive control also varied).

Importantly, the common disclosure does not identify any—let alone **which**—combinations of substitutions in a multiply-modified PH20 improve stability.¹²⁰ The common disclosure thus does not describe or provide meaningful guidance concerning which of the claimed 10⁶⁰⁺ multiply-modified PH20 polypeptides may have increased stability.

(d) The Common Disclosure's Research Plan Does Not Identify Any Multiply-Mutated Enzymatically Active PH20 Polypeptides

The common disclosure does not describe any multiply-modified PH20 polypeptides that are “active mutants.”¹²¹ Instead, it simply presents **the idea** of making such multiply-modified PH20 polypeptides.

First, it observes that “[a] modified PH20 polypeptide **can have** up to 150 amino acid replacements,” “[t]ypically” contains between 1 and 50 amino acid replacements and “can include any one or more other modifications, in addition to at least one amino acid replacement as described herein.”¹²² 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:

¹²⁰ EX1003, ¶¶ 69, 76.

¹²¹ EX1003, ¶¶ 151-52.

¹²² EX1001, 47:1-11.

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).”¹²³

None of these statements *identify* any actual multiply-modified PH20 polypeptides (*i.e.*, PH20 polypeptides with specific sets of 2 or more amino acid substitutions). They simply draw boundaries around immense numbers of PH20 polypeptides that may or may not be enzymatically active.

The common disclosure also describes no multiply-modified, active PH20 polypeptides that were made and tested. Instead, it provides only a prophetic research plan requiring “iterative” make-and-test experiments that *might discover* such PH20 polypeptides, stating they “*can be* modified or further modified” and “*can be* identified.”¹²⁴ This research plan does not identify *which* multiply-modified PH20 polypeptides can be made or *are* active mutants.¹²⁵

¹²³ EX1001, 98:31-45 (emphasis added).

¹²⁴ EX1001, 140:35-47 (emphases added); *see also id.* at 41:3-10, 133:51-56; EX1003, ¶¶ 183-87.

¹²⁵ EX1003, ¶¶ 183, 194-95, 198; EX1001, 42:24-26; *see generally id.*, 133:5-50, 133:59-135:34, 135:61-140:34.

Alternatively, it proposes mutations that *can be* “targeted near” “critical residues” which supposedly “*can be* identified because, when mutated, a normal activity of the protein is ablated or reduced.”¹²⁶ But Tables 5 and 10 report at least one substitution at each of 405 positions between positions 1 and 444 of PH20₁₋₄₄₇ resulted in an inactive mutant.¹²⁷ This guidance to target locations “near” ~90% of the amino acids in PH20₁₋₄₄₇ is no different than targeting *every residue*.¹²⁸

These prophetic research plans, based entirely on unfocused, iterative “make-and-test” experiments, do not identify to a skilled artisan which of the 10⁶⁰⁺ multiply-modified PH20 polypeptides within the claims’ scope *are* enzymatically active.¹²⁹ Instead, they require a skilled artisan to perform repeated cycles of mutagenesis, screening and selecting until 10⁶⁰⁺ modified PH20 polypeptides are made and screened.¹³⁰ That in no way demonstrates possession of all active mutants within each claim’s scope.

¹²⁶ EX1001, 140:48-141:6; EX1003, ¶¶ 188-89.

¹²⁷ EX1003, ¶ 190, Appendix A-3.

¹²⁸ EX1003, ¶ 190.

¹²⁹ EX1003, ¶ 201.

¹³⁰ EX1003, ¶¶ 185-87, 198-99; EX1001, 135:42-47, 135:35-59, 138:53-57, 139:1-6, 139:23-37.

The specification also incorrectly equates hyaluronidase activity with “stability.”¹³¹ As Dr. Hecht explains, to assess a protein’s stability requires experiments that measure the energy associated with the protein’s transition between its folded and unfolded states.¹³² Activity can be influenced by stability but is not itself a measure of stability.¹³³

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

The common disclosure does not identify the structural features or significance of any of the ~2,500 mutations that yielded single residue “active mutant” PH20₁₋₄₄₇ polypeptides (or the ~3,400 inactive mutants or ~830 uncharacterized mutants). For example, it does not identify the effect of any replacement on any domain structure, any structural motif(s) or even the local secondary structure at the site of the substitution in the PH20 polypeptide, nor does it identify how any such (possible) structural change(s) is/are responsible for the

¹³¹ EX1003, ¶¶ 67, 69, 189.

¹³² EX1003, ¶¶ 63-66.

¹³³ EX1003, ¶ 67.

measured change in hyaluronidase activity.¹³⁴ Instead, it simply lists single replacements to random amino acids that yielded “active mutants.”¹³⁵

The common disclosure also does not identify any *sets* of specific amino acid replacements that correlate to changes in structural domains or motifs that positively or negatively influence hyaluronidase activity, much less *predictably* increase activity to defined thresholds.¹³⁶

The common disclosure’s empirically identified examples of “active mutant” single-replacement PH20₁₋₄₄₇ mutants do not *by themselves* identify any “structure-function” relationship between “active mutants” and the set of single-replacement modified PH20₁₋₄₄₇ polypeptides.¹³⁷ Nor do they do so for the unknown number of multiply-modified active mutant PH20 polypeptides of varying lengths with between 2 and 42 substitutions.¹³⁸

The common disclosure *does not even contend* that a particular amino acid replacement at a particular position (*e.g.*, 313) that makes PH20₁₋₄₄₇ an “active

¹³⁴ EX1003, ¶¶ 146-47, 156.

¹³⁵ EX1001, 232:28-56; EX1003, ¶¶ 146-47.

¹³⁶ EX1003, ¶¶ 55, 149-150.

¹³⁷ EX1003, ¶¶ 61, 150, 162, 164.

¹³⁸ EX1003, ¶ 162.

mutant” will make any other modified PH20 polypeptide with that replacement plus 1-41 additional substitutions an “active mutant.”¹³⁹ 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.¹⁴⁰ Thus, even the inventors did not view their compilation of empirical test results as identifying a structure-function relationship for $10^{60}+$ multiply-modified “active mutants.”

The common disclosure, thus, does not identify to a skilled artisan *any structural features* shared by all “active mutant” modified PH20 polypeptides within the scope of the claims.

(f) The Common Disclosure Does Not Describe a Representative Number of Multiply-Modified Enzymatically Active PH20 Polypeptides

The ~2,500 active mutant single-replacement PH20₁₋₄₄₇ polypeptides in the disclosure are not representative of the sub-genus of “active mutant” PH20 polypeptides encompassed by the claims.¹⁴¹

¹³⁹ EX1003, ¶¶ 172, 202-04.

¹⁴⁰ EX1003, ¶¶ 56-57.

¹⁴¹ EX1003, ¶¶ 61, 150, 160, 164.

Single-replacement PH20₁₋₄₄₇ examples are not representative of the 10⁶⁰⁺ PH20₁₋₄₄₇ polypeptides having **2 to 42 additional substitutions** to any of 19 other amino acids at any of hundreds of positions within the protein.¹⁴² The latter group includes a massive number of structurally distinct proteins (*e.g.*, distinct sequences, secondary structures, structural motifs, etc.) that form when PH20 sequences with multiple amino acid substitutions successfully fold.¹⁴³ None of them are described in the common disclosure.

Multiple substitutions made to a protein can cause different interactions between neighboring residues relative to those caused by single substitutions.¹⁴⁴ For example, a first amino acid substitution can 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).¹⁴⁵ A second substitution in that region may reverse those interactions (or not), and a third substitution may do the

¹⁴² See § IV.D.1; EX1003, ¶¶ 61, 150, 164.

¹⁴³ EX1003, ¶¶ 58-63.

¹⁴⁴ EX1003, ¶¶ 55-56, 58, 60, 163, 166.

¹⁴⁵ EX1003, ¶¶ 56-58.

same, and so on up to 21 rounds permitted by the narrowest claims, each potentially causing different interactions.¹⁴⁶

The common disclosure, however, does not identify effects of any single substitution on the various domains, secondary structures and structural motifs within any PH20 polypeptides within the scope of the claims.¹⁴⁷ And the activity of a protein with multiple substitutions is rarely dictated by only one of the substitutions—it is dictated by the unique structure that reflects *the totality* of effects of those substitutions.¹⁴⁸ The common disclosure provides no information on structural effects of multiple substitutions.

The single-replacement active mutant PH20 polypeptides in the disclosure thus are not representative of the unidentified number of undisclosed enzymatically active multiply-substituted PH20 mutants within the claims' scope, which comprise myriad combinations of substitutions that each can uniquely impact the structures and properties of the mutated protein.¹⁴⁹

¹⁴⁶ EX1003, ¶¶ 58-60, 149.

¹⁴⁷ EX1003, ¶¶ 162-63, 240.

¹⁴⁸ EX1003, ¶¶ 61, 148.

¹⁴⁹ EX1003, ¶¶ 150, 163-64.

Enzymatically active single-replacement PH20₁₋₄₄₇ polypeptides also are not representative of multiply modified PH20 polypeptides that incorporate changes that render wild-type PH20 inactive (*e.g.*, truncations terminating below position 429, or single substitutions that rendered PH20₁₋₄₄₇ inactive).¹⁵⁰ Such single-replacement active mutants do not contain the additional and distinct structural features that rendered the latter PH20 polypeptides enzymatically *inactive*. For example, the M313K PH20₁₋₄₄₇ polypeptide would not be considered representative of a PH20 terminating at position 419 with that M313K substitution, as the former omits the structural feature (the C-terminal truncation) that rendered the latter inactive.¹⁵¹ The common disclosure does not teach—and a skilled artisan could not have predicted from its examples of single-replacement PH20₁₋₄₄₇ mutants—which single substitutions would restore enzymatic activity to a truncated PH20 mutant that was inactive, much less identify all of the precise combinations that do.¹⁵²

The common disclosure thus provides a very narrow set of working examples relative to the diversity of active modified PH20 polypeptides being

¹⁵⁰ EX1003, ¶¶ 166-68.

¹⁵¹ EX1003, ¶¶ 170-73.

¹⁵² EX1003, ¶ 172.

claimed.¹⁵³ The examples are restricted to *one type of change* (a single amino acid replacement) in *one type of PH20 polypeptide* (SEQ ID NO: 3).¹⁵⁴ By contrast, the claims encompass changes in up to 37 different unmodified PH20 sequences, and include, in addition to a replacement at position 313, between 20 and 41 additional changes.¹⁵⁵ The simple figure below illustrates how *non-representative* the single-replacement PH20₁₋₄₄₇ mutants are for claim 2.

	Number of Changes																						
SEQ	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
3	■																						
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																							

Consequently, a skilled artisan would not have viewed the examples of single amino acid replacements in PH20₁₋₄₄₇ in the common disclosure to be

¹⁵³ EX1003, ¶ 160.

¹⁵⁴ EX1003, ¶¶ 100, 102, 106, 111-12.

¹⁵⁵ EX1003, ¶¶ 125-129.

representative of the diversity of “active mutant” modified PH20 polypeptides encompassed by the claims.¹⁵⁶

2. Dependent Claims 3-4, 6, 17-22, and 26-40 Lack Written Description

(a) Claims 3, 6, 27, 28

Claims 3, 6, 27, and 28 require modified PH20 polypeptides within the genus defined by claim 1 that exhibit (i) increased stability (claim 3) or (ii) increased hyaluronidase activity (claims 6, 27, 28) relative to unmodified PH20₁₋₄₄₇.

The reasons provided in § V.A.1 explaining why the claims generally lack written description apply fully to these claims.

In addition, the recitation in claims 3, 6, 27, and 28 of a *desired* level of stability or hyaluronidase activity does not identify *which* of the 10⁶⁰⁺ PH20 polypeptides with 91% or 95% sequence identity to SEQ ID NOS: 3, 7, or 32-66 and any replacement at position 313 will exhibit those functional properties.¹⁵⁷

First, the singly-substituted position 313 PH20₁₋₄₄₇ polypeptides in the common disclosure that exhibited increased activity are not representative of each claim’s genus, which includes PH20 polypeptides with up to 22 or 41 additional

¹⁵⁶ EX1003, ¶ 150.

¹⁵⁷ EX1003, ¶¶ 195, 202-04.

substitutions and/or truncations.¹⁵⁸ While some single substitution position 313 PH20₁₋₄₄₇ mutants were active and one was inactive, none were in multiply-modified PH20 polypeptides.¹⁵⁹

Second, the common disclosure identifies no common structural feature shared by multiply-modified PH20 polypeptides (if any) exhibiting increased activity or stability.¹⁶⁰ The presence of a single position 313 substitution does not demonstrate possession of all multiply-modified PH20 polypeptides with that substitution and exhibit increased activity or stability, and the common disclosure does not contend otherwise.¹⁶¹

Claims 3, 6, 27, and 28 lack written description in the common disclosure.

(b) Claim 4

Claim 4 requires the modified PH20 polypeptide to be “soluble.”

Claim 4 lacks written description support for the same reasons as claim 1.

In addition, claim 4 lacks written description because it encompasses modified PH20 polypeptides the common disclosure suggests will be insoluble. It

¹⁵⁸ EX1001, 256 (Table 9); EX1003, ¶¶ 164, 202-04.

¹⁵⁹ EX1003, ¶ 71; *see* § V.A.1.c.ii.

¹⁶⁰ EX1003, ¶¶ 162, 195, 201.

¹⁶¹ EX1003, ¶¶ 151, 172, 195.

explains that “a soluble PH20 lacks all or a portion of a glycosylphosphatidylinositol (GPI) attachment sequence,” which was known to be hydrophobic,¹⁶² and identifies position 456 as the first residue of the GPI sequence in PH20 (position 491 in SEQ ID NO: 6).¹⁶³ It also states that a soluble PH20 “is a polypeptide that is truncated after amino acid 482 of ... SEQ ID NO: 6” (*i.e.*, 447 in SEQ ID NO:3).¹⁶⁴ The common disclosure thus suggests that human PH20 sequences that terminate below position 448 are soluble while those terminating above position 456 are insoluble.¹⁶⁵

Claim 4 encompasses PH20 polypeptides based on SEQ ID NOS:59-66, which terminate between positions at 457 to 464 respectively (*i.e.*, beyond position 456). It also requires a replacement at position 313. Consequently, claim 4 captures modified PH20 polypeptides that are C-terminally truncated but, per the

¹⁶² EX1001, 44:52-54, 70:22-23, 46-58, 72:40-52; EX1005, 86:18-22; EX1003, ¶¶ 92-94.

¹⁶³ EX1001, 70:46-58.

¹⁶⁴ EX1001, 73:30-32; EX1005, 3:57-62.

¹⁶⁵ EX1003, ¶¶ 92-93.

common disclosure, **are not** “soluble modified PH20 polypeptide[s]” because each contains “all or a portion of” the GPI attachment sequence.¹⁶⁶

Patentee may contend that some unidentified number of modified PH20 polypeptides based on SEQ ID NOS: 59-66 **may** be soluble, citing the common disclosure as suggesting that between 1-10 residues within the GPI anchor “can be retained, provided the polypeptide is soluble.”¹⁶⁷ But the common disclosure does not identify **which** modified PH20 polypeptides terminating above position 448 (particularly between 457 and 464) **are** soluble, provides no examples of such soluble PH20 mutants, and provides no reason to expect that many modified PH20 polypeptides within the claim’s scope are soluble.

Claim 4 is unpatentable for this independent reason.

(c) Claims 17-22, 26-36

Dependent claims 17-22 and 26-36 concern additional characteristics (claims 17-22, 26-27), pharmaceutical compositions (28-33), or methods of

¹⁶⁶ EX1001, 45:12-18.

¹⁶⁷ EX1001, 72:33-39.

treatment (34-36) that reference the genus of claim 1. They lack written description for the same reasons explained in § V.A.1.¹⁶⁸

(a) *Claims 37-40*

Claims 37-40 concern methods for “increasing delivery of a therapeutic agent to a subject” (*e.g.*, an antibody (claim 40)) by administering any of the PH20 polypeptides within claim 1’s scope with the other agent (together or separately in sequence) (claims 37, 39), or subcutaneously (claim 38).

The common disclosure attributes PH20’s “increasing delivery” capability to its ability to cause “spreading” or “diffusion,” and indicates the PH20 must *at least* have hyaluronidase activity.¹⁶⁹ It also describes testing modified PH20 polypeptides in a live mouse assay to determine if they increase delivery (even if they have hyaluronidase activity).¹⁷⁰ But the common disclosure does not identify which of the claimed 10⁶⁰⁺ PH20 polypeptides possess (i) hyaluronidase activity

¹⁶⁸ *Idenix*, 941 F.3d at 1155, 1165; *Boehringer*, PGR2020-00076, Paper 42, at 40-41.

¹⁶⁹ EX1001, 179:45-54, 180:49-61, 71:36-61; EX1003, ¶¶ 174-75; EX1080 (Bookbinder), 230-231.

¹⁷⁰ EX1001, 177:63-178:16; EX1003, ¶ 178.

and (ii) cause “spreading”/“diffusion” activity per its mouse assay.¹⁷¹ Indeed, it tested only *one* (F204P PH20₁₋₄₄₇) that falls *outside* the claims.¹⁷²

The modified PH20 polypeptides within claim 1’s genus also include those with multiple substitutions in the Hyal-EGF region of PH20 (positions 337-409).¹⁷³ By 2011, it was believed the Hyal-EGF domain mediated protein-protein interactions, and mutations to it substantially eliminated hyaluronidase activity in otherwise unaltered PH20 polypeptides.¹⁷⁴ A skilled artisan would have thus believed that making multiple substitutions to the Hyal-EGF domain could alter its structure and disrupt not only PH20’s hyaluronidase activity but any protein-protein interactions that might be involved in PH20’s spreading activity *in vivo*.¹⁷⁵

Claims 37-40 thus lack written description because the common disclosure does not identify which of the 10⁶⁰⁺ modified PH20 polypeptides within claim 1’s

¹⁷¹ EX1003, ¶ 174.

¹⁷² EX1001, 312:47-315:17.

¹⁷³ EX1004, ¶ 98; EX1006, 6912.

¹⁷⁴ EX1003, ¶¶ 85, 86, 89, 90, 98; EX1006, 6912, 6913, 6916-17; EX1010, 9439; EX1005, 87:52-88:24; EX1079, 84.

¹⁷⁵ EX1003, ¶¶ 98-100, 174, 178.

genus can be used in methods of increasing delivery of another therapeutic agent.¹⁷⁶

3. Certain Claims Lack Written Description Under the Logic of *Gentry Gallery*

The common disclosure 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). *See* § V.A.1(b). Claims 3, 5-7, 10, 13-15, 23-25, 27-28, and 30-40 require enzymatically active PH20 polypeptides or their use, yet do not limit their scope to omit PH20 polypeptides with such mutations. *See* § IV.D.3. These claims 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.

B. All Challenged Claims Are Not Enabled

All claims are also unpatentable for lack of enablement.

“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

¹⁷⁶ EX1003, ¶ 179.

one must enable.”¹⁷⁷ “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.”¹⁷⁸ “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.”¹⁷⁹

Although not required, enablement may be assessed using the *Wands* factors, which consider: “(1) the quantity of experimentation necessary; (2) how routine any necessary experimentation is in the relevant field; (3) whether the patent discloses specific working examples of the claimed invention; (4) the amount of guidance presented in the patent; (5) the nature and predictability of the field; (6) the level of ordinary skill; and (7) the scope of the claimed invention.”¹⁸⁰

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

¹⁷⁷ *Amgen*, 598 U.S. at 610 (emphases added).

¹⁷⁸ *Idenix*, 941 F.3d at 1159.

¹⁷⁹ *Wyeth & Cordis Corp. v. Abbott. Labs*, 720 F.3d 1380, 1383-84 (Fed. Cir. 2013).

¹⁸⁰ *Idenix*, 941 F.3d at 1156 (citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)).

and error to narrow down the potential candidates to those satisfying the claims’ functional limitations—the asserted claims are not enabled.”¹⁸¹

“It is well established that the enablement requirement of § 112 incorporates the utility requirement of § 101.”¹⁸² A claimed invention must be *presently useful*—stating a hypothesis and proposing testing to determine its accuracy is insufficient.¹⁸³ Further, if a claim encompasses significant numbers of inoperative embodiments, and a skilled artisan must engage in undue experimentation to identify the operative ones, that renders the claims non-enabled.¹⁸⁴

Here, the common disclosure utterly fails to enable the immense genus of modified PH20 polypeptides claimed. Using the disclosure and knowledge in the prior art, the skilled artisan would have to perform undue experimentation to

¹⁸¹ *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).

¹⁸² *In re Fisher*, 421 F.3d 1365, 1379 (Fed. Cir. 2005).

¹⁸³ *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).

¹⁸⁴ *Crown Operations Intern. Ltd v. Solutia Inc.*, 389 F.3d 1367, 1380, FN8 (Fed. Cir. 2002); *Atlas Powder Co. v. E.I.Dupont De Nemours*, 750 F.2d 1569, 1577 (Fed. Cir. 1984).

identify which of the 10^{60} + PH20 polypeptides having multiple amino acid replacements and/or truncations within the scope of the claims that are useful because they are “active mutants,” those “inactive mutants” that the disclosure contends are useful as a contraceptive antigen, and those which have no utility.¹⁸⁵

1. Claims 1-2, 5, 7-16, and 22-25 Are Not Enabled

This case is a textbook example of claims that are not enabled under the reasoning articulated by the Supreme Court in *Amgen*. An analysis of the common disclosure under 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.

(a) *Extreme Scope of the Claims*

As explained in § IV.D.1, claims 1-2, 5, 7-16, and 22-25 capture between 10^{60} and 10^{113} modified PH20 polypeptides that have (i) any or particular substitution(s) at position 313, and (ii) 1 to 41 additional substitutions anywhere in a PH20 polypeptide sequence ranging from 430 to 474 residues. Within these immense sets of PH20 polypeptides is a subgenus having an unknown and undisclosed number of “active mutant” PH20 polypeptides.

¹⁸⁵ EX1003, ¶¶ 180-82, 201.

Practicing the full scope of just this “active mutant” subgenus within the claims requires navigating substantial scientific questions left unanswered by the common disclosure. Other than by making and testing $\sim 10^{60}$ to 10^{113} multiply-modified PH20 polypeptides the various claims encompass, the common disclosure does not explain how to determine *which* combinations of substitutions (in addition to position 313) will yield active mutants.

The common disclosure would have led a skilled artisan to believe there were many types of PH20 mutants that would *not* be enzymatically active, but which are nonetheless captured by the claim language, including those that:

- (i) have substitutions the disclosure instructs to not include in an enzymatically active modified PH20 polypeptide because they rendered PH20₁₋₄₄₇ an inactive mutant;¹⁸⁶
- (ii) terminate before position 429, which the disclosure reports will eliminate activity in unmodified PH20 proteins;¹⁸⁷ and
- (iii) include substitutions at positions that the common disclosure instructs “are less tolerant to change or required for hyaluronidase activity.”¹⁸⁸

¹⁸⁶ EX1001, 78:27-29.

¹⁸⁷ EX1001, 68:13-22; EX1003, ¶¶ 96, 157-59, 168-70.

¹⁸⁸ EX1001, 75:59-76:4.

Whether there are any (or how many) such “active mutant” PH20 polypeptides within the scope of the claims is unknown, but the common disclosure identifies none.¹⁸⁹

The common disclosure also does not provide any guidance that a skilled artisan could use to identify which of the 10^{60} - 10^{113} modified PH20 polypeptides with a position 313 substitution and 1-41 additional substitutions *are* inactive and useful as a contraceptive antigen, or, alternatively, cannot be produced and thus have no utility at all.

In short, the claims capture a massive number of multiply-modified PH20 polypeptides that have *unknowable* properties absent the skilled artisan producing and testing 10^{60} and 10^{113} distinct mutants pursuant to the common disclosure’s prophetic “make and test” methodology.¹⁹⁰

Claims that capture a massive and 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,¹⁹¹ while in *Idenix*, the court found that a skilled artisan would “understand that ‘billions and billions’ of

¹⁸⁹ EX1003, ¶ 171.

¹⁹⁰ EX1003, ¶¶ 161-63, 173.

¹⁹¹ 598 U.S. at 603.

compounds literally meet the structural limitations of the claim.”¹⁹² In both cases (as here), the enormous claim scope was contrasted to limited working examples in the patent, the field of technology was unpredictable, and an immense quantity of experimentation was required to practice the claims’ full scope (*Wands* Factors 1, 3, 4, and 7). Importantly, as the *Idenix* court observed, it is improper to rely on the knowledge and efforts of a skilled artisan to try to “fill the gaps in the specification” regarding which of the “many, many thousands” of possible compounds should be selected for screening, which in this case is impossible.¹⁹³

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

The common disclosure provides an extremely narrow set of working examples: ~5,917 randomly generated single-replacement PH20₁₋₄₄₇ polypeptides, of which ~2,500 were “active mutants,” ~3,380 were “inactive mutants” and ~830 mutants characterized only by their desired sequence—neither “active” nor “inactive” mutants.¹⁹⁴ Combined, these examples are a tiny fraction of the 10⁶⁰ to 10¹¹³ modified PH20 polypeptides covered by the claims. They provide no guidance that would help a skilled artisan bypass the common disclosure’s “trial-

¹⁹² 941 F.3d at 1157.

¹⁹³ *Id.* at 1159.

¹⁹⁴ EX1003, ¶¶ 111-12.

and-error” methodology for making multiply-modified PH20 polypeptides: none incorporate more than one substitution and none truncate PH20 before position 447.¹⁹⁵

The common disclosure provides no credible guidance on practicing the full scope of the claims.¹⁹⁶ Instead, it describes a prophetic, “iterative” “make and test” process for *discovering* active mutant PH20 polypeptides. *See* § V.A.1.d. And its research plan requires a skilled artisan to engage in undue experimentation.

First, the common disclosure describes a process requiring manually performing iterative rounds of *randomized* mutations (up to 41 rounds per starting molecule under the broadest claims) to *discover* which of the 10⁶⁰+ possible modified PH20 polypeptides the claims encompass might possess hyaluronidase activity.¹⁹⁷

¹⁹⁵ EX1003, ¶¶ 160-64, 171.

¹⁹⁶ EX1003, ¶¶ 141, 147.

¹⁹⁷ EX1003, ¶¶ 189-191; *see also* EX1018, 382 (“combinatorial randomization of only five residues generates a library of 205 possibilities (3.2 x 10⁶ mutants), too large a number for manual screening”). Chica credited a “ground-breaking” predictive molecular modeling technique that was later shown to be

Second, the common disclosure provides no meaningful guidance or information that a skilled artisan could use to implement the prophetic procedure it discloses for making and discovering “active mutant” modified PH20 polypeptides:

- (i) it does not identify *any* specific combination of two or more replacements within any PH20 polypeptide that yield “active mutants”;
- (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.¹⁹⁸

false. EX1018, 384, 382; EX1030, 569; EX1034, 258; EX1036, 275, 277; EX1048, 859.

¹⁹⁸ EX1001, 140:49-61; EX1003, ¶¶ 151, 163, 182, 194-95.

Instead, the common disclosure requires the skilled artisan to iteratively repeat its prophetic research plan to make and test $10^{60}+$ multiply-modified PH20 polypeptides to discover which are enzymatically active.¹⁹⁹

Regardless whether individual rounds of “iterative” production and testing of PH20 mutants might be considered “routine,” the aggregate scale of experimentation required to practice the full scope of the claims goes far beyond undue—it is impossible. Simply put, the common disclosure’s prophetic, iterative and labor-intensive process requires making and screening an immense number of modified PH20 polypeptides, before which the skilled artisan will not know which multiply-modified PH20 polypeptides are within the claims’ scope.²⁰⁰ The “*iterative, trial-and-error process[es]*” the common disclosure specifies here are thus indistinguishable from those consistently found to not enable broad genus claims to modified proteins or other useful compounds.²⁰¹

¹⁹⁹ EX1003, ¶¶ 182, 194-95.

²⁰⁰ EX1003, ¶¶ 182, 194-95, 200.

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 changes to its amino acid sequence.²⁰² Introducing changes can alter the local structure of the protein where the change is made, which may disrupt secondary structures or structural motifs within the protein that are important to its biological activity (*e.g.*, catalysis, ligand binding, etc.) and/or stability.²⁰³

As explained in § VI below, by 2011, skilled artisans could have assessed whether certain *single* amino acid substitutions at certain positions would be tolerated within the PH20 protein structure with a reasonable (though not absolute) expectation of success.²⁰⁴ By contrast, skilled artisans around this time period could *not* have predicted the effects of making more than a few concurrent amino acid replacements within a PH20 polypeptide.²⁰⁵

More generally, introducing *multiple* concurrent changes into a particular region of a protein greatly increases the likelihood of disrupting secondary structures and structural motifs essential to the protein's activity and/or stability,

²⁰² EX1003, ¶ 61.

²⁰³ EX1003, ¶¶ 61, 202-03.

²⁰⁴ EX1003, ¶ 205.

²⁰⁵ EX1003, ¶¶ 163, 240.

and can even introduce new ones into the protein.²⁰⁶ Replacing multiple amino acids thus can introduce an immense number of simultaneous influences on a protein's structure that cannot be predicted.²⁰⁷

The cumulative effects of multiple changes would also have rapidly exceeded the capacity of computer-based, rational design techniques to reliably predict the effects of each change on the protein's structure.²⁰⁸ For example, the greater the differences between the modeled amino acid sequence and structure and the naturally occurring sequence and/or the original model's structure became, the less reliable the model became at predicting effects.²⁰⁹ Depending on the structural template used to produce the model, regions of the protein not supported by a corresponding structure could not be reliably used to assess particular changes.²¹⁰ And the time required to carry out rational design techniques to "practice" the full scope of the claimed genus would be unimaginable.²¹¹

²⁰⁶ EX1003, ¶¶ 59-60, 195, 202.

²⁰⁷ EX1003, ¶¶ 55, 58, 61.

²⁰⁸ EX1003, ¶ 163.

²⁰⁹ EX1003, ¶¶ 163, 201, 240; EX1004, ¶¶ 167-168.

²¹⁰ EX1003, ¶¶ 163, 240; EX1004, ¶¶ 157-159; EX1012, 4, 8.

²¹¹ EX1003, ¶¶ 51, 201; EX1059, 1225-26; EX1018, 378.

Consequently, a skilled artisan could not have used conventional rational design techniques to identify multiply-modified PH20 polypeptide sequences having more than a few substitutions, and certainly not 20 or 42 substitutions.²¹² Moreover, 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.²¹³

(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 skilled artisan was highly skilled, the field of protein engineering was unpredictable and tools did not exist that permitted accurate modeling of the range of multiply-changed PH20 polypeptides being claimed.²¹⁴ Likewise, while there was significant public knowledge about hyaluronidases, there was no solved structure of the PH20 protein. Also, the public literature generally reported on *loss of activity* from mutations in hyaluronidases, and did not

²¹² EX1003, ¶¶ 50, 199.

²¹³ EX1003, ¶¶ 163, 201.

²¹⁴ EX1003, ¶¶ 163, 240.

predictably teach how to introduce changes that preserved or *enhanced* stability or activity of such proteins.²¹⁵

Practicing the full scope of claims 1-2, 5, 7-16, and 22-25 thus would have required a skilled artisan to engage in undue experimentation.

2. Dependent Claims 3-4, 6, 17-22, and 26-40 Are Not Enabled

(a) Claims 3, 6, 27, 28

Claims 3, 6, 27, and 28 require the modified PH20 polypeptides to have increased activity (*i.e.*, >100% of unmodified PH20) or increased resistance to or stability in denaturing conditions.

These claims are not enabled for the same reasons that claims 1-2, 5, 7-16, and 22-25 are not enabled (*see* § V.B.1). Specifically, a skilled artisan could not have predicted which of the $10^{60}+$ PH20 polypeptides having up to 41 changes beyond a required change at position 313 would exhibit increased activity or stability relative to unmodified PH20.²¹⁶ Instead, a skilled artisan would need to make-and-test each molecule in order to practice the “full scope” of the claims.²¹⁷

²¹⁵ EX1011, 812-814; EX1010, 9437-9439.

²¹⁶ EX1003, ¶¶ 195, 201.

²¹⁷ *Id.*

(b) *Claim 4*

Claim 4 requires “soluble” forms of PH20. Because claim 4 encompasses a substantial portion of the genus of claim 1, it is not enabled for the same reasons.

Additionally, as explained in § V.A.2.b, the common disclosure suggests that PH20 polypeptides extending past position 456 are “insoluble.” A skilled artisan would have expected the presence of the hydrophobic GPI sequence in a PH20 protein to cause aggregation, loss of activity, and/or reduced expression.²¹⁸ The common disclosure recognizes these problems, but provides no examples of modified PH20 polypeptides extending past position 456 that are soluble, much less a broader solution. Instead, each has to be made and tested.

(c) *Claims 17-22, 26-36*

Claims 17-22 and 26-36 recite either further modifications (*e.g.*, glycosylation, conjugation) to the modified polypeptides (claims 17-22, 26-27), pharmaceutical compositions (28-33), or methods of treatment (34-36) within the genus of claims 1 or 6. These claims are not enabled for the same reasons as claims 1 and 6.²¹⁹

²¹⁸ EX1003, ¶¶ 92-93, 207, 234.

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

(a) *Claims 37-40*

Claims 37-40 encompass methods of increasing delivery of a therapeutic agent using any of the modified PH20 polypeptides within claim 1's genus.

The common disclosure indicates that a modified PH20 must possess hyaluronidase activity to be capable of increasing delivery of a therapeutic agent.²²⁰ Because the common specification does not enable claim 1's genus of "active mutant" modified PH20 polypeptides (*see* § V.B.1), it cannot enable methods dependent on using "active mutant" modified PH20 polypeptides within claim 1's genus.

Claims 37-40 are not enabled for another reason. The common disclosure attributes the PH20's "increased delivery" capability to its ability to cause "spreading" / "diffusion."²²¹ The common disclosure then explains that one can determine if any modified PH20 polypeptide can cause "spreading" by testing it in an *in vivo* assay: "[t]he ability of a PH20 polypeptide ... to act as a spreading or diffusing agent can be assessed" using a specified *in vivo* experiment using a mouse.²²² Notably, this is a different test than the *in vitro* assay used to detect

²²⁰ EX1001, 179:45-54, 180:49-61, 71:36-61.

²²¹ See § V.A.2.d; EX1001, 179:45-54, 180:49-61, 71:36-61.

²²² EX1001, 177:63-178:16, 302:40-303:8; EX1003, ¶¶ 175-76, 178.

hyaluronidase activity.²²³ And, the common disclosure identifies only one mutant with this “spreading” capability determined using its mouse test.²²⁴

In other words, to determine which of the 10^{60+} modified PH20 polypeptides within claim 1’s genus can be used in the claimed method of increasing delivery of another agent of claims 37-40, a skilled artisan must make and test each of the mutants in a mouse experiment.²²⁵ Practicing the full scope of claims 37-40, thus, would require a skilled artisan to engage in an impossible amount of “make and test” experiments, rendering each of those claims not enabled.

C. Inactive PH20 Polypeptides Are Not Useful and Do Not Remedy the § 112(a) Deficiencies of the Claims

Patentee may contend certain claims do not require the modified PH20 polypeptides to be “active mutants,” but that would only compound the written description and enablement problems of those claims.

First, all claims *encompass* all enzymatically active PH20 polypeptides meeting the parameters of the claims. *See* § V.B.2.a. Claims 6, 27, and 28, for example, require “active mutants” or their use within a portion of this sub-genus in claim 1’s scope (*i.e.*, those with >100% hyaluronidase activity). The failure of the

²²³ EX1001, 194:24-39, 229:49-231:67; EX1003, ¶ 193.

²²⁴ EX1001, 312:47-315:17.

²²⁵ EX1003, ¶ 196.

common disclosure to describe or enable the full scope of this subgenus of “active mutants” within each claim’s scope renders each claim unpatentable. *See* §§ V.A and V.B.²²⁶

Second, the common disclosure reports one position 313 “inactive” mutant (M313C), that 14 were “active mutants,” and nothing about 5 other position 313 substitutions.²²⁷ There also is no guidance in the common disclosure about how to *intentionally* produce inactive multiply-mutated PH20 polypeptides, much less those with a position 313 substitution. Instead, it describes processes that select mutants in successive mutagenesis rounds because they exhibited *activity*.²²⁸ Disclosure of one position 313 inactive mutant does not demonstrate possession of 10⁶⁰⁺ others.

The common disclosure also identifies no correlation between the 10⁶⁰⁺ multiply-modified PH20 polypeptides within the claims’ scope and either of the

²²⁶ *ABS Glob., Inc. v. Inguran*, 914 F.3d 1054, 1070, 1074 (7th Cir. 2019) (citing *Alcon Research, Ltd. v. Apotex, Inc.*, 687 F.3d 1362, 1367-68 (Fed. Cir. 2012)).

²²⁷ EX1001, 217-219 (Table 8), 256 (Table 9).

²²⁸ EX1003, ¶¶ 184, 186, 193; EX1001, 133:51-56, 138:53-57.

mutually exclusive sub-genera of active and inactive mutants.²²⁹ To determine which are one or the other (or neither), the skilled artisan must perform trial-and-error testing of those 10^{60+} modified PH20 polypeptides.²³⁰ Claims read to encompass all inactive mutant M313-substituted PH20 polypeptides thus lack written description in, and are not enabled by, the common disclosure.

Finally, the only putative utility identified for “inactive mutants” is as “antigens in contraception vaccines,”²³¹ which is not scientifically credible. The disclosure cites two studies involving guinea pig PH20,²³² but ignores other evidence—subsequent peer reviewed journal articles published before 2011—that demonstrated that immunizing *other mammals* with their species’ PH20 did *not* cause contraception.²³³ And Halozyme’s own published clinical studies of

²²⁹ EX1003, ¶ 151.

²³⁰ EX1003, ¶ 195-96.

²³¹ EX1001, 74:3-5, 193:7-26.

²³² EX1001, 193:7-26; EX1022, 1142-43; EX1023, 1133-34.

²³³ See EX1019, 325, 331-33 (“recombinant mPH20 is not a useful antigen for inclusion in immunocontraceptive vaccines that target mice”); EX1020, 179-81 (“immunization [of rabbits] with reproductive antigens ... are unlikely to

unmodified human PH20₁₋₄₄₇ (what the claims concern) showed that “[a]lthough some antisperm antibodies are associated with decreased fertility [], no evidence of negative effects on fertility could be determined in rHuPH20-reactive antibody-positive subjects of either sex.”²³⁴

Settled law holds that a claimed invention “must have ‘substantial utility’ and ‘specific benefit exist[ing] in currently available form’”—a theoretical or unproven utility is insufficient.²³⁵ Where an asserted utility is implausible (as here), credible evidence is required to support it.²³⁶ There is none in the common disclosure:

- it identifies *no* “inactive mutants” that were tested for, much less proven to have contraceptive effects;

result in reduced fertility ...”); EX1021, 30310, 30314 (“PH-20 is not essential for fertilization, at least in the mouse ...”).

²³⁴ EX1024, 87-88; *see also* EX1061, 1154; EX1003, ¶¶ 119-120.

²³⁵ *In re '318 Patent Infringement Litigation*, 583 F.3d. 1317, 1324 (Fed. Cir. 2009), citing *Brenner v. Manson*, 383 U.S. 519, 86 S.Ct. 1033 (1966) at 86 S.Ct. 1033.

²³⁶ EX1003, ¶¶ 121-23.

- it provides *no* guidance on selecting “inactive mutants” with contraceptive utility;
- it identifies *no* epitopes or structures on PH20 that induce antibody production that confers contraceptive effects, and
- it provides *no* evidence that any such epitopes/structures are preserved in every multiply-modified M313 PH20 “inactive mutant.”²³⁷

Given this absence of information, a skilled artisan could not have reasonably predicted from the common disclosure whether *any* “inactive mutant” PH20 polypeptide within the scope of the claims would cause contraceptive effects, much less that up to 10^{60+} M313 mutants would.²³⁸

There also is no basis for assuming that every PH20 polypeptide that is not an “active mutant” is an “inactive mutant” useful for contraception. A skilled artisan would have considered it highly likely that some number of modified PH20 polypeptides within the 10^{60+} mutants being claimed cannot be produced and/or recovered.²³⁹ For example, instability caused by amino acid substitutions can induce cells to break down rather than secrete proteins, prevent proper folding,

²³⁷ EX1003, ¶¶ 119, 122.

²³⁸ EX1003, ¶ 122.

²³⁹ EX1003, ¶ 113.

expose hydrophobic residues leading to aggregation, and cause other problems.²⁴⁰

Modified PH20 polypeptides that cannot be produced or are not properly folded will not retain the native protein structure of PH20 and cannot be “useful” “inactive mutants”—they have no utility.²⁴¹

The common disclosure also did not demonstrate that ~3,380 properly folded “inactive mutant” PH20 polypeptides were produced. The experimental protocol instead equated the *absence* of hyaluronidase activity in the supernatant from each transfected cell with proof of production of an “inactive mutant.”²⁴² But an absence of hyaluronidase activity in the supernatant would also be observed if the cell did not secrete the mutant or if the secreted mutant did not fold.²⁴³

The common disclosure also does not report the measured hyaluronidase activity values of the 3,380 “inactive mutants” or ~830 (12%) unclassified mutants,

²⁴⁰ *Id.*; EX1081, 895-897.

²⁴¹ EX1003, ¶¶ 122-23; *See Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1323 (Fed. Cir. 2005).

²⁴² EX1003, ¶¶ 107, 109-110.

²⁴³ EX1003, ¶¶ 108-110.

but did so for the “active mutants” in Table 9.²⁴⁴ It is thus impossible to determine from the common disclosure which of the ~ 4,180 “inactive” mutants (i) properly folded and were enzymatically inactive, (ii) were not successfully produced by or secreted from the transfected cells, or (iii) were secreted but did not fold.²⁴⁵

Even if a fraction of a percent of the 10^{60+} multiply-modified PH20 polypeptides within the scope of the claims cannot be produced or did not properly fold, they represent a massive absolute number of inoperative embodiments that must be identified by making and testing 10^{60+} polypeptides. Performing the scale of testing necessary to identify such inoperative species within the scope of the claims independently demonstrates a lack of enablement.²⁴⁶

²⁴⁴ EX1003, ¶¶ 110-12, 114-15; EX1001, 232:55-266:54 (Table 9), 268:10-277:43 (Table 10).

²⁴⁵ EX1003, ¶¶ 109, 112.

²⁴⁶ EX1003, ¶¶ 122-25; *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984); *Pharm. Res., Inc. v. Roxane Labs., Inc.*, 253 F. App'x. 26, 30 (Fed. Cir. 2007).

The common disclosure thus presents only a “research proposal” to discover “inactive mutants” with contraceptive utility, which is insufficient.²⁴⁷ It does not demonstrate possession of or teach “how to make and use” all inactive PH20 polypeptides with contraceptive utility (if any exist) within the claims. Thus, regardless of whether the claims are appropriately limited to “active mutants” or also include “inactive mutants,” they are unpatentable under § 112(a).

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

The specifications of the pre-AIA '731 Application and AIA '692 Patent are substantially identical, and neither supports the challenged claims as § 112(a) requires. The claims are both PGR-eligible and unpatentable under § 112(a).

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

²⁴⁷ See *Janssen Pharmaceutica N.V. v. Teva Pharms. USA, Inc.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009).

combinations of amino acid replacements (from dozens listed), others encompassed substitutions at unspecified locations.²⁴⁸ The original claims do not provide § 112 support for the challenged claims.²⁴⁹

VI. Challenged Claims 1-2, 4-5, 7-26, and 29-40 Are Unpatentable Under § 103

Claims 1-2, 5, 7-16, and 22-25 define genera of modified PH20 polypeptides that encompass one specific modified PH20 polypeptide: M313K PH20₁₋₄₄₇. *See* § IV.D.2. Because this mutant would have been obvious from the '429 Patent in view of Chao and the knowledge of a skilled artisan, each of those claims is unpatentable. Claims 4, 17-22, 26, and 29-40 are also obvious, as each recites attributes of M313K PH20₁₋₄₄₇, or are suggested by the '429 Patent alone or with Chao and knowledge in the art.

A. The Prior Art

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

²⁴⁸ EX1026, 335.

²⁴⁹ *See, e.g., Ariad Pharms.*, 598 F.3d at 1349; *Fiers v. Revel*, 984 F.2d 1164, 1170-71 (Fed. Cir. 1993).

Chao (EX1006) was published in 2007. Chao is not discussed in the common disclosure of the '692 Patent and '731 Application and was not cited during examination.

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

B. Because M313K PH20₁₋₄₄₇ Is Obvious, Claims 1-2, 5, 7-16, and 22-25 Are Unpatentable

Patentee's '429 Patent would have motivated a skilled artisan to produce modified PH20₁₋₄₄₇ polypeptides having a single amino acid substitution in non-essential regions of the protein. Guided by her familiarity with rational protein design and the teachings of the '429 Patent and Chao, the artisan would have readily identified single amino acid substitutions within non-essential regions of PH20₁₋₄₄₇ that would have been tolerated (*i.e.*, a PH20₁₋₄₄₇ with that single substitution that retains enzymatic activity). M313K PH20₁₋₄₄₇ is one such example. Because claims 1-2, 5, 7-16, and 22-25 encompass at least this obvious variant of PH20₁₋₄₄₇, each is unpatentable.

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

Patentee’s ’429 Patent describes its invention as soluble PH20 hyaluronidase glycoproteins (“sHASEGPs”) that are enzymatically active at neutral pH.²⁵⁰ It exemplifies and claims one such “sHASEGP” that terminates at position 447 (positions 36-482 of SEQ ID NO: 1).²⁵¹

The ’429 Patent explains that sHASEGPs are useful in human therapy, including, *inter alia*, to increase delivery of other therapeutic agents (*e.g.*, antibodies, chemotherapeutics), treating cancer and hyaluronidase disorders.²⁵² PH20₁₋₄₄₇ was approved by the FDA as Hylenex[®] in 2005.²⁵³ The ’429 Patent’s teachings combined with knowledge of PH20₁₋₄₄₇ as an approved human therapeutic before 2011 would have induced a skilled artisan to focus on this PH20 polypeptide.²⁵⁴

²⁵⁰ EX1005, 6:4-10, 10:30-59.

²⁵¹ EX1005, 86:18-33, 86:64-87:13, 88:8, 89:52-90:15, 153:36-40.

²⁵² EX1005, 8:25-9:4, 54:40-65, 56:34-57:36, 60:38-61:4, 63:41-61, 74:10-29, 76:19-77:36, 99:28-100:47.

²⁵³ EX1049, 1.

²⁵⁴ EX1003, ¶ 206.

Patentee's '429 Patent defines sHASEGPs as including wild-type PH20₁₋₄₄₇ and "equivalent" proteins "with amino acid substitutions that do not substantially alter activity" of the protein.²⁵⁵ As it states:

Suitable conservative substitutions of amino acids are known to those of skill in this art and can be made generally without altering the biological activity, for example enzymatic activity, of the resulting molecule. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity ...²⁵⁶

The '429 Patent also explains that single amino acid substitutions can include "conservative" substitutions in Table 1, but that "[o]ther substitutions are also permissible and can be determined empirically or in accord with known conservative substitutions."²⁵⁷ Notably, lysine is identified as an exemplified "conservative" substitution that the '429 Patent suggests for methionine in non-essential positions of PH20.²⁵⁸

²⁵⁵ EX1005, 9:65-10:13, 18:64-19:6.

²⁵⁶ EX1005, 16:14-22.

²⁵⁷ EX1005, 16:24-36.

²⁵⁸ *Id.*; EX1003, ¶ 204.

The '429 Patent thus teaches making a *particular* type of modification (a single amino acid substitution) in *particular* locations (non-essential regions of PH20) in a *particular* PH20 sequence (PH20₁₋₄₄₇) to yield equivalents that do not substantially alter the activity or function of PH20₁₋₄₄₇.²⁵⁹ The '429 Patent also motivates skilled artisans to undertake this effort to make single-amino acid substituted PH20₁₋₄₄₇ proteins by assuring them their efforts will be successful.²⁶⁰ A skilled artisan would have reasonably expected a PH20₁₋₄₄₇ mutant with a single amino acid substitution in a non-essential region to have the same utility, therapeutic applications, and other characteristics that the '429 Patent identifies for wild-type PH20₁₋₄₄₇.²⁶¹

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

In 2011, a skilled artisan looking to implement the '429 Patent's suggestion to make a single-amino acid modification in a non-essential region of PH20₁₋₄₄₇ would have used rational design to do so, which would require determining (i)

²⁵⁹ EX1003, ¶¶ 217; EX1004, ¶ 32.

²⁶⁰ EX1003, ¶ 218.

²⁶¹ EX1003, ¶¶ 210-13, 218, 234.

which regions are non-essential in PH20, and (ii) which single amino acids are appropriate to substitute into positions in those non-essential regions.²⁶²

The '429 Patent was written eight years before 2011. Given that, a skilled artisan would have reviewed literature providing insights into the structure of human hyaluronidase enzymes such as PH20.²⁶³ That would have led to Chao (EX1006), which reported an experimentally determined structure for human HYAL1 and provided new insights into the shared characteristics of human hyaluronidase enzymes.²⁶⁴

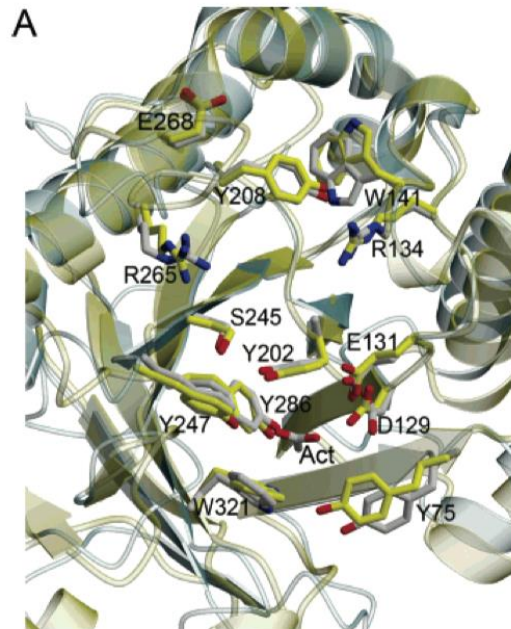
Chao showed that human and non-human hyaluronidases share a highly conserved active site and identified residues that interact with HA, *inter alia*, by superimposing HYAL1 and bee venom hyaluronidase structures.²⁶⁵

²⁶² EX1003, ¶¶ 223-25.

²⁶³ EX1003, ¶¶ 98, 220-21.

²⁶⁴ EX1003, ¶¶ 81-88; EX1004, ¶ 88; EX1006, 6912-17.

²⁶⁵ EX1006, 6917 (Figure 4A); *see also id.* at 6914-16, Figure 2C; EX1004, ¶¶ 89-91; EX1003, ¶¶ 81-82.



The '429 Patent likewise used the bee venom hyaluronidase structure to identify critical residues in PH20,²⁶⁶ and taught that hyaluronidase domains share similarity among species, including residues necessary for enzymatic activity.²⁶⁷

Second, using an alignment of five human hyaluronidases, Chao identified predicted secondary structures (*e.g.*, β -sheets, α -helices) (Figure 3, below), as well as invariant conserved positions (blue), residues involved in catalysis (red), conserved cysteines that form disulfide bonds (gold) and conserved asparagine residues that are glycosylated (turquoise).²⁶⁸

²⁶⁶ EX1005, 4:12-22, 86:49-53, 88:14-24.

²⁶⁷ EX1005, 2:6-67, 4:11-22.

²⁶⁸ EX1006, 6916; EX1003, ¶¶ 83, 222; EX1004, ¶ 92.

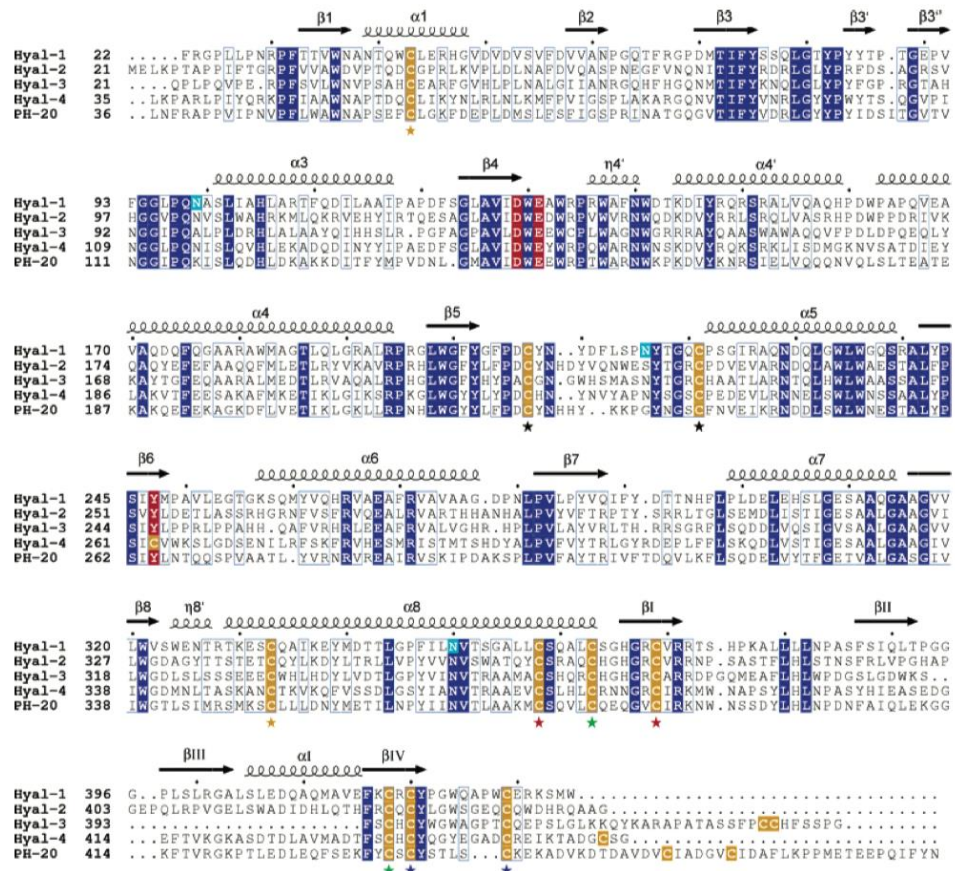


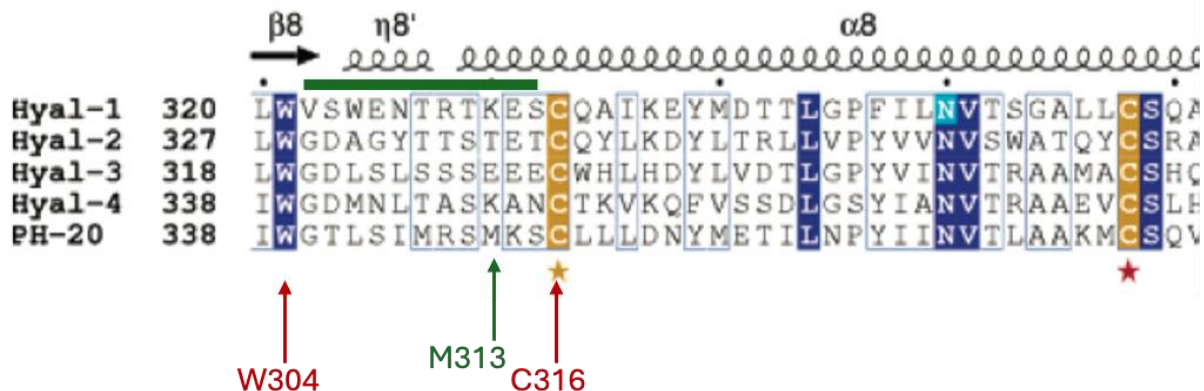
FIGURE 3: Structure-based sequence alignment of human hyaluronidases. Invariant residues are shown in blue except for three key catalytic residues that are colored red. Cysteine residues are colored yellow. The hHyal-1 N-glycosylated asparagines residues are colored turquoise. Residues exhibiting conservative replacements are blocked in blue. Pairs of cysteine residues that form disulfide bonds are indicated by stars with matching colors. Secondary structure units are labeled as in Figure 2B.

Third, Chao reported the presence of “a novel, EGF-like domain” in the C-terminal region of human hyaluronidases that was “closely associated” with the catalytic domain (discussed above, § V.A.1.b.iii). It identified a characteristic pattern for the Hyal-EGF domain, which in PH20 is at positions 337-409.²⁶⁹

²⁶⁹ EX1006, 6911; EX1004, ¶¶ 97-98; EX1003, ¶¶ 84, 87.

Dr. Sheldon Park, an expert in protein sequence and structure analysis with extensive personal experience before 2011, performed these steps. He identified 88 homologous hyaluronidase protein sequences published by December 29, 2011.²⁷³ Then he prepared a multiple-sequence alignment of these sequences, as Chao did with the five human hyaluronidases, and from that alignment identified essential (Appendix D-3) and non-essential (Appendix D-2) residues.²⁷⁴

Position 313 is within a non-essential region of PH20₁₋₄₄₇—Dr. Park’s analysis and Chao’s Figure 3 both report the same bounding essential residues (*i.e.*, W304 and C316) (below).²⁷⁵



²⁷³ EX1004, ¶¶ 27, 149-152; EX1053; EX1054; EX1055; EX1056; EX1064, 1, 4, 10, 23-28.

²⁷⁴ EX1004, ¶¶ 28-32, 153-154, Appendix D; EX1057; EX1058; EX1043, 1-2, 4-5; EX1065, 1, 4.

²⁷⁵ EX1003, ¶ 228; EX1004, ¶¶ 31-32, Appendix D-2; EX1006, 6916.

Thus, a skilled artisan in December 2011 using conventional sequence analysis tools would have readily identified position 313 as being a position within a non-essential region of PH20₁₋₄₄₇ per the '429 Patent.²⁷⁶

4. A Skilled Artisan Would Have Viewed Lysine as an Obvious Single Amino Acid Substitution for Methionine at Position 313 of PH20₁₋₄₄₇

The multiple-sequence alignment reveals a second powerful insight: it identifies *which* amino acids have been tolerated at specific positions in the amino acid sequence of homologous, stable and active, naturally occurring hyaluronidase enzymes.²⁷⁷ This derives from evolutionary selection principles, which over the course of millions of years, function to eliminate from the genome of organisms those variations in the sequences of a protein that do not yield stable and active forms of the protein.²⁷⁸

²⁷⁶ EX1003, ¶ 232; EX1004, ¶¶ 31-32, 104, Appendix D-2; EX1005, 16:14-22, 16:24-36; EX1006, 6916.

²⁷⁷ EX1003, ¶ 225; EX1004, ¶¶ 21-22.

²⁷⁸ EX1003, ¶ 225; EX1004, ¶¶ 25, 31, 41-42; EX1017, 224 (evolutionarily conserved sequences useful for determining protein structure and function); EX1014, 351.

Using a multiple-sequence alignment, a skilled artisan can readily compile a list of amino acids tolerated at positions within non-essential regions of PH20.²⁷⁹ Dr. Park did this: using his multiple-sequence alignment of the 88 hyaluronidase proteins known by December 2011, he identified the identity and frequency of different amino acids that occur at positions corresponding to position 313 in PH20 in homologous hyaluronidases (below).²⁸⁰

AA at position 348/313 in PH20 ₁₋₄₄₇	↘		↙	Most frequent AA at position in set of proteins
wt 348:	M	13.63		K 39.77
res387:	K	35	39.77	
res387:	E	15	17.04	
res387:	M	12	13.63	
res387:	T	5	5.68	
res387:	A	4	4.54	
res387:	R	4	4.54	
res387:	Q	4	4.54	
res387:	Y	2	2.27	
res387:	V	2	2.27	
res387:	N	2	2.27	
res387:	P	1	1.13	
res387:	L	1	1.13	
res387:	-	1	1.13	

% of occurrence of AA
in set of proteins

The wild-type residue at position 313 in PH20 is methionine (M), which occurs at positions corresponding to position 313 in ~14% of homologous

²⁷⁹ EX1003, ¶¶ 225-26; EX1004, ¶¶ 21-22.

²⁸⁰ EX1004, ¶¶ 30-32, 41-43, 106, 113, Appendix D-1; EX1003, ¶¶ 226, 228-29.

proteins.²⁸¹ Lysine (K) is the most prevalent amino acid found at those positions (~40%) (*i.e.*, leucine occurs in 35 different hyaluronidase proteins).²⁸²

The skilled artisan would have viewed lysine (K) as an obvious choice for a single substitution at position 313 in PH20₁₋₄₄₇.²⁸³ First, its high prevalence of occurrence and presence in 2 of the 5 human hyaluronidases signal that it was well-tolerated at this position in many different hyaluronidase enzymes.²⁸⁴ Second, lysine was known to have a high helix propensity, meaning it is favored in sequences that form α -helix secondary structures.²⁸⁵ Chao identified the “ $\alpha 8$ ” helix sequence as one such α -helix forming sequence in PH20, and position 313 of PH20 being in that $\alpha 8$ helix sequence (below).²⁸⁶

²⁸¹ EX1004, ¶¶ 105-106.

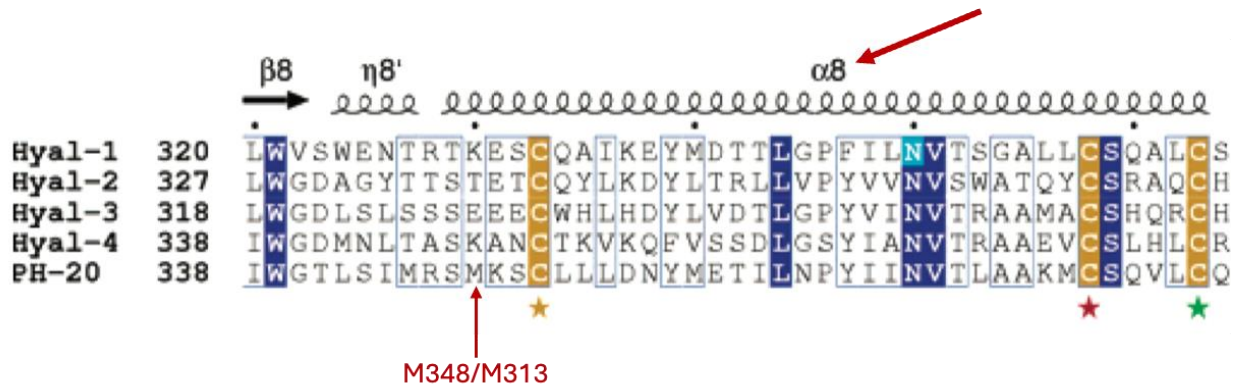
²⁸² EX1004, ¶ 113; EX1003, ¶ 229.

²⁸³ EX1003, ¶¶ 232-33; EX1004, ¶¶ 41-42, 106, 113.

²⁸⁴ EX1004, ¶¶ 43, 106, 113; EX1003, ¶ 229, 232-33 .

²⁸⁵ EX1050, 422-24, Table 2; EX1003, ¶¶ 230; EX1004, ¶¶ 69-70, 117.

²⁸⁶ EX1006, 6916, Figure 3; EX1003, ¶¶ 205, 230; EX1004, ¶¶ 32, 108.



Third, the '429 Patent describes lysine as being a suitable conservative amino acid substitution for methionine in non-essential regions of PH20.²⁸⁷

For all of the above reasons, a skilled artisan would have found lysine to be an obvious substitution for methionine at position 313 in PH20₁₋₄₄₇ pursuant to the guidance in the '429 Patent, Chao, and publicly available information.²⁸⁸

5. A Skilled Artisan Would Have Reasonably Expected the M313K PH20₁₋₄₄₇ to Be Enzymatically Active

(a) Patentee Cannot Contradict Its Past Representations to the PTO

Replacing methionine at position 313 with lysine yields a PH20₁₋₄₄₇ with a single amino acid substitution in a non-essential region of the polypeptide.²⁸⁹ In its '429 Patent, Patentee stated:

²⁸⁷ EX1005, 16:4-32, Table 1, 10:9-13; EX1003, ¶¶ 217-19.

²⁸⁸ EX1003, ¶¶ 218, 228-232; EX1004, ¶¶ 32, 108, 117-120.

²⁸⁹ See § VI.B.3; EX1003, ¶ 228; EX1004, ¶ 32.

Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity.²⁹⁰

Patentee also secured claims in the '429 patent to modified PH20₁₋₄₄₇ proteins with at least one substitution (*e.g.*, claim 1), despite not providing examples of PH20 proteins with any substitutions. Patentee, thus, made and relied on its statements that a skilled artisan would have expected *any* single amino acid substitution in *any* non-essential position of PH20₁₋₄₄₇ to not substantially affect the activity of the enzyme. Patentee should not be permitted to now contend a skilled artisan would not have reasonably expected that the M313K substitution in PH20₁₋₄₄₇ would yield an enzyme with comparable activity to unmodified PH20₁₋₄₄₇.

(b) Skilled Artisans Would Reasonably Expect the M313K Substitution to be Tolerated in PH20₁₋₄₄₇

Independently, a skilled artisan would have reasonably expected the M313K substitution to not substantially alter the biological activity (hyaluronidase activity) of PH20₁₋₄₄₇.

First, both experts noted that many naturally occurring homologous hyaluronidase proteins contain lysine at positions corresponding to position 313 in PH20 (including in 2 of 4 human homologs of PH20 (Chao)), which would have

²⁹⁰ EX1005, 16:17-20.

led a skilled artisan to believe that lysine would be tolerated at position 313 in PH20.²⁹¹

Second, Dr. Park's sequence alignment shows that many (11) other amino acids occur in homologous proteins at positions corresponding to position 313 in PH20.²⁹² These amino acids have diverse characteristics (*e.g.*, polar and non-polar, have high and low helix propensities, and have large or small side chains), which suggests that many different amino acids can be tolerated at position 313 in PH20.²⁹³

In view of these factors, a skilled artisan would have reasonably expected the M313K substitution to be tolerated in PH20₁₋₄₄₇.²⁹⁴

(c) *A PH20 Structural Model Confirms that PH20₁₋₄₄₇ Would Tolerate Lysine at Position 313*

Dr. Park also assessed whether single amino acid substitutions in PH20₁₋₄₄₇ would be tolerated, including M313K, using a PH20 protein structural model

²⁹¹ EX1003, ¶¶ 229, 231-32; EX1004, ¶¶ 106, 113.

²⁹² EX1004, ¶ 106.

²⁹³ EX1003, ¶ 231; EX1004, ¶ 106.

²⁹⁴ EX1003, ¶¶ 232-33; EX1004, ¶ 106.

generated by SWISS-MODEL using Chao's HYAL1 structure as the template, as would have been done in 2011 by a skilled artisan.²⁹⁵

Dr. Park explains that his PH20 model was reliable in the region of position 313 of PH20 based on QMEAN values²⁹⁶ and would be very similar to a PH20 model generated by SWISS-MODEL in 2011 (*e.g.*, it used 165 conserved positions in the backbone of the two proteins).²⁹⁷

Dr. Park also devised a consistent, objective methodology for assessing substitutions using the PH20₁₋₄₄₇ model.²⁹⁸ Factors he considered included, *inter alia*, the number of neighboring residues at position 313 (*i.e.*, those within 5 Å), the various possible interactions between neighbors (*e.g.*, hydrophobic, charged,

²⁹⁵ EX1004, ¶¶ 39-40, 155-156; EX1003, ¶¶ 235-39; EX1006, 6915, Figure 2; EX1017, 229; EX1012, 1-2, 4; EX1014, 348, 370; EX1038, 3382.

²⁹⁶ EX1004, ¶¶ 157-159 (satisfactory local and global QMEAN values); EX1037, 346-47; EX1069, 3; EX1012, 4, 8.

²⁹⁷ EX1004, ¶¶ 160-161, 165; EX1038, 3382-4; EX1017, 229-230; EX1012, 1-2; EX1014, 348, 370; EX1066, 5-11.

²⁹⁸ EX1004, ¶¶ 102-103; *see generally id.* at § IV.C (description of Dr. Park's methodology); EX1003, ¶¶ 226-27.

van der Walls, steric, etc.), and solvent accessibility.²⁹⁹ Where interactions were observed, Dr. Park assessed the impact of them (*e.g.*, hydrophobic-hydrophilic, effects on secondary structures, size related issues such as steric clashes, or creation/filling of “holes” in the structure).³⁰⁰

Dr. Park visually assessed the environment of position 313 of PH20 (both wild-type and with substitutions) using functionality within the viewer (PyMol) and as a modeled sequence generated in SWISS-MODEL for the PH20₁₋₄₄₇ sequence incorporating the single substitutions.³⁰¹ These technologies were all available in 2011.³⁰² He used his methodology to assess substitutions representing diverse interactions, and confirmed it provided a consistent, objective and unbiased evaluation of substitutions.³⁰³

²⁹⁹ EX1004, ¶¶ 44-47, 53-60, 65-85, Appendix D-5; EX1035, 1408, Table 2; EX1043, 2, Table 1.

³⁰⁰ EX1004, ¶¶ 62-63, 85.

³⁰¹ EX1004, ¶¶ 61, 107, 112, 115-116, 171-182; EX1003, ¶¶ 236-38.

³⁰² EX1004, ¶¶ 155, 160-161, 168-169, 172-173; EX1066, 1, 4, 7, 17, 25, 27, 35, 39, 41; EX1067, 1, 6-7, 53-57, 61-62; EX1012, 1-4; EX1003, ¶¶ 20-22.

³⁰³ EX1004, ¶¶ 102-103; EX1003, ¶¶ 226-27.

Dr. Park assigned a score for each substitution reflecting the aggregate effect of the interactions he observed (below).³⁰⁴

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

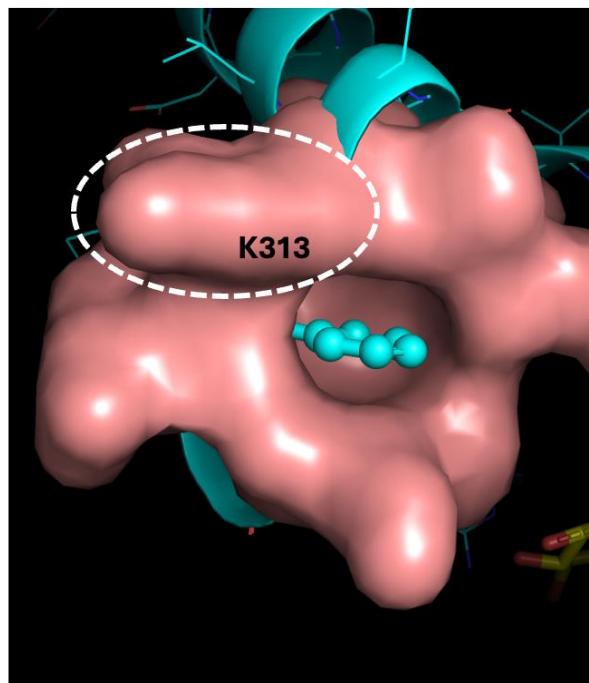
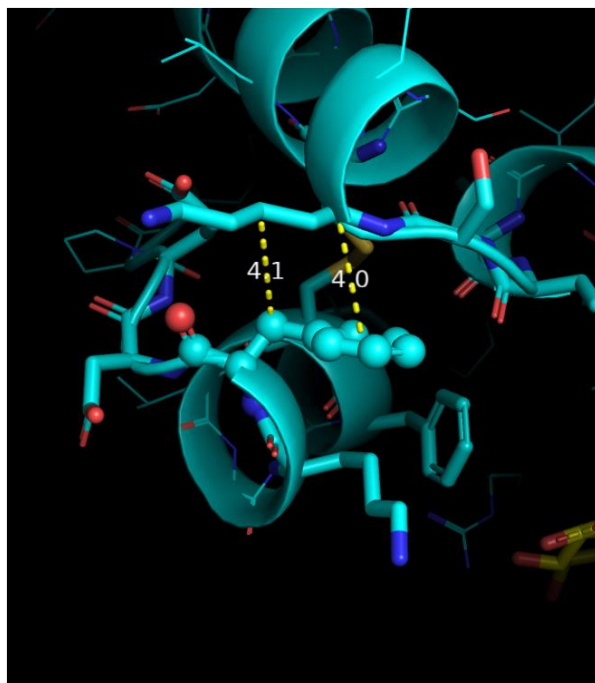
Dr. Park assigned a score of 3 for the M313K substitution in PH20₁₋₄₄₇, indicating that the substitution would be expected to confer improved stability.³⁰⁵ He observed that position 313 in wild-type PH20 contributes to a hydrophobic pocket around the phenylalanine (F) at position 29, but that position 313 also has a high solvent exposure.³⁰⁶ He found that while lysine and methionine have chemically different classifications, lysine within the environment of position 313 would be seen as a conservative substitution as it maintains several structural roles of methionine at that position (below).³⁰⁷

³⁰⁴ EX1004, ¶¶ 85-87.

³⁰⁵ EX1004, ¶ 120, Appendix C.

³⁰⁶ EX1004, ¶¶ 108-109.

³⁰⁷ EX1004, ¶¶ 118-119.



First, lysine at position 313 would maintain the three interactions that occur between the C- α , C- β and C- γ carbons of methionine with phenylalanine at position 29 and would help form a solvent-limited pocket around PH20 through interactions with F29 and H47,³⁰⁸ comparable to lysine's role at position 330 in HYAL1.³⁰⁹ Second, the lysine terminus is hydrophilic, making it more compatible in a solvent environment than the thiol group in methionine, and it may also form a salt-bridge with glutamic acid (E) at position 66.³¹⁰ As Dr. Park concluded, the net effect of these interactions with lysine at position 313 in PH20₁₋₄₄₇ would be

³⁰⁸ EX1004, ¶ 118.

³⁰⁹ *Id.*

³¹⁰ EX1004, ¶ 119.

stabilizing, suggesting it would be tolerated and that the M313K PH20₁₋₄₄₇ mutant would retain hyaluronidase activity.³¹¹

Dr. Park's visualization-based assessment was a prevalent technique used in 2011.³¹² Similarly, his technique of assessing interactions between neighbors and assigning an overall score reflecting the aggregate effects of those interactions is consistent with methods reported in peer review publications.³¹³

Dr. Hecht reviewed Dr. Park's analysis and conclusions concerning the M313K single substitution and agreed with them.³¹⁴ Through his own assessment, he observed that lysine substituted into position 313 would have a stabilizing effect due to (i) the compatibility of the shape of lysine with the solvent-exposed pocket

³¹¹ EX1004, ¶ 120.

³¹² EX1017, 228 (“... a structural biologist's intuition is often an important tool in the design of the desired variants, an approach that may be termed structure-based protein design to borrow a term from the drug design field. Visualization of the known reference structure is a key component of this.”); EX1004, ¶¶ 22, 33-36; EX1003, ¶¶ 237-39.

³¹³ EX1004, ¶¶ 48-52; EX1031, 459, 462-64, 469-71, Table 3; EX1032, 265-66; EX1003, ¶ 239.

³¹⁴ EX1003, ¶¶ 238, 241.

at that location, and (ii) the fact that the M313K substitution would introduce a hydrophilic residue (L) into a solvent-exposed position in the protein, all without disturbing pre-existing interactions with neighboring amino acids.³¹⁵

6. M313K PH20₁₋₄₄₇ Would Have Reasonably Been Expected to Be an Active Mutant

The common disclosure defines an “active mutant” as a modified PH20 polypeptide with at least ~40% of the activity of unmodified PH20₁₋₄₄₇.³¹⁶ Drs. Hecht and Park each independently concluded that the M313K substitution would have been tolerated by PH20₁₋₄₄₇.³¹⁷ A skilled artisan thus would have reasonably expected that the M313K PH20₁₋₄₄₇ polypeptide would exhibit at least 40% of the activity of unmodified PH20₁₋₄₄₇.³¹⁸

Based on the '429 Patent, Chao, and information available in 2011, the M313K PH20₁₋₄₄₇ polypeptide would have been obvious to a skilled artisan in 2011. And because claims 1-2, 5, 7-16, and 22-25 each encompass this single-substitution mutant, each claim is unpatentable.

³¹⁵ EX1003, ¶¶ 242-43.

³¹⁶ EX1001, 73:61-66; *also id.* at 77:43-47.

³¹⁷ EX1003, ¶¶ 241-43, 245; EX1004, ¶¶ 17, 120.

³¹⁸ EX1003, ¶ 245.

C. Dependent Claims 4, 17-22, 26, and 29-40 Are Obvious

Each of claims 4, 17-22, 26, and 29-40 defines subject matter that would have been obvious to a skilled artisan from the '429 Patent alone or with Chao and knowledge in the art.

1. Claim 4

Claim 4 requires the modified PH20 polypeptide of claim 1 to be “soluble.”

The '429 Patent indicates that PH20₁₋₄₄₇ omits the C-terminal residues containing the GPI anchor sequence and is thus soluble.³¹⁹ A skilled artisan would have expected that a single substitution in a non-essential region of PH20₁₋₄₄₇ that was tolerated, such as M313K, would remain soluble as it would not meaningfully alter the overall structure of PH20₁₋₄₄₇.³²⁰

2. Claims 17-19

Claims 17-19 specify post-translational modifications of PH20 including that they: (i) “comprise one or more modifications” including glycosylation (claim 17), is “glycosylated” (18), and “comprise an N-acetylglucosamine moiety linked to each of at least three asparagine (N) residues” (19).

The '429 Patent teaches (i) that human PH20 must be glycosylated to exhibit activity, and (ii) expression of PH20₁₋₄₄₇ in mammalian (CHO) host cells yields

³¹⁹ EX1005, 3:57-62, 87:52-88:24.

³²⁰ EX1003, ¶¶ 207, 214, 234.

active glycosylated forms of PH20₁₋₄₄₇.³²¹ It further teaches that “N- and O-linked glycans are attached to polypeptides through asparagine-N-acetyl-D-glucosamine ... linkages,” and claims PH20 polypeptides (including PH20₁₋₄₄₇) having asparagine-linked sugar moieties.³²² Frost confirmed that recombinant production of PH20₁₋₄₄₇ in CHO cells “resulted in a 447 amino acid 61 kDA glycoprotein with a properly processed amino terminus and 6 N-linked glycosylation sites.”³²³

Based on the '429 Patent and knowledge in the art, a skilled artisan would have found it obvious to produce M313K PH20₁₋₄₄₇ in a CHO cell, which causes its six N-linked glycosylation sites to be glycosylated as claims 17-19 specify.³²⁴

3. Claims 20-22, 26

Claims 20-22 and 26 specify modified PH20 polypeptides: (i) that are conjugated to a polymer (*e.g.*, polyethylene glycol) (claims 20-21) or (ii) comprise a heterologous signal sequence (22, 26).

³²¹ EX1005, 95:13-30, 40:41-51, 89:53-91:67, 88:5-9.

³²² EX1005, 3:27-35, claims 1, 6.

³²³ EX1013, 432.

³²⁴ EX1003, ¶¶ 208-09, 214-15.

A skilled artisan would have found the '429 Patent to suggest each of these requirements.³²⁵ First, it teaches (as claims 20-21 specify) that PH20₁₋₄₄₇ proteins with mutations (“sHASEPGs”) can be “modif[ied]” “with polymers such as polyethylene glycol.”³²⁶ Second, it describes expression of modified PH20 polypeptides that incorporate heterologous signal sequences (as claims 22 and 26 specify).³²⁷ Claims 20-22 and 26 thus would have been obvious.

4. Claims 29-40

Claims 29-40 specify pharmaceutical compositions and methods that comprise or use modified PH20 polypeptides of claim 1.

The '429 Patent provides extensive guidance concerning pharmaceutical compositions comprising PH20 polypeptides (*e.g.*, PH20₁₋₄₄₇) (claim 29), including with other therapeutically active agents (30) such as an “antibody” (a “protein”) (31, 33) or “chemotherapeutic agent” (32).³²⁸ It describes using PH20 polypeptides (*e.g.*, PH20₁₋₄₄₇) in methods of treating hyaluronan-associated disease (34), such as

³²⁵ EX1003, ¶¶ 215-16.

³²⁶ EX1005, 3:64-4:1, 4:45-53, 26:20-28:4.

³²⁷ EX1005, 34:33-37; 88:28-90:15.

³²⁸ EX1005, 54:40-57:21, 73:4-74:29, 58:67-59:12, 61:14-57, claims 14, 29, 33.

cancer (35) or solid tumors (36).³²⁹ It also describes methods of subcutaneously administering formulations that combine enzymatically active “sHASEPGs” (e.g., PH20₁₋₄₄₇ with one substitution) with another therapeutic agent to increase delivery of the therapeutic agent (claim 37),³³⁰ such as an antibody (40).³³¹ It teaches that they can be administered together or sequentially (39), and subcutaneously (38).³³²

A skilled artisan would have expected the M313K PH20₁₋₄₄₇ polypeptide to have a comparable structure and activity as unmodified PH20₁₋₄₄₇, and thus would share the latter’s utility in the pharmaceutical compositions and therapeutic methods described in the ’429 Patent.³³³ Indeed, in the ’429 Patent, Patentee secured claims encompassing pharmaceutical compositions containing PH20 polypeptides with 1+ substitutions and chemotherapeutic agents despite no exemplification.³³⁴ Claims 29-40 impose no other restrictions on the

³²⁹ *Id.*

³³⁰ *Id.*; also EX1005, 8:25-38, 54:40-45, 56:36-57:21, 63:40-64:4, 73:4-20, 76:18-77:37, 97:36-98:18, 98:49-99:24, claim 27; EX1003, ¶¶ 208, 211-13.

³³¹ EX1005, 54:40-45, claims 29, 33.

³³² EX1005, 75:25-50, 63:40-44; EX1003, ¶¶ 211-13.

³³³ EX1003, ¶¶ 205-08, 213-16, 228, 234.

³³⁴ EX1005, claims 29, 30, 50.

pharmaceutical composition that comprise or methods that use modified PH20 polypeptides of claim 1.

A skilled artisan thus would have found the claimed methods to have been obvious from the '429 Patent.³³⁵

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

Evidence of secondary indicia cannot support non-obviousness if it does not have nexus to the claims. A key question in a nexus analysis is whether such evidence is commensurate with the scope of the claims. The answer here is a definitive no.

Patentee may contend the M313K PH20₁₋₄₄₇ variant has unexpectedly high hyaluronidase activity. Demonstrating that result for one of the $\sim 10^{60}$ to 10^{113} modified PH20 polypeptides encompassed by the claims utterly fails to establish a nexus. As explained in § V.A.1, the single-substitution M313K PH20₁₋₄₄₇ mutant is not representative of the numerous, structurally different proteins encompassed by the claims, particularly those expected to be inactive.

If Patentee advances evidence or arguments concerning nexus, that issue should be deferred until after institution, and Petitioner reserves its right to contest such evidence.

³³⁵ EX1003, ¶¶ 210-13, 218, 234.

VII. The Board Should Not Exercise Its Discretion Under § 324(a) or § 325(d)

There is no proper basis for the Board to exercise its discretion to not institute trial.

Since November 2024, Merck has diligently filed 11 PGRs against this family of patents. To date, Halozyme has disclaimed rather than defend claims expressly requiring increased hyaluronidase activity, increased stability, or solubility. *E.g.*, PGR2025-00003 (claims 5-7), PGR2025-00004 (claims 5-6), PGR2025-00006 (claims 5-7), PGR2025-00009 (claims 3-5, 15). This raises serious doubts about the patentability of all challenged claims, including claims 3-4, 6, and 27-28.

The examination record does not warrant exercising discretion to not institute. As explained in § IV.C, no obviousness rejections were raised during prosecution.³³⁶ The present obviousness grounds rely on Chao (EX1006), which was not cited or considered during examination, and are supported by evidence not available to the Examiner (*e.g.*, expert testimony of Drs. Hecht and Park).

³³⁶ EX1002, 612-49.

Also, while indefiniteness rejections were overcome by claim amendments,³³⁷ the Examiner erred by not rejecting the claims for lack of written description and non-enablement. *See* §§ V.A-B.

Halozyme's recently-filed complaint alleging infringement of the '692 Patent does not warrant denial under the factors in *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11, 5-6 (P.T.A.B. Mar. 20, 2020). To the extent Halozyme contends discretionary denial is warranted, Merck reserves the right to respond separately pursuant to the Acting Director's March 26, 2025 Memorandum.³³⁸

VIII. Conclusion

For the foregoing reasons, the challenged claims are unpatentable.

Dated: April 29, 2025

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

³³⁷ EX1002, 631, 703-07.

³³⁸ <https://www.uspto.gov/sites/default/files/documents/InterimProcesses-PTABWorkloadMgmt-20250326.pdf>.

EXHIBIT LIST

No.	Exhibit Description
1001	U.S. Patent No. 12,091,692
1002	File History of U.S. Patent No. 12,091,692
1003	Declaration of Dr. Michael Hecht
1004	Declaration of Dr. Sheldon Park
1005	U.S. Patent No. 7,767,429
1006	Chao et al., "Structure of Human Hyaluronidase-1, a Hyaluronan Hydrolyzing Enzyme Involved in Tumor Growth and Angiogenesis," <i>Biochemistry</i> , 46:6911-6920 (2007)
1007	WO 2010/077297, published 8 July 2010
1008	Stern et al., "The Hyaluronidases: Their Genomics, Structures, and Mechanisms of Action," <i>Chem. Rev.</i> 106:818-839 (2006)
1009	Jedzrejas et al., "Structures of Vertebrate Hyaluronidases and Their Unique Enzymatic Mechanism of Hydrolysis," <i>Proteins: Structure, Function and Bioinformatics</i> , 61:227-238 (2005)
1010	Zhang et al., "Hyaluronidase Activity of Human Hyal1 Requires Active Site Acidic and Tyrosine Residues," <i>J. Biol. Chem.</i> , 284(14):9433-9442 (2009)
1011	Arming et al., "In vitro mutagenesis of PH-20 hyaluronidase from human sperm," <i>Eur. J. Biochem.</i> , 247:810-814 (1997)
1012	Bordoli et al., "Protein structure homology modeling using SWISS-MODEL workspace," <i>Nature Protocols</i> , 4(1):1-13 (2008)
1013	Frost, "Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration," <i>Expert Opinion on Drug Delivery</i> , 4(4):427-440 (2007)
1014	Branden & Tooze, "Introduction to Protein Structure," Second Ed., Chapters 1-6, 11-12, 17-18 (1999)
1015	Table Associating Citations from the '692 Patent (EX1001) to Corresponding Citations in the '731 Application (EX1026)

No.	Exhibit Description
1016	Steipe, "Consensus-Based Engineering of Protein Stability: From Intrabodies to Thermostable Enzymes," <i>Methods in Enzymology</i> , 388:176-186 (2004)
1017	Green, "Computer Graphics, Homology Modeling, and Bioinformatics," <i>Protein Eng'g & Design</i> , Ch. 10, 223-237 (2010)
1018	Chica et al., "Semi-rational approaches to engineering enzyme activity: combining the benefits of directed evolution and rational design," <i>Curr. Opin. Biotechnol.</i> , (4):378-384 (2005)
1019	Hardy et al., "Assessment of contraceptive vaccines based on recombinant mouse sperm protein PH20," <i>Reprod.</i> , 127:325-334 (2004)
1020	Pomering et al., "Restricted Entry of IgG into Male and Female Rabbit Reproductive Ducts Following Immunization with Recombinant Rabbit PH-20," <i>Am. J. Reprod. Immunol.</i> , (3):174-82 (2002)
1021	Baba et al., "Mouse Sperm Lacking Cell Surface Hyaluronidase PH-20 Can Pass through the Layer of Cumulus Cells and Fertilize the Egg," <i>J. Biol. Chem.</i> , 277(33):30310-4 (2002)
1022	Primakoff et al., "Reversible Contraceptive Effect of PH-20 Immunization in Male Guinea Pigs," <i>Biol Reprod.</i> , 56(5):1142-6 (1997)
1023	Tung et al., "Mechanism of Infertility in Male Guinea Pigs Immunized with Sperm PH-20," <i>Biol. Reprod.</i> , 56(5):1133-41 (1997)
1024	Rosengren et al., "Recombinant Human PH20: Baseline Analysis of the Reactive Antibody Prevalence in the General Population Using Healthy Subjects," <i>BioDrugs</i> , 32(1):83-89 (2018)
1025	U.S. Patent No. 9,447,401
1026	U.S. Patent Application No. 13/694,731
1027	2024 Chemistry Nobel Prize Background
1028	[Reserved]
1029	Gmachl et al., "The human sperm protein PH-20 has hyaluronidase activity," <i>FEBS Letters</i> , 3:545-548 (1993)

No.	Exhibit Description
1030	Sills, "Retraction," <i>Science</i> , 319:569 (2008)
1031	Yue et al., "Loss of Protein Structure Stability as a Major Causative Factor in Monogenic Disease," <i>J. Mol. Biol.</i> , 353:459-473 (2005)
1032	Wang & Moulton, "SNPs, Protein Structure, and Disease," <i>Hum. Mutation</i> , 17:263-270 (2001)
1033	Marković-Housley et al., "Crystal Structure of Hyaluronidase, a Major Allergen of Bee Venom," <i>Structure</i> , 8:1025-1035 (2000)
1034	"Negative Results," <i>Nature: Editorials</i> , 453:258 (2008)
1035	Lins et al., "Analysis of Accessible Surface of Residues in Proteins," <i>Protein Sci.</i> , 12:1406-1417 (2003)
1036	Hayden, "Chemistry: Designer Debacle," <i>Nature</i> , 453:275-278 (2008)
1037	Benkert et al., "Toward the Estimation of the Absolute Quality of Individual Protein Structure Models," <i>Bioinformatics</i> , 27:343-350 (2010)
1038	Schwede et al., "SWISS-MODEL: An Automated Protein Homology-Modeling Server," <i>Nucleic Acids Res.</i> , 31:3381-3385 (2003)
1039	Alberts, "Molecular Biology of the Cell," Fifth Edition, Chapter 3 (2007).
1040	He et al., "NMR Structures of Two Designed Proteins with High Sequence Identity but Different Fold and Function," <i>PNAS</i> , 105:14412-14417 (2008)
1041	Alexander et al., "A Minimal Sequence Code for Switching Protein Structure and Function," <i>PNAS</i> , 106:21149-21154 (2009)
1042	Ruan et al., "Design and Characterization of a Protein Fold Switching Network," <i>Nature Comm.</i> , 14 (2023)
1043	Sievers et al., "Fast, Scalable Generation of High-Quality Protein Multiple Sequence Alignments Using Clustal Omega," <i>Molecular Sys. Biology</i> , 7.1 (2011)
1044	Mihel, "PSAIA – Protein Structure and Interaction Analyzer," <i>BMC Structural Biology</i> , 8:21 (2008)

No.	Exhibit Description
1045	Redline Comparison of the '731 and '692 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	KEGG, DRUG: Hyaluronidase (<i>human recombinant</i>), available at: https://www.genome.jp/entry/D06604
1050	Pace & Scholtz, "A Helix Propensity Scale Based on Experimental Studies of Peptides and Proteins," Biophysical J. 75:422-427 (1998)
1051	U.S. Patent Application No. 61/631,313
1052	U.S. Patent Application No. 61/796,208
1053	Hom_pre2011
1054	Hom_pre2011_header
1055	Hom_pre2011_header_clean
1056	Hom_pre2011.fasta
1057	Ph20_pre2011.aln-clustal_num
1058	Ph20_pre2011 Alignment html
1059	Leisola & Turunen, "Protein Engineering: Opportunities and Challenges," Appl. Microbiol. Biotechnol. 75:1225-1232 (2007)
1060	Hecht et al., "De Novo Proteins from Designed Combinatorial Libraries," Protein Sci., 13:1711-1723 (2004)
1061	Rosengren et al., "Clinical Immunogenicity of rHuPH20, a Hyaluronidase Enabling Subcutaneous Drug Administration," AAPS J., 17:1144-1156 (2015)
1062	[Reserved]
1063	[Reserved]

No.	Exhibit Description
1064	Collection of BLAST Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20111022151531/http://www.clustal.org/omega/
1065	Collection of Clustal Omega Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20111022151531/http://www.clustal.org/omega/
1066	Collection of SWISS-MODEL Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20110519141121/http://swissmodel.expasy.org/?pid=smh01&uid=&token=
1067	Collection of PyMol Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20110701072314/http://pymol.org/
1068	Declaration of Jeffrey P. Kushan
1069	Swiss Model Printout of PH20 Model
1070	Swiss Model Printout of PH20 Model with M313K Mutation
1071	Swiss Model Printout of PH20 Model with M313A Mutation
1072	Swiss Model Printout of PH20 Model with M313R Mutation
1073	Swiss Model Printout of PH20 Model with M313Y Mutation
1074	Swiss Model Printout of PH20 Model with M313P Mutation
1075	Swiss Model Printout of PH20 Model with M313L Mutation
1076	[Reserved]
1077	[Reserved]
1078	[Reserved]
1079	Hunnicutt 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

No.	Exhibit Description
	Enhanced Interstitial Transport of Therapeutics,” J. Controlled Release, 114:230-241 (2006)
1081	Goldberg, “Protein degradation and protection of against misfolded or damaged proteins,” Nature, 426:895-899 (2003)

CERTIFICATE OF COMPLIANCE

I hereby certify that this brief complies with the type-volume limitations of 37 C.F.R. § 42.24, because it contains 18,676 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: April 29, 2025

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 29th day of April, 2025, I caused to be served a true and correct copy of the foregoing and any accompanying exhibits by FedEx on the following counsel:

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

Dated: April 29, 2025

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