Paper No. 1
Filed: March 23, 2026

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyme Inc.,
Patent Owner.

Case No. IPR2026-00314
U.S. Patent No. 11,066,656

PETITION FOR INTER PARTES REVIEW

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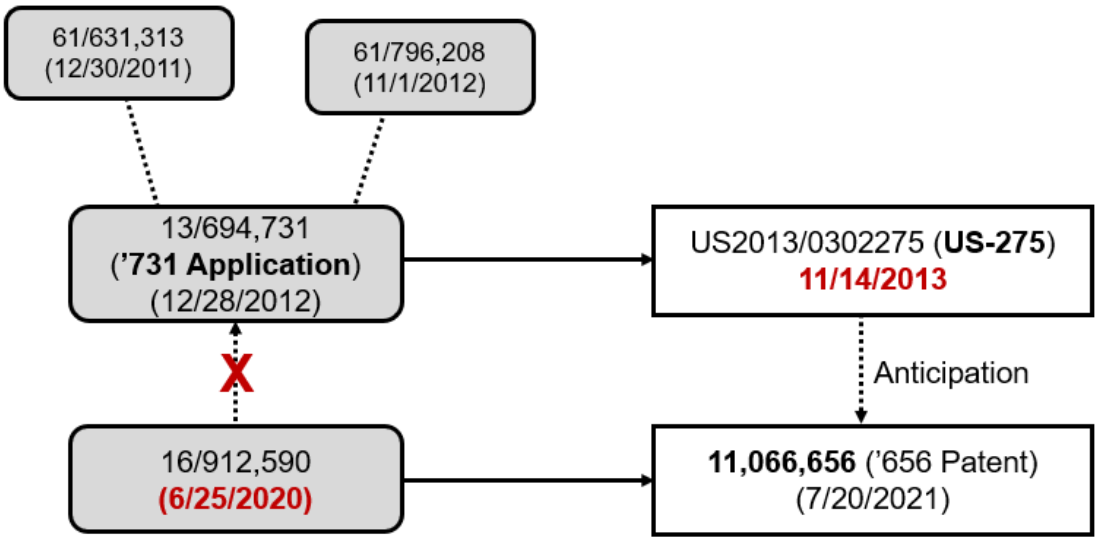
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I. Introduction

Petitioner Merck Sharp & Dohme LLC ("Merck") requests *inter partes* review of U.S. Patent No. 11,066,656 ("'656 Patent"). Claims 1-25 (the "challenged claims") are not entitled to the benefit of U.S. Application No. 13/694,731 (the "'731 Application") under 35 U.S.C. § 120, as they are not supported by that application's disclosure as § 112 requires.[1] As such, US-275,[2] which published the contents of the '731 Application on November 14, 2013, is prior art that anticipates each of these claims (illustrated below).



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

[2] EX1004 (US2013/0302275) ("US-275").

The challenged claims require modified PH20 polypeptides that "exhibit[] ***increased hyaluronidase activity***" compared to an unmodified PH20 polypeptide. The written description and enablement deficiencies of these claims relative to the '731 Application mirror those of claims in fourteen other patents in the same family for which post-grant review (PGR) proceedings have been instituted. *See infra* § II.B.2. Tellingly, Patentee has statutorily disclaimed claims in 13 of these other PGR-challenged patents that explicitly require the modified PH20s to possess activity or other functional properties.[3]

The challenged claims here require enzymatically active modified PH20 polypeptides that (i) must contain one amino acid substitution at position 309 but (ii) may have other modifications at up to 9% of the positions in one of 32 reference sequences (*i.e.*, between 20 to 41 ***optional*** modifications). The number

[3] PGR2025-00003, EX2003 (claims 5-7); PGR2025-00004, EX2003 (claims 5-6); PGR2025-00006, EX2003 (claims 5-7); PGR2025-00009, EX2003 (claims 4-5, 15); PGR2025-00017, EX2003 (claims 4-5, 16); PGR2025-00024, EX2003 (claims 4-5, 16); PGR2025-00030, EX2003 (claims 4-5); PGR2025-00033, EX2003 (claims 4-5, 35); PGR2025-00039, EX2003 (claims 5-6); PGR2025-00042, EX2003 (claims 4, 6); PGR2025-00046, EX2003 (claims 4, 6); PGR2025-00050, EX2003 (claims 4-5); PGR2025-00053 (claim 4).

and identity of such PH20 polypeptides with ***multiple*** changes within the massive "sequence space" of the claims (*i.e.*, sets of 10^{59}-10^{113}+ distinct amino acid sequences) is unidentified and unknowable.[4] Determining which are enzymatically active PH20s with increased hyaluronidase activity—a further limitation of all claims—requires producing and testing them, an impossible task that would consume an aggregate mass (~3.93 x 10^{38} kg) that exceeds that of Earth (~6 x 10^{24} kg)![5]

The '731 Application fails to provide adequate written description support for the claims. The examples it describes have only ***one*** amino acid substitution in ***one*** sequence (*i.e.*, $PH20_{1\text{-}447}$). Of those ~6,700 single-substitution $PH20_{1\text{-}447}$ mutants, ~800 exhibited >100% activity. But there are ***no examples*** of ***any multiply***-modified $PH20_{1\text{-}447}$ polypeptides (with or without increased activity). The disclosure also does not identify or describe common structural features shared by enzymatically active ***multiply-modified*** PH20s (much less those with increased activity). At most, the disclosure supplies a prophetic, make-and-test, research plan to ***discover*** such PH20 polypeptides with increased activity. And given that POSAs

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

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

could not even estimate what portion of the claims' sequence space will properly fold and exhibit increased activity, the '731 Application cannot demonstrate possession of the claimed ***multiply***-modified PH20 polypeptides with increased activity.

The '731 Application also does not enable the claims. It provides ***no examples*** of a multiply-modified PH20 polypeptide with increased hyaluronidase activity and does not otherwise guide a POSA to select combinations of changes (substitutions, deletions and additions) that will yield properly folded, enzymatically active PH20s. Instead, it provides only a single, prophetic method that requires producing 10^{59}-10^{113}+ mutants and screening them to discover which (if any) exhibit increased hyaluronidase activity. The POSA is left to navigate the unpredictable effects that combinations of mutations have on polypeptides, including on their production, folding, stability, and enzymatic activity. The impossible scale of experimentation required to practice the full scope of the claims renders them non-enabled.

These written description and enablement deficiencies prevent the claims from being entitled to the benefit of the filing date of the '731 Application or either of the provisional applications. US-275 is thus prior art to these claims. And because US-275 discloses several position 309 single-substitution $PH20_{1\text{-}447}$ mutants that exhibited increased activity, including I309N, that fall within the

scope of the challenged claims, it anticipates every claim. Institution and a final written decision finding the claims unpatentable is warranted.

II. Compliance with IPR Requirements

A. Certification of Standing

Petitioner certifies (i) this Petition for *inter partes* review is filed within one year of service of a complaint alleging infringement of the ’656 Patent and (ii) it is not barred or estopped from requesting this IPR. Petitioner and its privies have not filed a civil action challenging the validity of any claim of the ’656 Patent.

B. Mandatory Notices

1. Real Party-in-Interest

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

2. Related Proceedings

PGR2025-00003, PGR2025-00004, PGR2025-00006, PGR2025-00009, PGR2025-00017, PGR2025-00024, PGR2025-00030, PGR2025-00033, PGR2025-00039, PGR2025-00042, PGR2025-00046, PGR2025-00050, PGR2025-00052,

PGR2025-00053, PGR2025-00087, IPR2026-00312, and IPR2026-00313 are related proceedings.

On April 24, 2025, Patent Owner filed a complaint in *Halozyme, Inc. v. Merck Sharp & Dohme Corp.*, Case No. 2-25-cv-03179 (D.N.J.), alleging infringement of, *inter alia*, the '656 Patent.

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III. Ground

Claims 1-25 are anticipated under 35 U.S.C. § 102 by US-275.

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

The full-length PH20 protein (SEQ ID NO: 6) includes a 35 amino acid signal sequence, and mature forms of PH20 differ from SEQ ID NO: 6 by 35

residues.[6] "$PH20_{1\text{-}n}$" refers to a sequence of 1-n residues in PH20 (*e.g.*, $PH20_{1\text{-}447}$ is SEQ ID NO: 3), and "AxxxB" is used to identify the position of a substitution (*e.g.*, "I309N").

IV. Background on the '656 Patent

A. Field of the Patent

The '656 Patent concerns the human PH20 hyaluronidase enzyme and making structurally altered forms of that protein that retain or enhance enzymatic activity.[7]

1. Protein Structures

Proteins are comprised of sequences of amino acids. A protein's activity derives from its unique, three-dimensional structure, which results when the amino acid sequence folds to adopt the native state of the protein.[8] That, in turn, is dictated by specific and often characteristic patterns of amino acids within its sequence. Those patterns of amino acids induce formation and maintenance of various secondary structures and higher-order structural motifs that are packed into

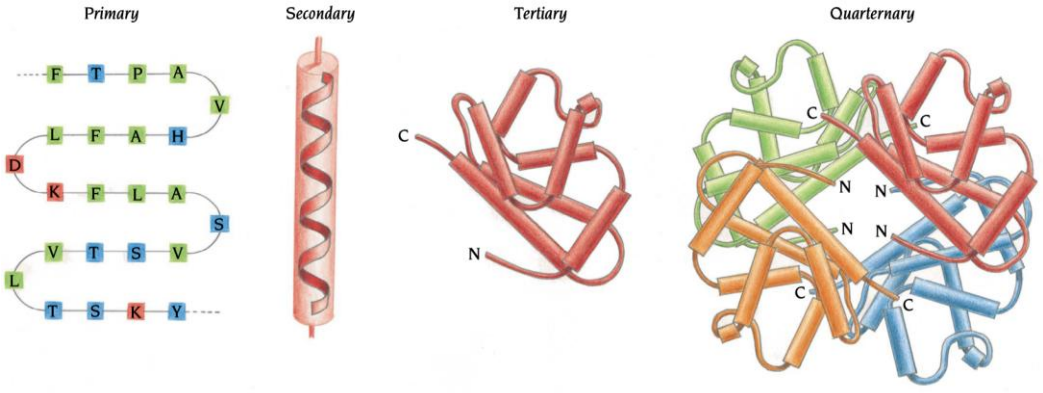
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6 EX1003, ¶ 16.

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

8 EX1003, ¶¶ 36-37.

compact domains that define the protein's overall structure (its "tertiary structure").[9]



For example, secondary structures (α-helices, β-strands) are formed and stabilized by different but characteristic patterns of amino acids (below).[10] "Loops" between sequences defining secondary structures are important too; they direct and facilitate positioning of the various secondary structures into higher-order structural motifs and the protein's overall structure.[11]

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

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

11 EX1003, ¶¶ 43-46; EX1014, 21-22.

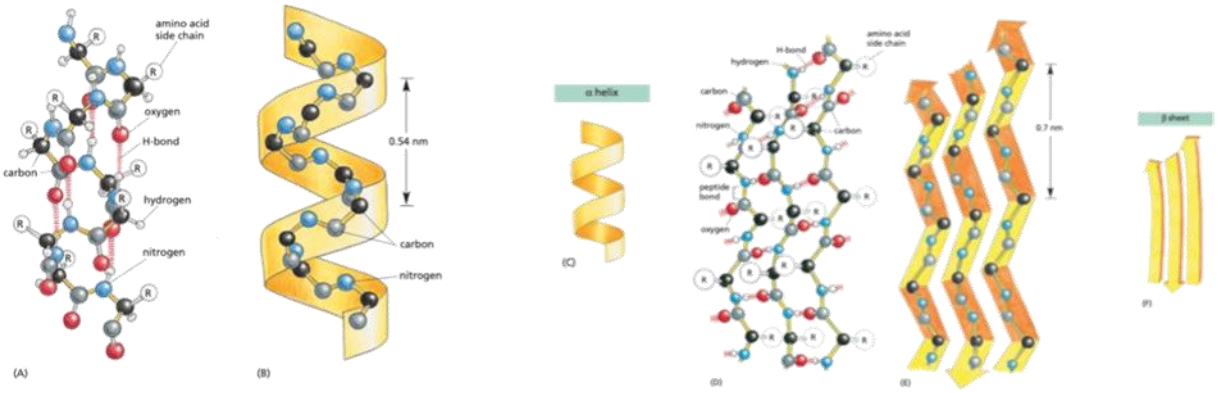


Figure 3–7 The regular conformation of the polypeptide backbone in the α helix and the β sheet. <GTAG> <TGCT> (A, B, and C) The α helix. The N–H of every peptide bond is hydrogen-bonded to the C=O of a neighboring peptide bond located four peptide bonds away in the same chain. Note that all of the N–H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

A PH20 polypeptide must fold into the tertiary structure of the wild-type human PH20 protein to have enzymatic activity.[12] During folding, however, it can adopt an immense number of intermediate conformations, each with different energetic states, which can slow or prevent the polypeptide from properly folding. For example, if the polypeptide does not fold efficiently, it will be degraded by the cell or can form aggregates (below).[13]

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

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

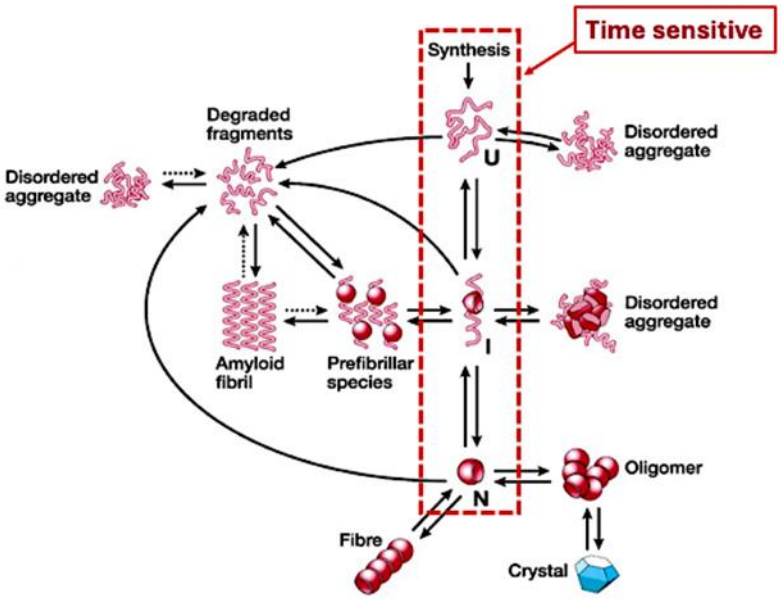


Fig. 5. Schematic representation of some of the states accessible to a polypeptide chain following its synthesis on a ribosome. The relative populations of the different states depend on the kinetics and thermodynamics of the various equilibria shown in the diagram. In living systems the fate of a given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

Changes to an enzyme's amino acid sequence can prevent it from being synthesized, properly folding, and/or remaining folded. Mutations can disrupt secondary structures and higher order motifs necessary to its tertiary structure, alter the spatial positioning of residues required for enzymatic activity or substrate binding, and/or destabilize the enzyme's structure.[14] Unstable proteins can unfold,

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

misfold and/or form aggregates.[15] Even a single modification can cause these effects.[16]

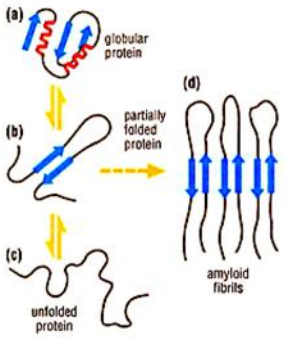


Figure 4-53 A possible mechanism for the formation of amyloid fibrils by a globular protein The correctly folded protein **(a)** is secreted from the cell. Under certain conditions, or because it contains a mutation, the protein unfolds partially **(b)** or completely **(c)**; the unfolded forms can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

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

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15 EX1003, ¶¶ 48, 52, 83, 195.

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

17 EX1003, ¶¶ 58, 73-75; EX1157, 808.

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

2. Hyaluronidase Enzymes

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

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

19 EX1003, ¶¶ 46, 75-78, 80.

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

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

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

23 EX1003, ¶ 119; EX1008, 819.

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

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

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

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

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

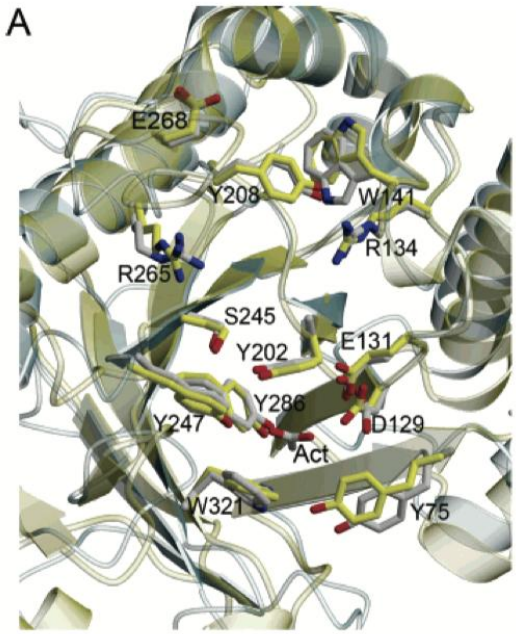
26 EX1011, 812-14; EX1010, 9435-39 (Table 1).

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

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

29 EX1006, 6914-18.

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



Among Chao's findings was that human hyaluronidases (including PH20) contain "a novel, EGF-like domain" in their C-terminal region[31] that is "closely

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

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

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

3. Protein Engineering

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

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

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

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

[35] EX1003, ¶¶ 59-61.

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

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

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

"Directed evolution" techniques arose due to the limits of rational design.[40] They use "trial-and-error" experiments to find mutants with randomly distributed changes that exhibit desired properties, but require creation and screening of large libraries of mutants, each with one amino acid randomly changed at one position in its sequence.[41] Importantly, until a desired mutant is made, found, and tested, whether it exists and its sequence are unknown.[42] The disclosure embodies this approach.[43]

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38 EX1003, ¶¶ 105-106, 132-133.

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

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

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

42 EX1003, ¶ 66.

43 EX1003, ¶¶ 68-71, 239-240, 253-54.

B. Person of Ordinary Skill in the Art

In 2011-2012 (*i.e.*, the filing date of the ’731 Application and the provisional applications incorporated-by-reference thereto), a POSA would have had an undergraduate degree, a Ph.D., and post-doctoral experience in scientific fields relevant to study of protein structure and function (*e.g.*, chemistry, biochemistry, biology, biophysics). From training and experience, the person would have been familiar with factors influencing protein structure, folding and activity, production of modified proteins using recombinant DNA techniques, and use of biological assays to characterize protein function, as well as techniques used to analyze protein structure (*i.e.*, sequence searching and alignments, protein modeling software, etc.).[44]

C. Prosecution History

During examination, the claims of the ’656 Patent were rejected for indefiniteness, improper dependent claims, and obviousness-type double patenting (“ODP”) over Application No. 15/226,489 and U.S. Patent No. 9,447,401.[45] To overcome the rejections, the claims were amended and a terminal disclaimer was

[44] EX1003, ¶¶ 12-13.

[45] EX1002, 446-452.

filed.[46] The prosecution history contains no indication that the Examiner considered written description or enablement issues, or whether the '656 Patent was entitled to a benefit date earlier than its filing date.

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

D. The Challenged Claims

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

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46 *Id.*, 490-505, 517-519.

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

48 EX1026, 50:31-32; 54:5-8.

49 EX1003, ¶¶ 201-204.

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

A clear understanding of the ***breadth*** of the claims also is important. Each claims an unknown (and unknowable) number of "active" mutants that are within a massive "sequence space" of between 10^{59}-10^{113} different amino acid sequences. Because the disclosure does not identify—much less describe and enable—those claimed "active" PH20s, the claims are not supported under § 112(a).

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

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

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

- ***must*** contain one ***amino acid replacement at position 309***; and
- ***may*** contain additional modifications, provided each polypeptide retains ***at least 91% sequence identity*** to one of 37 unmodified sequences (SEQ

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

[51] EX1003, ¶¶ 194-97.

ID NOS: 3, 7, and 32-66), ranging in length from 430 (SEQ ID NO: 32) to 474 residues (SEQ ID NO: 7).

Assuming use of the longest-recited unmodified SEQ ID in each claim, those parameters translate into between 10^{59}-10^{113} possible sequences (below):[52]

Claims	Max Length	Seq. Id. %	Max Changes	Pos. 309 Choices	# of Distinct Polypeptides
1, 14, 17-20, 22-23	474	91	42	19	1.20×10^{113}
2-3	474	95	23	19	9.85×10^{66}
4, 25	465	95	23	19	6.39×10^{66}
5	474	91	42	6	3.79×10^{112}
6	474	91	42	1	6.32×10^{111}
7, 16	465	91	41	1	1.41×10^{109}
8	433	91	38	1	1.00×10^{101}
9	430	95	21	1	4.39×10^{59}
10	433	95	21	1	5.01×10^{59}
11, 21	465	91	41	19	2.68×10^{110}
12	433	91	38	19	1.89×10^{102}
13	430	91	38	19	1.46×10^{102}
15	465	91	41	11	1.55×10^{110}
24	447	95	22	1	3.75×10^{62}

[52] EX1003, ¶ 186.

Importantly, the sequence identity percentage claim parameter imposes ***no constraints*** on the location or nature of modifications (other than one substitution)—it is a ***mathematical*** boundary that captures sequences with up to 21 to 42 modifications, including any combination of: (i) substitutions, each to any of 19 other amino acids, (ii) deletions, and/or (iii) additions (to any of 20 amino acids).[53] With one exception,[54] each modified PH20 can include modifications at ***any*** position(s) in its amino acid sequence–conserved or non-conserved positions, surface or buried residues, within the active site or at substrate binding locations.[55]

2. The Claims Expressly Require "Active Mutants"

The claims are expressly limited to a subset of one of what the disclosure portrays as two mutually exclusive types of modified PH20s: "active mutants" with "increased hyaluronidase activity" (i.e., >100% activity compared to unmodified

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

54 EX1026, 88:29-89:2.

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

PH20).[56] Dependent claim 14 further requires increased hyaluronidase activity that is "at least 120% of the hyaluronidase activity compared to the unmodified PH20 polypeptide." None of the claims encompass "inactive mutants."

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

For claims to be entitled to § 120 benefit of or § 119(e) priority to the filing date of an earlier-filed application, they must be described in and enabled by the disclosures of those earlier-filed applications, as § 112 requires. *See Arthrex, Inc. v. Smith & Nephew, Inc.*, 35 F.4th 1328, 1343 (Fed. Cir. 2022) (citing *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1571 (Fed. Cir. 1997)); *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1158 (Fed. Cir. 1998). If they are not, the claims' effective filing date can be no earlier than the filing date of the application that issued as the patent, and publication of the earlier-filed application can become invalidating prior art. *See, e.g., Indivior UK Ltd. v. Dr. Reddy's Labs. S.A.*, 18 F.4th 1323, 1330 (Fed. Cir. 2021); *Zenon Envtl., Inc. v. United States Filter Corp.*, 506 F.3d 1370, 1381-82 (Fed. Cir. 2007); *Arthrex*, 35 F.4th at 1342-44; *Reckitt Benckiser v. Ansell Healthcare*, IPR2017-00063, Paper 38, 5, 15-16 (P.T.A.B. Jan. 30, 2018).

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[56] EX1001, 299:35-300:44; *id.* at 303:17-304:54, EX1026, 56:24-27 ("increased activity" "means that, when tested under the same conditions, the modified PH20 hyaluronidase exhibits greater hyaluronidase activity…").

That is the situation here. The ’656 Patent claims the benefit of the ’731 Application, which claims priority to and incorporates-by-reference the contents of two provisional applications (61/631,313, filed November 1, 2012 and 61/796,208, filed December 30, 2011). But (as explained below), the claims are not entitled to the filing dates of the ’731 Application or the provisionals, as none of them provides written description and enablement support for those claims. Because the filing date of the claims is not prior to August 2, 2016, US-275, which published on November 14, 2013, anticipates each claim.[57]

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

The written description analysis focuses on the four corners of the patent disclosure.[58] “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

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[57] The provisionals contain less disclosure than the ’731 Application and are equivalently insufficient under § 112. EX1026, 1:3-11, 37:19-51:11, 140:15-150:26, 311:4-321:5, 6:25-26; EX1051; EX1052. The claims also lack § 112 support in the ’656 Patent’s disclosure, which is substantively identical to the ’731 Application (*see* EX1015).

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

sought, he or she was in possession of the invention, and demonstrate that by disclosure in the specification of the patent."[59] If the claims define a genus using functional language, "the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus."[60] "Otherwise, one has only a research plan, leaving it to others to explore the unknown contours of the claimed genus."[61]

"[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

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

60 *Ariad*, 598 F.3d at 1349.

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

the members of the genus.'"[62] "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."[63]

A disclosure that fails to "provide sufficient blaze marks to direct a POSA to the specific subset" of a genus with the claimed function or characteristic does not satisfy § 112(a).[64] "[M]erely drawing a fence around the outer limits of a purported genus" is insufficient.[65]

Four cases are especially probative here.

First, *Novozymes et al., v. DuPont Nutrition Biosciences et al.*, 723 F.3d 1336 (Fed. Cir. 2013) held claims directed to modified enzymes with one substitution, at least 90% sequence identity, and that exhibited "increased

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

63 *AbbVie*, 759 F.3d at 1299-1300.

64 *Idenix*, 941 F.3d at 1164.

65 *Ariad*, 598 F.3d at 1350-54.

thermostability" lacked written description.[66] The Court rejected the premise that written description could be established by combining individual attributes of the enzymes reported in the specification, holding instead the disclosure must describe specific enzyme variants that possess those combinations of attributes.[67] The Court also held that written description cannot be established by a disclosure describing experiments that might discover additional species of mutated enzymes within the genus, but instead "actually making and testing individual variants or at least identifying subclasses of variants that could be expected to possess the claimed properties…."[68] It also found insufficient the patent's "roadmap" for discovering mutant enzymes with the desired functional property (thermostability).[69]

Second, in *AbbVie*, the Federal Circuit found a disclosure of ~300 examples of a similar type of IL-12 antibodies was not representative of a genus of such

66 *Novozymes*, 723 F.3d at 1348.

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

68 *Novozymes*, 723 F.3d at 1350.

69 *Id.*

antibodies of varying types.[70] It also criticized a prophetic description as being "only a research plan, leaving it to others to explore the unknown contours of the claimed genus" using a "trial and error approach."[71]

Third, *Idenix* addressed method of treatment claims using a broad genera of compounds defined by "eighteen position-by-position formulas describing 'principal embodiments' of compounds that may treat HCV," each with "more than a dozen options" at each position (totaling "more than 7,000 unique configurations").[72] The court criticized the specification's failure to indicate which of the thousands of compounds would be effective, finding that "provid[ing] lists or examples of supposedly effective nucleosides," without "explain[ing] what makes them effective, or why" deprives a POSA "of any meaningful guidance into what compounds beyond the examples and formulas, if any, would provide the same result" because they "fail[] to provide sufficient blaze marks to direct a POSA to the specific subset of 2'-methyl-up nucleosides that are effective in treating HCV."[73]

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70 *AbbVie*, 759 F.3d at 1300-01.

71 *Id.*

72 *Idenix*, 941 F.3d at 1158-64.

73 *Id.* at 1164.

Finally, the Board in *Boehringer Ingelheim Animal Health USA Inc. v. Kan. State Univ. Research Found*., PGR2020-00076, Paper 42, 6 (P.T.A.B. Jan. 31, 2022) found unpatentable claims employing "90% sequence homology" language that captured a "broad genus of amino acid sequence homologues" but which (like these claims) imposed no restrictions where particular replacements could be made, thereby covering "at minimum, thousands of amino acid sequences."[74] The Board found fatal the specification's failure to "explain what, if any, structural features exist (*e.g.*, remain) in sequences that vary by as much as 10%" that allow them to retain antigenic characteristics.[75] As it observed, 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).[76]

The deficiencies of the challenged claims dwarf those in the aforementioned cases. They implicate much larger, more unpredictable, and more diverse sets of sequences, and the '731 Application's disclosure is far more limited. Because the '731 Application neither discloses representative species of increased activity

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74 *Boehringer*, at 15-16.

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

76 *Boehringer*, at 35-36.

modified PH20 polypeptides meeting the claim requirements, nor identifies structural features common to such modified PH20 polypeptides, it fails to demonstrate possession of the full scope of the challenged claims.

1. The Disclosure Does Not Describe the Genera Defined by Claims 1-2, 4-16, and 24

Claims 1-2, 4-16, and 24 claim genera of modified PH20 polypeptides exhibiting increased hyaluronidase activity within the claims' sequence identity parameters. But the '731 Application does not identify ***which*** of the 10^{59}-10^{113}+ polypeptides within those claim parameters exhibit increased activity, much less demonstrates possession of all of them. And simply reciting a ***desired*** hyaluronidase activity does not demonstrate possession of these genera. As explained in the sections below:

- the claims define structurally heterogeneous genera of multiply-modified PH20s;
- examples of singly-modified $PH20_{1-447}$ in the disclosure are not representative of the heterogeneity of the claimed genera;
- the disclosure does not identify a common set of structural features that correlates to multiply-modified PH20s with increased activity;
- the disclosure's research plans do not describe any multiply-modified PH20s; and

- the claims capture combinations of modifications the disclosure instructs POSAs to not make.

And in response written description challenges to comparable "activity" claims in its related patents, Patentee statutorily disclaimed (rather than defended) those claims.[77]

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

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

- mutants with up to 20-41 substitutions, deletions, or additions (or combinations thereof), in addition to a required substitution at position 309;
- making sets of modifications anywhere within the PH20 sequence (*i.e.*, clustered in a narrow region, spaced apart in groups, or spread randomly throughout the sequence);
- substitutions that introduce physicochemically different residues, that can be made at surface or buried positions, and that can be arranged in any manner.[78]

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77 *Supra* n.3.

78 EX1003, ¶¶ 180-183, 38-39; EX1026, 68:26-30, 53:1-3, 53:10-11, 46:19-23.

Sequence modifications permitted by the claim language can impair the ability of a mutated PH20 sequence to properly fold into and/or maintain the tertiary structure of PH20 required for activity.[79] For example, the claims permit introduction of a cluster of 5 hydrophobic residues at or near the protein surface, or substitutions resulting in random patterns of polar, charged, aliphatic, and aromatic amino acids. Such changes can prevent formation of or alter secondary structures (α-helices, β-strands), alter loops that position them, alter or prevent formation of higher order motifs and/or domains (*e.g.*, Hyal-EGF), and/or impair functions of structures responsible for substrate binding or catalysis.[80] Nothing in the '731 Application describes whether, or how, ***combination*** of mutations will or will not result in a modified PH20 polypeptide with increased activity.

Also claimed are multiply-modified PH20 polypeptides having up to 17 fewer (430) or 18 more (465) C-terminal amino acids than $PH20_{1-447}$: the only PH20 in which single mutations were tested. But data in applications incorporated-by-reference by the '731 Application show such truncations and additions unpredictably affect activity of wild-type PH20.[81] *See* § V.A.1(c)(iii). The

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79 EX1003, ¶¶ 197-198.

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

81 EX1105, ¶ 362, Tables 6-6A; EX1003, ¶ 144.

disclosure also contains ***no examples*** of single substitutions at positions beyond position 447.[82]

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

(i) Examples Show Unpredictable Effects from Even Single Mutations

The ’731 Application reports results from testing a portion of a library of ~6,753 single-replacement $PH20_{1-447}$ mutants.[83] The mutants were produced by transfecting CHO cells with plasmids encoding mutagenized $PH20_{1-447}$ sequences where one of the 447 positions in the sequence “was changed to one of about 15 amino acid residues, such that each member contained a single amino change.”[84] Substitutions were only investigated in one length of PH20 (*i.e.*, $PH20_{1-447}$) and activities were only reported relative to the unmodified $PH20_{1-447}$ (SEQ ID NO: 3). Approximately 900 of the single mutations made were not classified, about 1,741 (~20%) of the possible single substitutions were never made, and no substitutions were made at positions beyond position 447.[85]

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

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

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

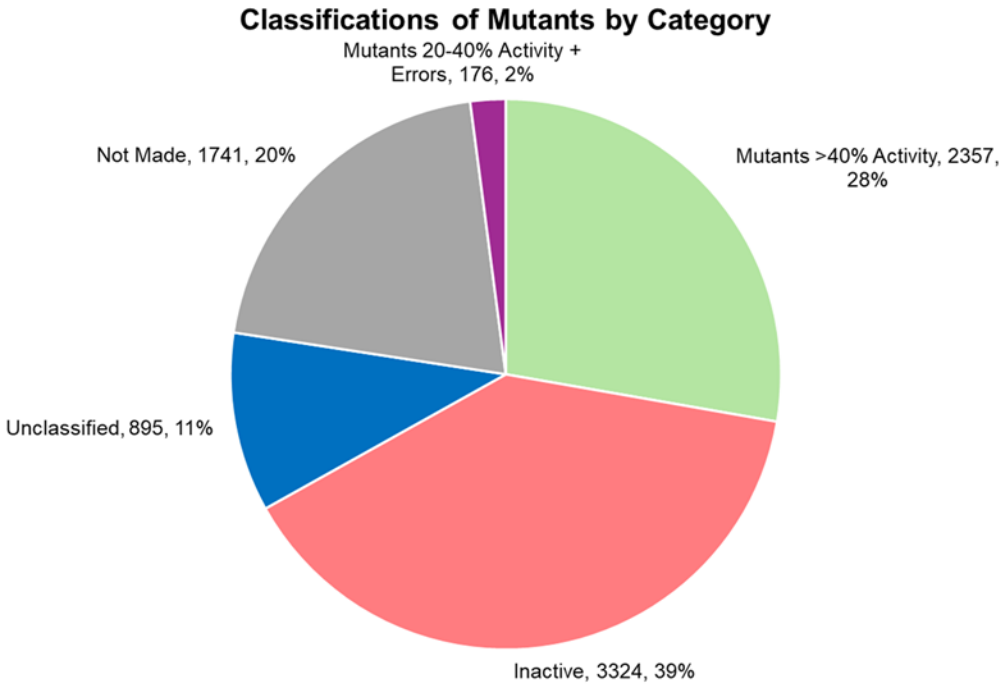
85 EX1003, ¶¶ 151, 218.

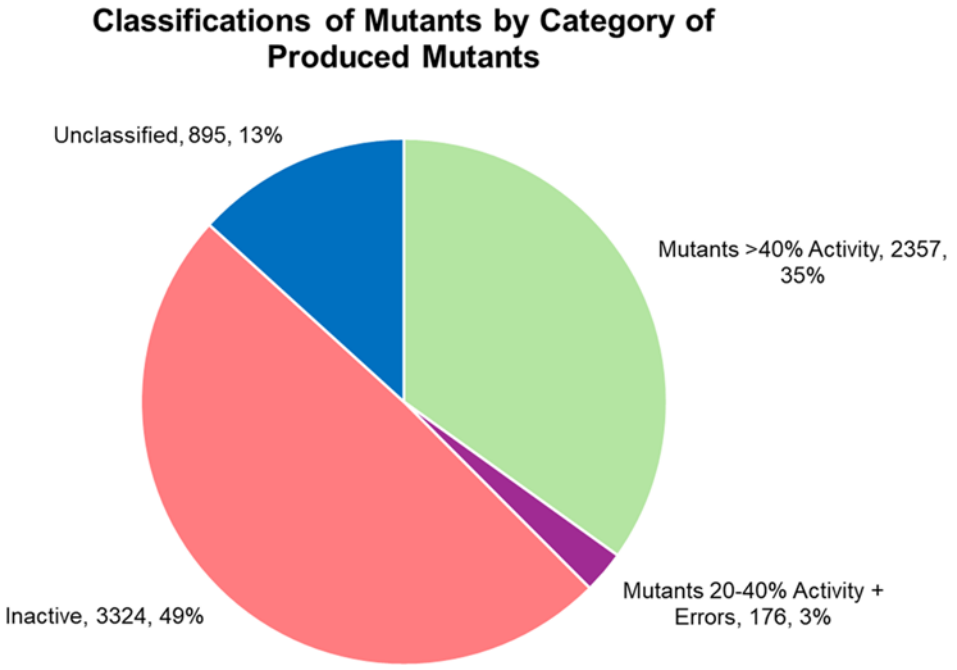
Approximately ~5,917 such mutants were classified as "active" or "inactive" mutants.[86] More than half (~57%) of the tested mutants were classified as "inactive mutants" and ~30% had less activity than unmodified $PH20_{1-447}$ (20%-100%).[87] Thus, per the disclosure, ~87% of the 5,917 single-replacement $PH20_{1-447}$ polypeptides had ***decreased or no*** activity compared to unmodified $PH20_{1-447}$.

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

86 EX1026, Tables 3, 5, 8-10; EX1003, ¶ 163. Inconsistent numbers and classifications of mutants are not explained: (i) Table 3 lists 2,516 single-replacement $PH20_{1-447}$ mutants as "active mutants," but Table 9 identifies only 2,376 mutants that exhibit >40% hyaluronidase activity; (ii) Tables 5 and 10 list 3,368 and 3,380 $PH20_{1-447}$ "inactive mutants," respectively, not accounting for errors.

87 EX1003, ¶ 163; EX1135.


Classifications of Mutants by Category
Mutants 20-40% Activity + Errors, 176, 2%
Not Made, 1741, 20%
Mutants >40% Activity, 2357, 28%
Unclassified, 895, 11%
Inactive, 3324, 39%


Classifications of Mutants by Category of Produced Mutants
Unclassified, 895, 13%
Mutants >40% Activity, 2357, 35%
Inactive, 3324, 49%
Mutants 20-40% Activity + Errors, 176, 3%

(ii) Unpredictable and Unexplained Effects of Single Substitutions

The empirical results reported in the ’731 Application do not provide any guidance to a POSA about ***any particular combinations*** of substitutions to make to yield PH20 polypeptides with increased enzymatic activity. Indeed, the data is not analyzed or interpreted in the ’731 Application at all—it is simply presented.[88] The disclosure also does not describe the effect of any single substitution on the tertiary structure of PH20, much less provide a description that would permit a POSA to predict the effect of particular combinations of substitutions or other modifications.[89]

The disclosure’s data by itself also does not reveal trends or correlations even for single-replacement $PH20_{1-447}$ polypeptides.[90] For example, different substitutions at the same position in $PH20_{1-447}$ yielded active and inactive mutants, and ~900 mutants were not even classified.[91]

88 EX1003, ¶¶ 175-176, 209-210, 214.

89 EX1003, ¶¶ 114, 175-176, 209.

90 EX1003, ¶¶ 173-175, 177.

91 EX1026, Tables 8, 9, 10.

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

POSAs recognized that changing multiple residues in PH20 polypeptides can cause unpredictable interactions within the protein's structure that can impact structure, stability, and function.[92] The empirical test results for single substitution mutants do not identify to a POSA which of the 10^{59}-10^{113}+ PH20 mutants with 21-42 substitutions may have increased activity, or for that matter, exhibit lesser activity, are inactive, or cannot be secreted and properly folded.[93] The data shows that ***most*** single-substitutions were (for unexplained reasons) deleterious to production, secretion, stability, and/or activity of PH20.[94]

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

92 EX1003, ¶ 177, 73-77.

93 EX1003, ¶¶ 172, 210, 213-215.

94 EX1003, ¶¶ 159-163, 175-176.

substitutions in $PH20_{1-447}$ at positions between 430 and 447 can render PH20 inactive.[95] Critically, it does not explain these unpredictable results.[96]

TABLE 5: Inactive Mutants

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

The data's quality is also questionable: in addition to unexplained double-counting errors,[97] no control values or statistical assessments are provided for the primary assay.[98] The disclosure also does not reveal the measured hyaluronidase activities of approximately 3,330 inactive mutants or ~900 unclassified mutants.[99] Measured activities of 17 samples of unmodified $PH20_{1-447}$ are, however, reported in Example 5, and show unusually high variability (*i.e.*, ~40%) (below) in the assay relative to the ~10% variability reported by US-457 for such assays.[100]

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

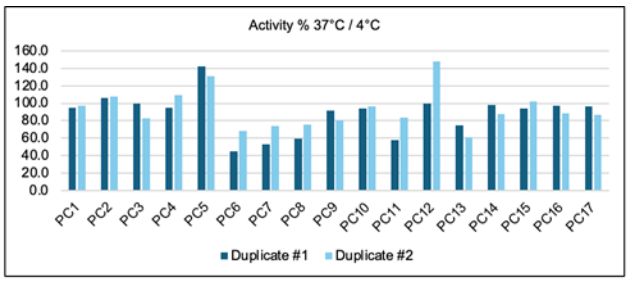
96 EX1003, ¶¶ 98, 173.

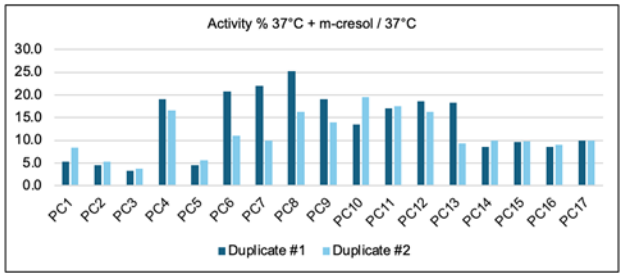
97 EX1003, ¶ 164.

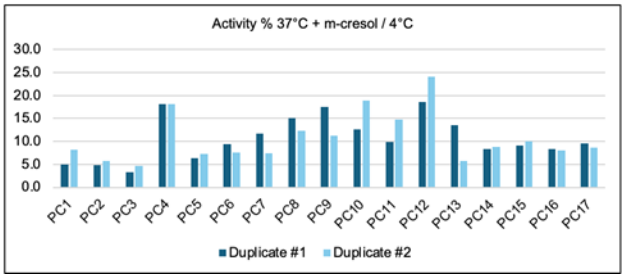
98 EX1003, ¶ 162.

99 EX1003, ¶¶ 159-163.

100 EX1105, ¶ 271.







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

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

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

as the ~3,330 "inactive mutants" for which no measurements are provided; no conclusions can be made about the effects of such mutations on the folding, stability or activity of PH20s.[101]

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

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

(i) Singly-Substituted $PH20_{1-447}$ Active Mutants Are Not Representative of Multiply-Modified PH20s

The '731 Application's disclosure of exemplified species of modified PH20s with increased activity–all of which contains only ***one*** type of modification (a ***single substitution***) in ***one*** truncated PH20 sequence ($PH20_{1-447}$)–does not reflect the structural diversity of the claimed genera of multiply-modified PH20s (§ V.A.1(a)).

[101] EX1003, ¶¶ 167-170; *see also* EX1026, 303:5-12 (positive control also varied); EX1148, 1235.

POSAs would not have expected enzymatically active PH20s with only one substitution to have a structure that is meaningfully different from the wild-type human PH20.[102] By contrast, POSAs would have expected that introducing multiple deletions, additions, and/or substitutions into the PH20 sequence could meaningfully alter portions of the PH20 tertiary structure.[103] For example, deletions/additions can shift positioning of residues required for formation or positioning of secondary structures or higher order motifs in PH20s.[104] Introducing combinations of substitutions can change or disrupt secondary structures and higher order structures even if they include one or more substitutions that individually did not impair folding or activity of a PH20.[105] These more significant structural changes within the PH20 also can impair folding, stability, and activity of the PH20.[106]

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

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

103 EX1003, ¶¶ 73-76, 210-213.

104 EX1003, ¶¶ 77-78, 213.

105 EX1003, ¶¶ 73-74, 78-80.

106 EX1003, ¶¶ 52, 58, 78, 90.

substitution may affect the neighbors of the replaced amino acid by (i) introducing a stabilizing interaction, (ii) removing a stabilizing interaction, and/or (iii) introducing a conflicting interaction (*e.g.*, adverse charge or hydrophobicity interactions).[107] A second substitution in that region may reverse some or all of those interactions (or not), and a third substitution may do the same, and so on up to 21 rounds permitted by the narrowest claim (and 42 for the broadest). Many of these types of changes when combined can cause different effects than each change would cause by itself (including long-distance effects) that cannot be predicted from single substitutions in PH20.[108]

Further, POSAs knew that the ability of a protein to properly fold and remain folded is dictated by the combined effects of all of the residues in the protein (and interactions they are involved in).[109] But making multiple changes to the protein's amino acid sequence will alter the net free energy of stabilization of a protein (which dictates whether it remains folded or unfolds) in ways that could not have been predicted by POSAs.[110] Despite this, the '731 Application provides no

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107 EX1003, ¶¶ 72, 75, 97.

108 EX1003, ¶¶ 73-75, 78, 210-212.

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

110 EX1003, ¶¶ 51-53.

information on structural effects of any of the single substitutions, much less sets of substitutions, or deletions/additions of amino acids.[111]

POSAs would thus not view single substitutions in active $PH20_{1-447}$ to reflect the structural and functional diversity of the enzymatically active PH20s having multiple changes, including those with numerous deletions, additions, and/or sets of substitutions.[112]

(ii) The '731 Application Discourages Multiply-Modified Active PH20s with Substitutions that Individually Render $PH20_{1-447}$ Inactive

The '731 Application instructs POSAs to not include in enzymatically active multiply-modified PH20 polypeptides substitutions that as single substitutions rendered $PH20_{1-447}$ inactive:

> ***To retain hyaluronidase activity***, modifications typically ***are not made*** at those positions that are less tolerant to change or required for hyaluronidase activity.[113]

It identifies these changes as: (i) ***any*** substitution at 96 different positions in the PH20 sequence, and (ii) ***313 specific substitutions*** in Tables 5 and 10.[114] The

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

112 EX1003, ¶¶ 97, 210-211, 219, 222.

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

114 EX1026, 91:31-92:20.

disclosure does not limit this observation to single-replacement $PH20_{1-447}$ mutants. It also does not identify exceptions to this guidance, such as particular combinations of substitutions that both retained and abolished activity in $PH20_{1-447}$ as single substitutions.[115]

A POSA thus would have understood from the '731 Application's disclosure that enzymatically active multiply-modified PH20 polypeptides (including those with increased activity) should not contain substitutions that, as single substitutions in $PH20_{1-447}$, resulted in "inactive mutants."[116] Logically, the '731 Application describes ***no examples*** of modified PH20s with such combinations. And despite this, the claim language does ***not*** explicitly exclude modified PH20 polypeptides having (i) one or more of the substitutions listed in Tables 3 or 9 ("active mutants"), plus (ii) one or more of the substitutions in Tables 5 and 10 ("inactive mutants").

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

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

115 EX1003, ¶¶ 226, 229.

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

none.[117] But the activity of C-terminal truncation mutants terminating between positions 430 and 465 varies unpredictably, particularly those terminating between positions 430-442 and 449-465 (below).[118] For example, the $PH20_{1-436}$ mutant exhibits ~130% more activity than the $PH20_{1-437}$ mutant, with the latter having only one more residue. Despite this unpredictability, the disclosure describes no examples of modified PH20 polypeptides other than ones terminating at position 447, and no examples of any mutants with single substitutions above position 447.[119] There is also no explanation in the disclosure or the prior art for this variability, or any structural characterization of this region of the PH20 protein in the disclosure or the prior art.[120]

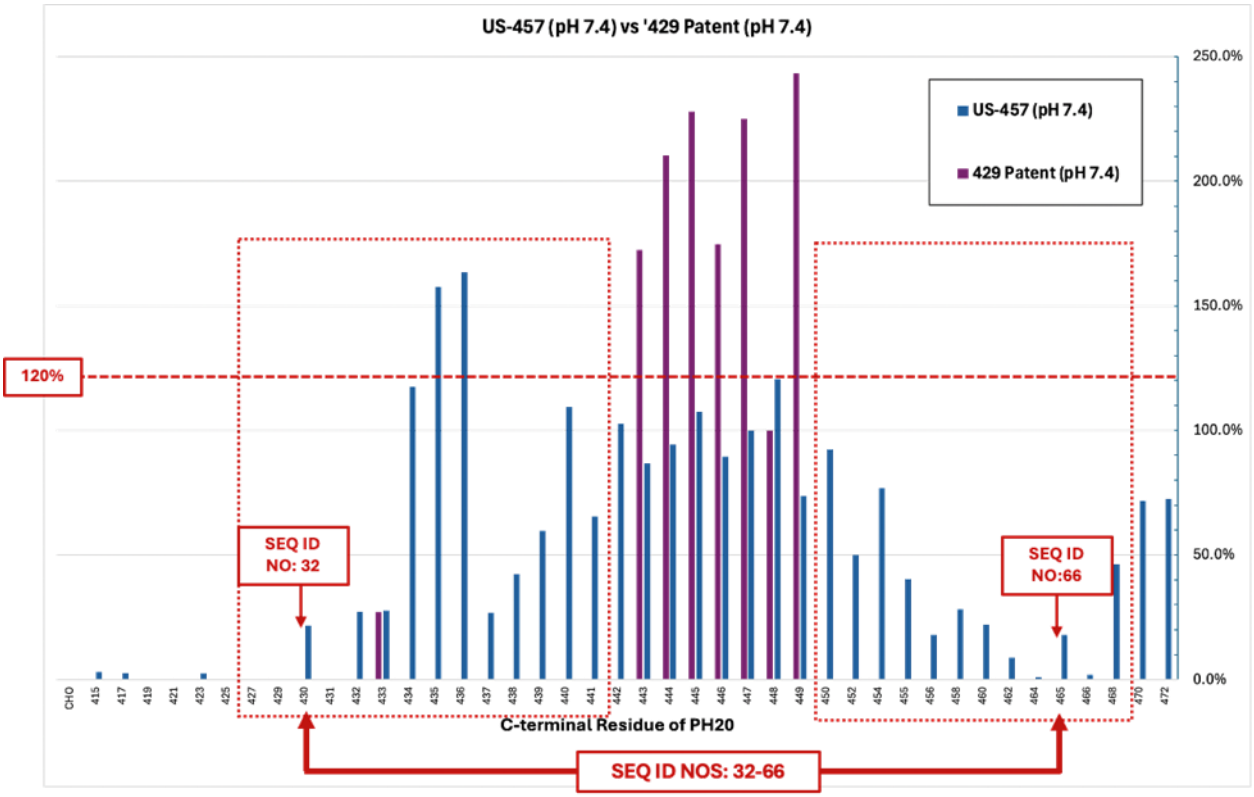
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117 EX1003, ¶¶ 151, 211-212, 218, 240; EX1026, 84:21-25.

118 *See* § V.A.1(a); EX1005, 87:52-88:24 ($PH20_{1-442}$ activity "decreased to approximately 10%"); EX1013, Fig. 2, 430-432 ("[l]ess than 10% activity was recovered when constructs terminated after amino acid 467 [432] or when using the full-length PH20 cDNA"); EX1003, ¶¶ 142-149.

119 EX1003, ¶¶ 143-144.

120 EX1003, ¶¶ 147-148, 151.

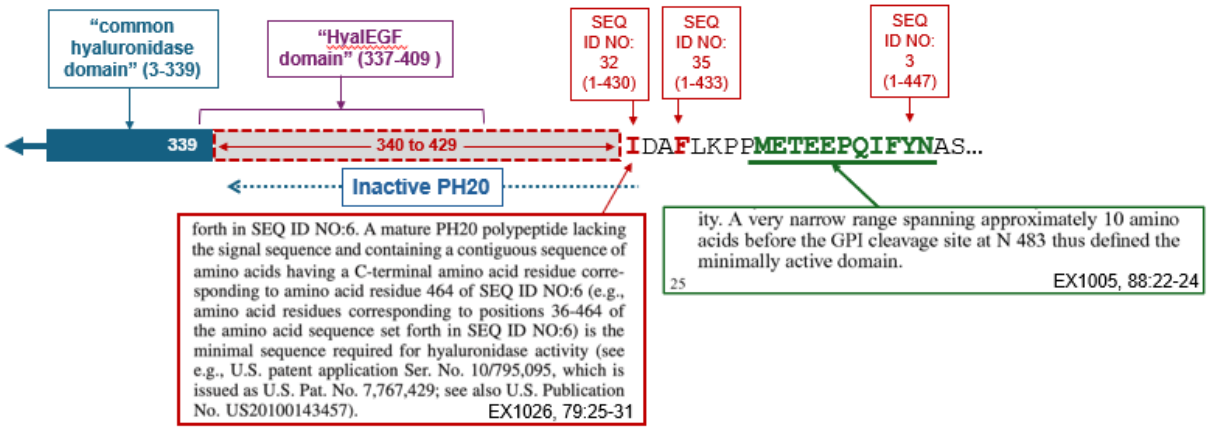


Compounding these deficiencies, the sequence identity language permits deletions to positions before position 430 and additions past position 465. But the disclosure portrays the sequence 1-429 as being necessary for enzymatically active PH20s, and inclusion of residues in the GPI anchor sequence causing PH20s to be insoluble.[121]

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

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

sequences, which runs from positions 337-409 in PH20.[122] In 2009, Zhang showed the Hyal-EGF domain was necessary for hyaluronidase activity—truncations terminating at position 409 of Hyal-1 were inactive and not secreted.[123] While the '731 Application references a "common core hyaluronidase domain" (3-339 in PH20), it make no mention of Chao or Zhang or their findings, and does not explain how positions 3-339 relate to any feature in the tertiary structure of human PH20.[124] These regions are illustrated below.



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

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

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

124 EX1003, ¶ 140.

between position 430 and 465.[125] It provides no examples of singly- or multiply-modified PH20 polypeptides truncated to positions before 430, between 430-446, between 448-465, or above position 465, much less ones with increased activity,[126] even though the claims capture such mutants.[127]

(iv) Disclosure Does Not Demonstrate Possession of Multiply-Modified PH20s With Increased Activity

As explained above, the '731 Application reports no examples of ***modified*** PH20 polypeptides with ***different lengths*** (*i.e.*, SEQ ID NOS: 7, 32-66) or with ***more than one substitution***.[128] Thus, despite claiming variants in PH20s having between 430 (SEQ ID NO: 32) and 465 (SEQ ID NO: 66) residues, and having between 2 and up to 23 changes, all of the examples in the disclosure contain only a single substitution in a single length of PH20 (1-447) (illustrated below). Thus, like *Abbvie*, the disclosure demonstrates possession of only a limited number of species found in one corner of an immense genus of modified PH20 polypeptides being claimed.

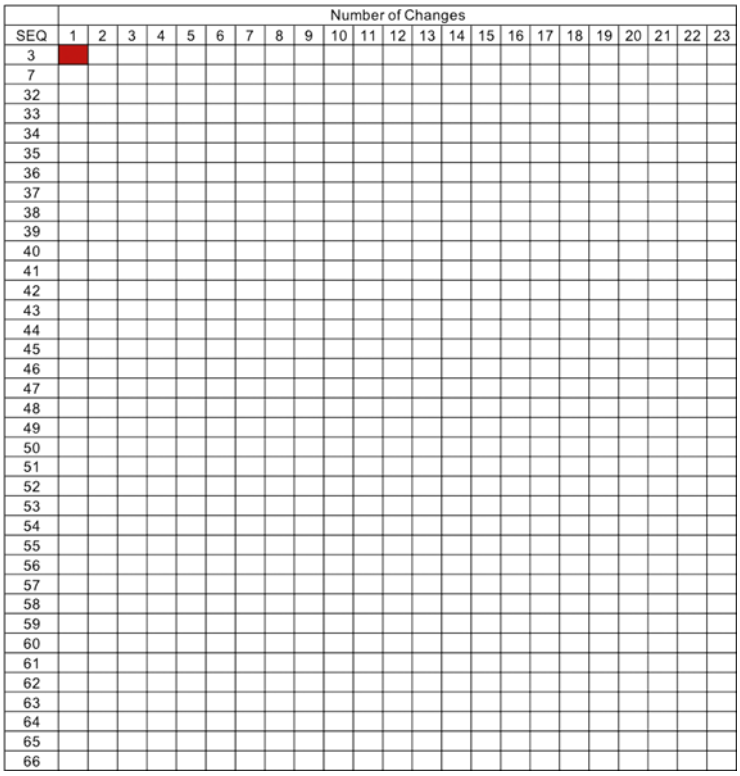
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125 EX1003, ¶¶ 149-151.

126 EX1003, ¶¶ 231, 234.

127 EX1003, ¶¶ 232-233.

128 EX1003, ¶ 231.



The disclosure also does not describe the impact of any single substitution on particular regions of the PH20 tertiary structure, much less to extrapolate results to suggest particular combinations of substitutions or other modifications.[129]

[129] EX1003, ¶¶ 114, 175-176, 209.

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

The '731 Application does not describe ***any*** multiply-modified "active" PH20 polypeptides (including those with increased hyaluronidase activity).[130] Instead, it simply presents ***the idea*** that multiply-modified PH20 polypeptides can be made that ***may*** have increased activity.[131]

The '731 Application posits 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."[132] It also contends a modified PH20 polypeptide with "a sequence of amino acids that exhibits" between 68% and 99% sequence identity with any of unmodified SEQ ID NOS: 74-855 "***can*** exhibit altered, such as improved or increased, properties or activities compared to the corresponding PH20 polypeptide not containing the amino acid modification (*e.g.*, amino acid replacement)."[133]

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

131 EX1003, ¶ 240.

132 EX1026, 54:8-14.

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

None of these statements ***identify any particular*** multiply-modified PH20 polypeptides (*i.e.*, PH20 polypeptides with specific sets of 2 or more amino acid substitutions) that will properly fold and exhibit >100% activity. They simply draw boundaries around immense numbers of sequences, or list optional substitutions that may be considered for combination. Neither is an adequate description of ***particular species*** of chemical compounds (PH20 proteins).[134]

The '731 Application does not describe ***any*** multiply-modified, enzymatically active PH20 polypeptides that were made and tested.[135] It provides only a prophetic research plan requiring "iterative" production of libraries of mutants, followed by screening that ***might discover*** such PH20 polypeptides, stating they "***can be*** modified or further modified" and "***can be*** identified."[136] This research plan does not identify ***which*** multiply-modified PH20 polypeptides can be

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

[135] EX1003, ¶¶ 212, 220-221, 234, 254.

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

made (*e.g.*, which fold and are secreted), which ***are*** active mutants, and which active mutants have ***increased activity*** compared to wild-type PH20.[137]

An alternative version of this "iterative" methodology suggests mutations ***can be*** "targeted near" "critical residues" which supposedly "***can be*** identified because, when mutated, a normal activity of the protein is ablated or reduced."[138] But Tables 5 and 10 report at least one substitution at each of 405 positions between positions 1 and 444 of $PH20_{1-447}$ resulted in an inactive mutant.[139] This guidance to "target" locations "near" ~90% of the amino acids in $PH20_{1-447}$ effectively "targets" ***every residue***.[140]

These prophetic research plans, based entirely on unfocused, iterative "make-and-test" experiments, do not identify to a POSA which of the 10^{59}-10^{113}+ multiply-modified PH20 polypeptides within the claims' sequence space ***are*** active.[141] Instead, they require a POSA to perform repeated cycles of mutagenesis,

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

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

139 EX1003, ¶ 249.

140 *Id.*

141 EX1003, ¶¶ 251, 253-254.

screening and selection until 10^{59}-10^{113}+ modified PH20 polypeptides are made and tested.[142] That in no way demonstrates possession of the ***full scope*** of increased activity modified PH20 polypeptides being claimed.

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

The '731 Application does not identify the structural significance of any of the ~2,500 mutations that yielded single residue "active mutant" $PH20_{1-447}$ polypeptides (or the ~800 mutations that exhibited increased activity).[143] Its data is also ***incapable*** of providing such structural insights for the ~3,400 inactive mutants and ~900 unclassified mutants.[144] For example, it does not identify the effect of any substitution on any domain structure, structural motif(s), or secondary structure at the site of the substitution, nor does it identify how any such (possible) structural change(s) is/are responsible for the measured change in hyaluronidase activity.[145] Instead, it simply lists ***single*** replacements that yielded "active

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

143 EX1003, ¶¶ 208-219.

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

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

mutants."[146] Notably, the '731 Application does not identify any ***sets*** of substitutions in a single PH20 polypeptide that correlate to changes in structural domains or motifs that positively influence hyaluronidase activity, much less ***predictably*** increase activity.[147] And the disclosure's examples of "active mutant" single-replacement $PH20_{1-447}$ mutants ***by themselves*** do not identify any "structure-function" relationship between "active mutants" and the set of single-replacement modified $PH20_{1-447}$ polypeptides, much less for mutant PH20 polypeptides of varying lengths with between 21 and 42 substitutions.[148] Each is a unique sequence with a unique measured result.

The '731 Application ***does not contend*** a particular amino acid replacement that makes $PH20_{1-447}$ an "active mutant" will make any other modified PH20 polypeptide with that replacement plus 20-41 additional substitutions also exhibit increased activity.[149] 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

146 EX1026, 251:2-20; EX1003, ¶¶ 214.

147 EX1003, ¶¶ 220-223.

148 EX1003, ¶¶ 208-219.

149 EX1003, ¶¶ 97, 211-212.

sequence.[150] Thus, the '731 Application does not portray its compilation of empirical test results as identifying a structure-function relationship for multiply-modified "active mutants" within the claims' sequence space of 10^{59}-10^{113}+ polypeptides.[151]

The '731 Application does not identify any particular structural features in the tertiary structure of native human PH20 as being "common structural features" of modified PH20 polypeptides with increased activity, and the human PH20 structure was not published until 2024.[152] It omits any discussion of the PH20 Hyal-EGF domain or its necessity for activity, and does not describe the active site relative to other features of the tertiary structure of mammalian hyaluronidases.[153] It also does not correlate any regions of the PH20 sequence to any such structural motifs.[154] And it nowhere mentions using a PH20 homology model to select combinations of changes to make that yield increased activity PH20s.[155]

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150 EX1003, ¶¶ 73-78, 198, 218.

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

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

153 EX1008, 824, 829; EX1006, 6913.

154 EX1003, ¶ 216, 222-223, 191-193.

155 EX1003, ¶¶ 209, 216-217.

The ’731 Application thus does not identify to a POSA the ***structural features*** shared by the claimed multiply-modified PH20 polypeptides having increased hyaluronidase activity within the scope of the claims.[156]

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

The ’731 Application instructs that certain changes are to be avoided in active mutant PH20 polypeptides (*i.e.*, substitutions listed in Tables 5/10 or C-terminal truncations before position 429).[157] It also provides no guidance on incorporating substitutions in an inactive mutant having one of the substitutions in Tables 5 or 10 that would fully restore—and increase—enzymatic activity.[158] Yet the claims purport to capture such increased-activity multiply-modified PH20 polypeptides having changes the disclosure says to omit from “active mutants” (if any exist).[159]

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

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

158 EX1003, ¶ 226-229.

159 EX1003, ¶ 229.

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

2. The '731 Application Does Not Describe the Subject Matter of the Remaining Dependent Claims

(a) Claim 3

Claim 3 requires the claimed modified PH20 polypeptides to be "soluble." In related PGR proceedings, Halozyme statutorily disclaimed such "soluble" claims in response to Merck's § 112(a) challenges.[160] That is not surprising, as determining whether a modified PH20 is "soluble" in the meaning of the disclosure requires making and testing it.

Initially, the '731 Application does not provide written description support for claim 3 for the same reasons identified in § V.A.1.

The '731 Application also does not identify ***which*** of the 10^{59}-10^{113}+ modified PH20 polypeptides in the claims' sequence space exhibit ***both*** increased activity ***and*** solubility. Solubility is not a characteristic that can be predicted solely

[160] *Supra* n.3.

from a modified PH20's sequence.[161] Instead, it depends on the effects of modifications (individually or collectively), and whether they cause structural changes that expose hydrophobic patches, which often renders a protein insoluble.[162] As the '731 Application explains, "a soluble PH20 refers to a polypeptide characterized by its solubility under physiological conditions,"[163] and solubility is determined by making and testing each modified PH20 polypeptide.[164] Because it is impossible to do that for the full sequence space of the claims, the '731 Application cannot demonstrate possession of the genera of claim 3.

Claim 3 also lacks written description because it encompasses modified PH20 polypeptides the '731 Application suggests would be insoluble. It explains that "a soluble PH20 lacks all or a portion of a glycophosphatidyl anchor (GPI) attachment sequence," which was known to be hydrophobic,[165] and identifies position 456 as the first residue of the GPI sequence in PH20 (position 491 in SEQ

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161 EX1003, ¶¶ 262-263.

162 EX1003, ¶¶ 98, 41; EX1014, 99, 117; EX1081, 897.

163 EX1026, 51:18-19, 52:1-5; EX1028, 1604-1605.

164 EX1026, 52:8-9, 84:6-11, 195:13-22; EX1003, ¶¶ 262-64.

165 EX1026, 51:19-21, 82:8-10, 82:24-31, 84:32-85:3; EX1005, 86:18-22; EX1003, ¶¶ 257-259.

ID NO: 6).[166] It also states that a soluble PH20 "is a polypeptide that is truncated after amino acid 482 of … SEQ ID NO: 6" (*i.e.*, position 447 in SEQ ID NO: 3).[167] The '731 Application thus suggests that human PH20 sequences that terminate below position 448 are soluble while those that terminate above position 456 are insoluble.[168] Claim 3, however, encompasses modified PH20 polypeptides that terminate above position 456. For example, SEQ ID NO: 66 has 465 residues before the up to 21-42 insertions permitted by the claims, and thus includes several residues of the GPI anchor that is described as causing insolubility.[169] The absence of examples of modified PH20s terminating above position 456 compounds these deficiencies.[170]

Claims 3 is unpatentable for these additional, independent reasons.

(b) Claims 17-23 and 25

Dependent claims 17-23 and 25 do not alter the genus of PH20 polypeptides encompassed by claim 1 (addressed above). They instead specify additional

166 EX1026, 82:24-31.

167 EX1026, 85:33-34; EX1005, 3:57-62.

168 EX1003, ¶¶ 258-260.

169 EX1026, 142:19-28.

170 EX1003, ¶¶ 231-235.

features (claims 17-22, 25) or pharmaceutical compositions (23) that reference the genus of claim 1. They lack written description for the same reasons explained in § V.A.1.[171]

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

"If a patent claims an entire class of … compositions of matter, the patent's specification must enable a person skilled in the art to make and use the ***entire*** class," *i.e.*, "the ***full scope*** of the invention," and so the "more one claims, the more one must enable."[172] "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."[173] "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."[174]

Although not required, enablement may be assessed using the *Wands* factors, which consider: "(1) the quantity of experimentation necessary; (2) how

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

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

173 *Idenix*, 941 F.3d at 1159.

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

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."[175]

As here, where the scope of the claims is large, few working examples are disclosed, and the only guidance to practice "the full scope of the invention [is] to use trial and error to narrow down the potential candidates to those satisfying the claims' functional limitations—the asserted claims are not enabled."[176]

"It is well established that the enablement requirement of § 112 incorporates the utility requirement of § 101."[177] A claimed invention must be ***presently useful***—stating a hypothesis and proposing testing to determine its accuracy is insufficient.[178] If a claim encompasses significant numbers of inoperative

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

176 *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).

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

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

embodiments, and a POSA must engage in undue experimentation to identify the operative ones, that renders the claims non-enabled.[179]

Here, the '731 Application utterly fails to enable the claimed genus of increased-activity modified PH20 polypeptides. Using the disclosure and knowledge in the prior art, the POSA would have to make and test $>10^{59}$-10^{113}+ polypeptides within the claims' sequence space to determine which exhibit increased hyaluronidase activity. Such testing would also be necessary to weed out mutants exhibiting increased activity from those that cannot stably fold or be produced.[180] But the scale of that experimentation is beyond undue–it is impossible.

1. Claims 1-2, 4-16, and 24 Are Not Enabled

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

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

180 EX1003, ¶¶ 172, 194-197.

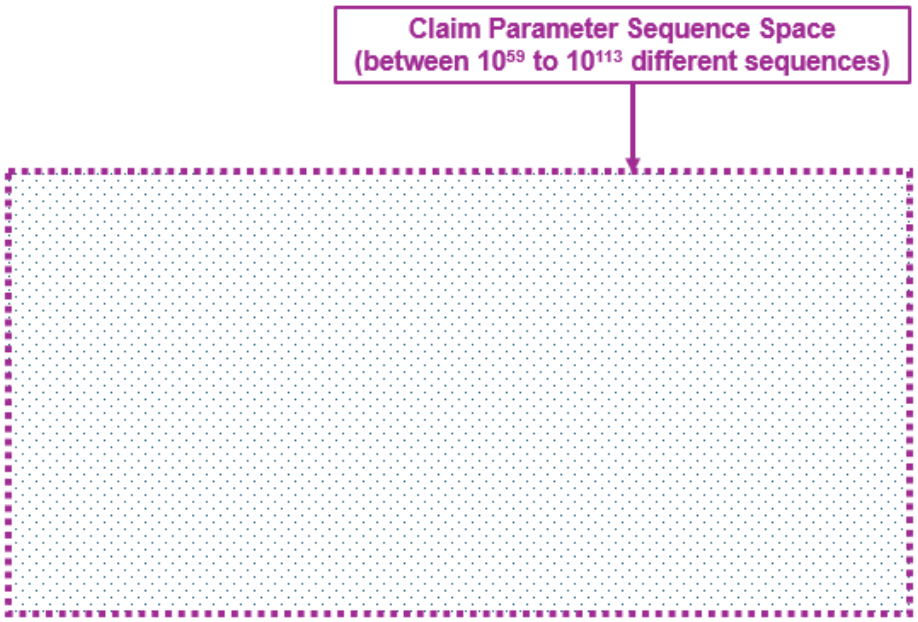
(a) Extreme Scope of the Claims

As explained in § IV.D.1, the claim parameters define a sequence space of between 10^{59}-10^{113}+ distinct amino acid sequences with (i) a required substitution at position 309 and (ii) up to 20 or 41 additional modifications (substitutions, deletions or additions) at any other position within 36 reference PH20 sequences having between 430 (SEQ ID NO: 32) and 474 (SEQ ID NO: 7) residues.

The growth in the sequence space of claim 9 for each additional mutation is illustrated below:

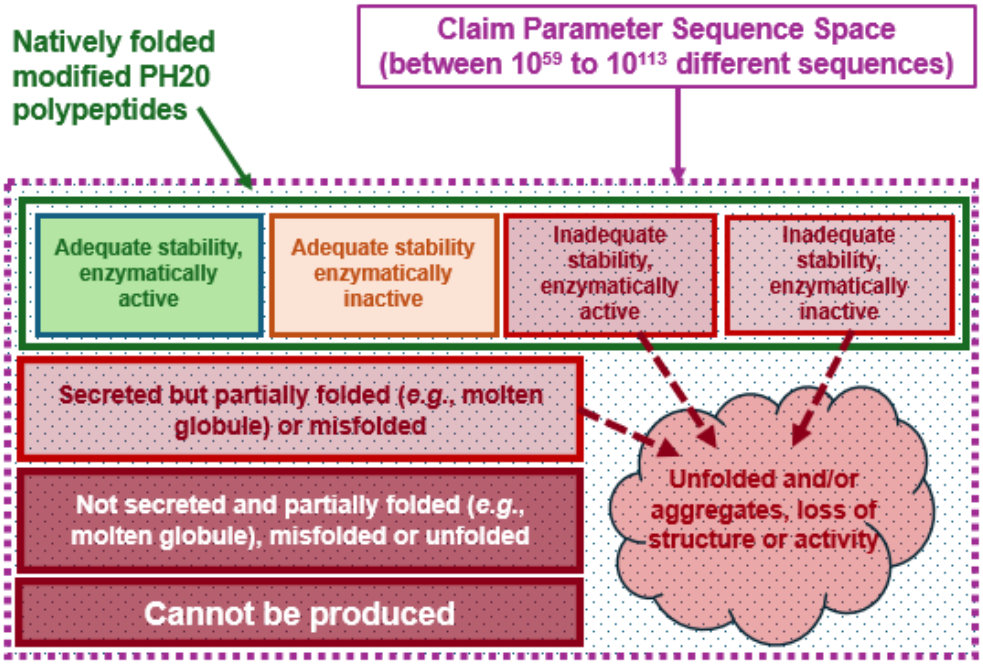
Additional Mutations	Sequences	#	% of Total
1	429	4.29E+02	0.00%
2	91,806	9.18E+04	0.00%
3	13,067,054	1.31E+07	0.00%
4	1,391,641,251	1.39E+09	0.00%
5	118,289,506,335	1.18E+11	0.00%
6	8,359,125,114,340	8.36E+12	0.00%
7	505,129,989,052,260	5.05E+14	0.00%
8	26,645,606,922,506,700	2.66E+16	0.00%
9	1,246,422,279,375,040,000	1.25E+18	0.00%
10	52,349,735,733,751,500,000	5.23E+19	0.00%
11	1,994,049,024,767,440,000,000	1.99E+21	0.00%
12	69,459,374,362,732,700,000,000	6.95E+22	0.00%
13	2,228,043,008,404,580,000,000,000	2.23E+24	0.00%
14	66,204,706,535,450,300,000,000,000	6.62E+25	0.00%
15	1,831,663,547,480,790,000,000,000,000	1.83E+27	0.00%
16	47,394,294,291,065,500,000,000,000,000	4.74E+28	0.00%
17	1,151,402,561,306,470,000,000,000,000,000	1.15E+30	0.00%
18	26,354,325,292,126,000,000,000,000,000,000	2.64E+31	0.00%
19	570,085,668,161,251,000,000,000,000,000,000	5.70E+32	0.26%
20	11,686,756,197,305,600,000,000,000,000,000,000	1.17E+34	100.00%

The sequence space is simplistically illustrated below:



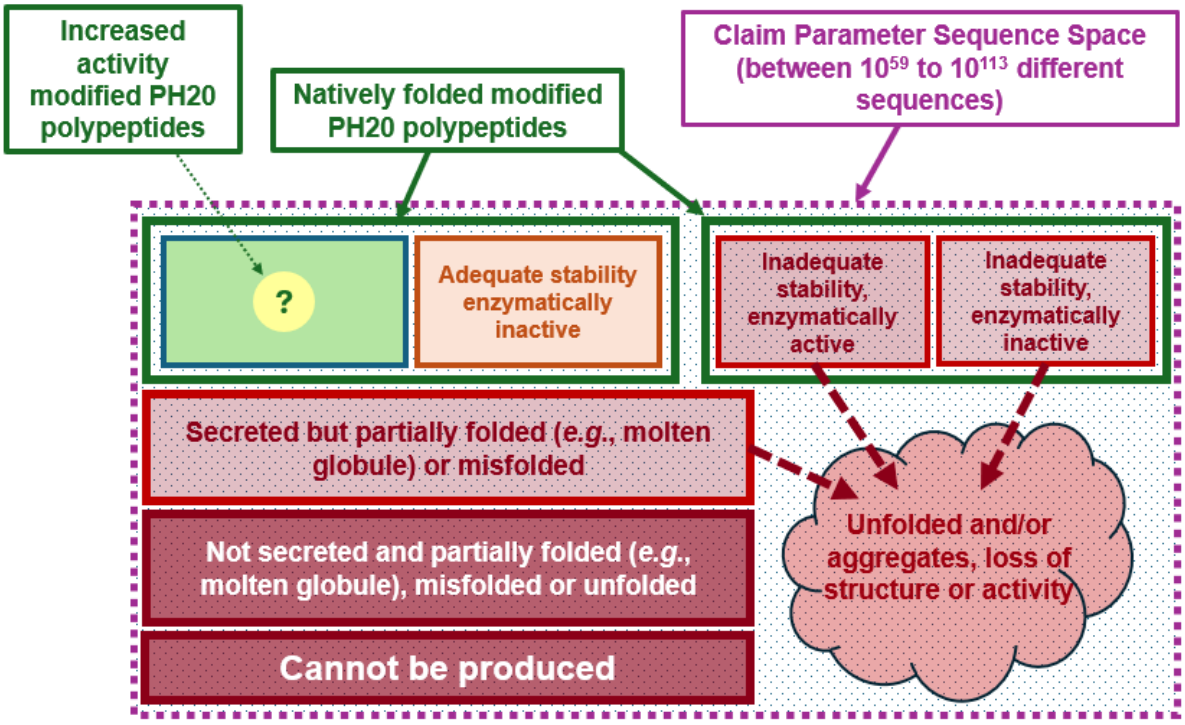
The modified PH20s within that sequence space will exist in a variety of forms, including forms that: (i) never leave the cell because they cannot be produced or secreted, (ii) are secreted but partially folded or misfolded, (iii) are properly folded but unstable. Many of those in the last two categories exist as unfolded and/or in aggregates (below).[181]

[181] EX1003, ¶¶ 172, 195-197; *see also* EX1087, 944.



Multiply-modified PH20 polypeptides with increased activity constitute an unidentified and unknowable portion of the sequence space containing properly folded PH20s (below). Determining what constitutes that portion of the sequence space requires an impossible scale of experimentation.[182]

[182] EX1131, 63:19-64:17; EX1003, ¶¶ 196-197.



Claims that capture massive and structurally diverse sets of proteins such as those here have routinely been found non-enabled. For example, the claims in *Amgen* covered "millions" of different, untested antibodies,[183] while in *Idenix*, the Court found that a POSA would "understand that 'billions and billions' of compounds literally meet the structural limitations of the claim."[184] In both cases (as here), the enormous claim scope was contrasted to limited working examples in the patent, the unpredictability in the field of technology, and the immense quantity of experimentation required to practice the claims' full scope (*Wands* Factors 1, 3,

183 598 U.S. at 603.

184 941 F.3d at 1157.

4, and 7). As in *Idenix*, it is improper to rely on the knowledge and efforts of a POSA to try to "fill the gaps in the specification" regarding which of the "many, many thousands" of possible compounds should be selected for screening, and which in this case is impossible.[185]

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

The '731 Application provides an extremely narrow set of working examples of the claimed PH20s: ~800 single-replacement $PH20_{1-447}$ polypeptides with increased activity, which represents ~13.5% of the single-mutants classified in the '731 Application, and ~9% of the total possible (8,493) single-mutant PH20s.[186] As a percentage of the claimed sequence spaces, it is effectively 0%.

More generally, the examples provide no insights into the effects of combining 5, 10, 15, or 20+ substitutions in one PH20 polypeptide.[187] Similarly, ***none*** of the exemplified PH20 polypeptides is based on a PH20 polypeptide

185 *Id.* at 1159.

186 EX1003, ¶¶ 163, 208. Only 10 of those increased-activity single mutants have a position 309 replacement: I309E, I309G, I309H, I309L, I309M, I309N, I309Q, I309R, I309S, and I309T $PH20_{1-447}$. EX1026, Table 9.

187 EX1003, ¶¶ 209-214, 239.

truncated before position 447 or extending beyond that position, even though activities of such truncation mutants vary extensively.[188]

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

First, the disclosed method requires performing iterative rounds of ***randomized*** mutations (up to 41 rounds per starting molecule under the broadest claims) to ***discover*** which of the 10^{59}-10^{113}+ possible modified PH20 polypeptides in the claims' sequence space might possess increased hyaluronidase activity.[189]

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188 EX1003, ¶¶ 151, 218, 231-234.

189 EX1003, ¶¶ 241-243, 252-254; *see also* EX1018, 382 ("[C]ombinatorial randomization of only five residues generates a library of 205 possibilities (3.2×10^6 mutants), too large a number for manual screening."). Chica credited a "ground-breaking" predictive molecular modeling technique that was later shown to be false. EX1018, 384, 382; EX1030, 569; EX1034, 258; EX1036, 275, 277; EX1048, 859.

Second, the disclosure provides no meaningful guidance or information that a POSA could use to implement the prophetic procedure it discloses for making and discovering modified PH20 polypeptides with increased hyaluronidase activity relative to $PH20_{1-447}$:

(i) it does not identify ***any*** specific combination of two or more replacements within any PH20 polypeptide that yield mutants with increased activity;

(ii) it provides no data from testing ***any*** PH20 polypeptide with two or more substitutions; and

(iii) it does not identify the regions or residues in PH20 polypeptides that are "associated with activity and/or stability of the molecule" or "critical residues that are involved in the structural folding or other activities of the molecule" particularly when two or more replacements have been made.[190]

Instead, the disclosure requires the POSA to iteratively repeat its prophetic mutagenesis research plan to make and screen 10^{59}-10^{113}+ multiply-modified PH20 polypeptides to discover which will exhibit increased activity.[191]

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

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

Regardless of whether individual rounds of "iterative" production and screening of PH20 mutants might be considered "routine," the aggregate scale of experimentation required to practice the full scope of the claims goes far beyond undue—it is impossible.[192] For example, screening technologies in the 2011-2012 timeframe could not screen enzyme libraries with more than ~10^9 mutants, a small fraction of the sequence spaces of the claims (*e.g.*, ~10^{59} to ~10^{113}) (below).[193]

Additional Mutations	Sequences	#
1	429	4.29E+02
2	91,806	9.18E+04
3	13,067,054	1.31E+07
4	1,391,641,251	1.39E+09
5	118,289,506,335	1.18E+11
6	8,359,125,114,340	8.36E+12
7	505,129,989,052,260	5.05E+14
8	26,645,606,922,506,700	2.66E+16
9	1,246,422,279,375,040,000	1.25E+18
10	52,349,735,733,751,500,000	5.23E+19
11	1,994,049,024,767,440,000,000	1.99E+21
12	69,459,374,362,732,700,000,000	6.95E+22
13	2,228,043,008,404,580,000,000,000	2.23E+24
14	66,204,706,535,450,300,000,000,000	6.62E+25
15	1,831,663,547,480,790,000,000,000,000	1.83E+27
16	47,394,294,291,065,500,000,000,000,000	4.74E+28
17	1,151,402,561,306,470,000,000,000,000,000	1.15E+30
18	25,354,325,292,126,000,000,000,000,000,000	2.64E+31
19	570,085,658,161,251,000,000,000,000,000,000	5.70E+32
20	11,686,756,197,305,600,000,000,000,000,000,000	1.17E+34

Limits of Screening Technologies in 2011-2012

The disclosure's prophetic and iterative directed evolution techniques thus could not be used by a POSA to identify the sequences of multiply-modified

192 EX1003, ¶¶ 71, 238-240.

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

PH20s that exhibit increased activity until they are made, discovered and characterized.[194]

Patentee may contend that a POSA could make individual increased activity multiply-modified PH20s by selecting particular combinations of single-substitutions that yielded $PH20_{1-447}$ mutants that retained activity. But even if a POSA were to exclude changes at essential or highly conserved positions identified in the prior art,[195] and only make 5 substitutions in each potential mutant, the POSA would still need to perform an impossible scale of assessments of such potential substitution mutants (*i.e.*, ~10^{59}+), and would have no guidance about mutants that incorporate deletions or additions in PH20 variants terminating at positions other than position 447. The POSA thus could not reasonably predict which of those 10^{59}+ combinations of substitutions would properly fold and preserve activity, much less predict which would exhibit increased activity.[196]

194 EX1003, ¶¶ 253-254, 256.

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

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

These "***iterative***, ***trial-and-error process[es]***" are indistinguishable from those consistently found to not enable broad genus claims to modified proteins and other therapeutically active compounds.[197]

(c) Making Multiple Changes to PH20 Polypeptides Was Unpredictable

Like any protein, the activity of PH20 can be unpredictably influenced by even a single change to its amino acid sequence.[198] The data in the '731 Application concerning single substitutions shows these unpredictable effects on activity of PH20s. For example, ~86.5% of tested single mutants reduced activity below 100%.[199] In addition, even at positions where many substitutions retained activity, the amount of that activity varied unpredictably.[200]

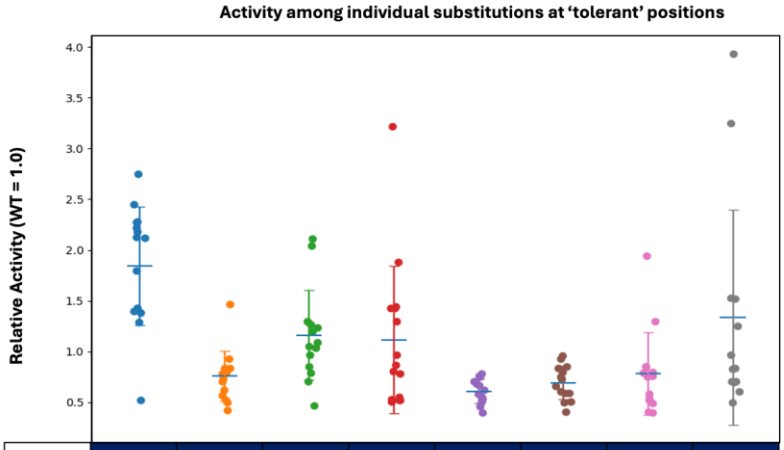
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197 *Idenix*, 941 F.3d at 1161-63 (emphasis added); *see also Amgen*, 598 U.S. at 612-15; *Wyeth*, 720 F.3d at 1384-86; *Baxalta*, 597 F. Supp. 3d at 616-19.

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

199 *See* § V.A.1(b).

200 EX1003, ¶¶ 173-174.



	T74	L146	T147	L26	K28	Q140	N205	K93
Mean activity	1.84	0.76	1.16	1.12	0.61	0.70	0.78	1.33
Std. dev.	0.58	0.25	0.44	0.73	0.12	0.17	0.41	1.06
CV	32%	33%	38%	65%	20%	24%	52%	80%
Tested	15	15	15	15	14	14	14	13
Active (>40%)	15	15	15	15	14	14	14	13

Introducing ***multiple*** modifications (especially within a particular region of the protein) greatly increases this unpredictability. Sets of changes can prevent a modified PH20 from efficiently folding into its native state, or unpredictably affect its stability if it does properly fold.[201] Multiple modifications can alter or transform secondary structures, alter positioning of secondary structures or higher order motifs, or otherwise alter features within the tertiary structure of PH20 that are important to its catalytic and substrate binding functions.[202] Mutations can also cause long-distance effects, and can alter activity even without causing significant

201 EX1131 (Petsko Dep.), 99:4-22.

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

changes in the tertiary structure of the PH20.[203] Combinations thus can introduce an immense number of simultaneous influences on a PH20's structure, the effects of which are unpredictable.[204]

The cumulative effects of multiple changes would have rapidly exceeded the capacity of computer-based protein engineering techniques to reasonably predict changes to the protein's structure in the 2011-2012 timeframe.[205] For example, PH20 models based on the experimentally determined structure of a homologous protein (*e.g.*, Hyal-1) become unreliable after a few changes to the wild-type amino acid sequence and in areas of the model with insufficient quality, and the sole published PH20 homology model was known to be inaccurate by 2007.[206] Also, while homology models can assess effects of a single substitution on the local structure of a protein, they cannot detect steric changes below the resolution of the model, non-steric effects (*e.g.*, long-distance charge or van der Waals effects), nor

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203 EX1003, ¶¶ 76, 178.

204 EX1003, ¶¶ 73-78, 212-213.

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

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

can they predict particular effects on activity.[207] And the disclosure nowhere proposes the use of homology models to guide selections of combinations of changes to a PH20, much less show how to make such selections to yield ≥120% active forms of multiply-modified PH20s.[208]

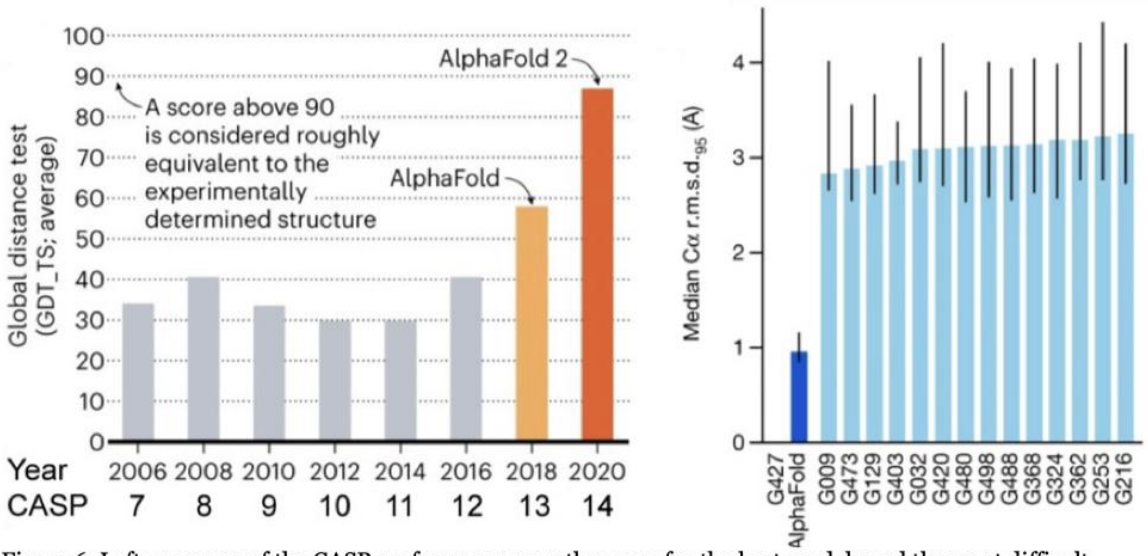


Figure 6. Left: progress of the CASP performance over the years for the best models and the most difficult targets.[38] Right: performance of AlphaFold2 relative to the top 15 entries by other groups in CASP14. Data are the median coordinate error and the 95% confidence interval of the median, estimated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

For all of these reasons, POSAs in the 2011-2012 timeframe could ***not*** have predicted the effects of making more than a few concurrent amino acid replacements within a PH20 polypeptide.[209] Predicting the effects of 10, 15 or 20+

207 EX1003, ¶¶ 105-106.

208 EX1003, ¶¶ 109, 216.

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

modifications in the 2011-2012 on the ability of a PH20 to properly fold, remain stably folded or on its overall activity was impossible.

Consequently, a POSA could not have used rational design techniques or computational tools available in the 2011-2012 timeframe to identify which multiply-modified PH20 polypeptides in the claimed sequence spaces will exhibit increased activity.[210] And using such techniques to identify even a handful of active mutant PH20 polypeptides with more than 1 substitution would have taken an extreme amount of time and effort (*i.e.*, billions of days for even a small subset of the sequence space).[211]

(d) Other Wands Factors and Conclusion

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

For example, while a POSA was highly skilled, the field of protein engineering was unpredictable and tools did not exist that permitted accurate modeling of the range of multiply-changed PH20 polypeptides being claimed.[212] Likewise, while there was significant public knowledge about hyaluronidases,

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210 EX1003, ¶¶ 64, 108, 254-255.

211 EX1003, ¶¶ 64, 240, 254-255.

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

there was no experimentally-determined structure of the PH20 protein.[213] Also, the public literature generally reported on ***loss of activity*** from mutations in hyaluronidases, and did not predictably teach how to introduce changes that ***enhanced*** stability or activity of such proteins.[214]

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

2. The Remaining Dependent Claims Are Not Enabled

(a) Claim 3

Claim 3 requires "soluble" forms of PH20. This claim is not enabled for the same reasons presented in § V.B.1.

Additionally, the '731 Application does not enable the full scope of "soluble" multiply-modified PH20 polypeptides being claimed. As explained in § V.A.2(a), determining whether a modified PH20 polypeptide is "soluble" requires testing.[215] Doing that for even the portion of the claims' sequence space that corresponds to modified PH20 polypeptides with increased activity would

[213] EX1003, ¶¶ 102, 120-122, 126-132.

[214] EX1011, 812-814; EX1010, 9437-9439.

[215] EX1026, 52:8-9, 84:6-11, 195:13-22; EX1003, ¶¶ 259-265.

require an immense amount of such individualized testing, which constitutes undue experimentation.[216]

(b) Claims 17-23, 25

Claims 17-23 and 25 recite further modifications (*e.g.*, glycosylation, polymer conjugation, heterologous signal sequence) to the modified PH20 polypeptides (claims 17-21, 25), inclusion of the modified PH20 polypeptide in a chimeric polypeptide (claim 22), or a pharmaceutical composition comprising the modified PH20 polypeptides (claim 23). These claims do not limit the structure of polypeptides in those claims and are not enabled for the same reasons as claims 1-16 and 24 (*see* § V.B.1).[217]

C. Inactive PH20 Polypeptides Within the Recited Sequence Spaces Underscore the § 112(a) Deficiencies of the Claims

The sequence parameters in the claims capture an unknown number of PH20 polypeptides that exhibit lower hyaluronidase activity than unmodified $PH20_{1-447}$,

[216] EX1003, ¶¶, 264-265; *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.

[217] *See, e.g.*, *Idenix*, 941 F.3d at 1155, 1165.

are "inactive mutants" or cannot be produced or will not fold (and thus have no utility).[218]

The disclosure does not explain how to distinguish modified PH20 polypeptides with increased hyaluronidase activity from the other 10^{59}-10^{113}+ multiply-modified PH20 polypeptides captured by the sequence identity parameters of the claims.[219] Identifying polypeptides that cannot be made or will not properly or stably fold requires trial-and-error testing of the full sequence space of 10^{59}-10^{113}+ multiply-modified PH20 polypeptides.[220]

The disclosure provides scant guidance regarding mutations that may result in an "inactive" mutant. For example, it does not identify why ~3,330 sequences exhibited <20% activity.[221] The experimental protocol incorrectly equates the ***absence*** of hyaluronidase activity in the supernatant from each transfected cell with proof of production of a properly folded but otherwise "inactive" mutant.[222] An absence of hyaluronidase activity in the supernatant could mean different

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218 EX1003, ¶¶ 195-197, 281-288.

219 EX1003, ¶¶ 197, 239-240.

220 EX1003, ¶¶ 196-197, 253.

221 EX1003, ¶¶ 160-161, 215.

222 EX1003, ¶¶ 159-162, 215.

things; it would also be observed if the cell did not secrete the mutant or if the secreted mutant did not fold.[223] However, because no activity measurements are provided for these mutants, it is impossible to determine from the disclosure which of these ~3,330 mutants were (i) actually expressed, properly folded and enzymatically inactive, (ii) were not successfully produced by or secreted from the transfected cells, or (iii) were secreted but did not fold.[224] It also does not even classify ~900 (13%) of the single-substituted $PH20_{1-447}$ polypeptides, likewise rendering it impossible to know what effects these single-substitutions had.[225]

These deficiencies are significant in assessing the enablement and written description requirements. Even if a fraction of a percent of the 10^{59}-10^{113}+ multiply-modified PH20 polypeptides within the claims' sequence space cannot be produced or did not properly fold, they represent a massive absolute number of inoperative and non-useful embodiments that must be identified by making and testing 10^{59}-10^{113}+ polypeptides.[226] Performing the scale of testing necessary to

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223 EX1003, ¶¶ 160-162; EX1026, 251:21-272:1 (Table 9), 272:23-282:2 (Table 10).

224 EX1003, ¶¶ 160-162, 215.

225 EX1003, ¶ 165.

226 EX1003, ¶¶ 197, 199, 215.

identify such inoperative species within the scope of the claims independently demonstrates a lack of enablement.[227]

The disclosure thus presents only a "research proposal" to discover increased activity mutants with multiple modifications, and requires use of a labor and resource-intensive process to sort them from any "inactive mutants" and inoperative mutants having no utility.[228]

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

The original claims of the '731 Application do not demonstrate written description or enablement of increased activity multiply-modified PH20 polypeptides being claimed. Those original claims recited broad genera via sequence identity language (*e.g.,* 85% to SEQ ID NOS: 3, 7, or 32-66) (claims 1-3) or having up to "75 or more amino acid replacements" (claim 4). Certain dependent claims listed single positions (claim 12) or replacements (claims 13-16) in those polypeptides. None of the original claims are supported by an adequate

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

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

written description or enabled by the disclosure, for the reasons set forth in §§ V.A-V.C.

VI. US-275 Anticipates Every Claim of the ’656 Patent

US-275 (EX1004) was published on November 14, 2013, years before the application that issued as the ’656 Patent was filed (June 25, 2020). *See* § V. Thus, US-275 is prior art to the challenged claims under 35 U.S.C. § 102(a)(1) and is not subject to any of the 35 U.S.C. § 102(b) exceptions.

US-275 has a substantively identical disclosure as the ’731 Application.[229] It describes production and testing of single amino acid substitutions in SEQ ID NO: 3 (*i.e.*, $PH20_{1-447}$).[230] US-275 also describes methods and uses of modified PH20 polypeptides that derive from the ability of such modified PH20 polypeptides to degrade hyaluronan, including their use in combination with other therapeutic agents.[231] For example, US-275 explains that enzymatically active modified PH20 polypeptides can be used to increase the delivery and/or bioavailability of subcutaneously administered therapeutic agents.[232] With regard to active mutants,

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229 *See* EX1068, ¶ 20.

230 EX1004, [0603]-[0631].

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

232 EX1004, [0044], [0545].

US-275 specifically highlights the class of ~530 single amino acid substitutions of $PH20_{1-447}$ (which includes I309N-$PH20_{1-447}$) that exhibit ***at least 120%*** of the activity of unmodified $PH20_{1-447}$ (SEQ ID NO: 3).[233]

The modified PH20 polypeptide I309N-$PH20_{1-447}$ is a polypeptide having a single amino acid replacement of isoleucine (I) to asparagine (N) at position 309 of SEQ ID NO: 3.[234] Because I309N-$PH20_{1-447}$ has only a single amino acid replacement relative to SEQ ID NO: 3, it has >91% and >95% sequence identity to SEQ ID NO: 3 (446/447 = 99.8% sequence identity), and 100% sequence identity to SEQ ID NO: 581.[235] The substitution of I to N at position 309 in SEQ ID NO: 3 "confer(s) the increased hyaluronidase activity" observed in I309N-$PH20_{1-447}$ compared to wildtype $PH20_{1-447}$ (SEQ ID NO: 3), as its activity is reported in

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233 *See, e.g.*, EX1004, [0626] (Table 9), pp. 120-138 ("For example, about 536 mutants exhibit 120% or greater than 120% of the hyaluronidase activity of wildtype PH20…"); [0011] ("In some instances, among the PH20 polypeptides provided herein, the modified PH20 polypeptide exhibits at least 120%, 130%...").

234 EX1004, [0606] (Table 8), p. 112; [0626] (Table 9), p. 133 (I309N exhibits 311% relative activity); [0642] (Table 11), p. 147; [0642] (Table 12), p. 152.

235 EX1004, [0622]-[0626].

Example 4 as a 3.11-fold increase (*i.e.*, 311%) compared to $PH20_{1-447}$ (SEQ ID NO: 3), which is greater than a 120% increase, and the 309 substitution is the only modification compared to SEQ ID NO: 3.[236] Example 4 of US-275 reports that the hyaluronidase activity of SEQ ID NO: 3 and each of the single-substitution mutants were measured under identical conditions.[237] US-275's I309N-$PH20_{1-447}$ mutant thus recites every element of, and therefore anticipates, claims 1-2, 4-7, 11, 14-16, and 24.[238]

US-275 also anticipates claim 3 because I309N-$PH20_{1-447}$ meets all requirements of claim 2, and I309N-$PH20_{1-447}$ is a soluble PH20 polypeptide. US-275 discloses that "soluble PH20 polypeptides include any that has the sequence of amino acids set forth in SEQ ID NOS: 3 … or … exhibits at least 85% sequence identity… to … SEQ ID NOS: 3."[239] US-275 further explains that "a soluble human PH20 polypeptide is a polypeptide that is truncated after amino acid 482"

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236 EX1003, ¶¶ 268-70.

237 EX1004, [0622]-[0626].

238 EX1003, ¶¶ 266, 270, 280, Appendix B-14.

239 EX1004, [0250]; *see also id.*, [0016], [0017], [0020], [0116], [0238], [0256]; EX1003, ¶ 271.

(*i.e.*, position 447 without the signal sequence).[240] As noted, I309N-PH20$_{1-447}$ has >85% sequence identity to SEQ ID NO: 3 (99.8%), and is truncated at position 447.[241] As such, a POSA would reasonably believe this single-substitution mutant of PH20$_{1-447}$ is soluble, which anticipates claim 3.[242]

US-275 (and its I309N-PH20$_{1-447}$ increased activity mutant) also anticipates claims 17-23 and 25, which all depend from claim 1.

- US-275 anticipates claim 17 because it discloses that modified PH20 polypeptides, including I309N-PH20$_{1-447}$, can be modified by glycosylation, sialation, albumination, farnesylation, carboxylation, hydroxylation, or phosphorylation.[243] The I309N-PH20$_{1-447}$ mutant was produced in CHO cells, which is known to glycosylate the PH20$_{1-447}$ sequence.[244]
- US-275 anticipates claim 18. US-275 reports that the modified PH20 polypeptides described "can be glycosylated, such as by containing at

240 EX1004, [0251].

241 EX1003, ¶ 269; EX1004, [0606].

242 EX1003, ¶ 271; EX1004, [0015], [0251].

243 EX1004, [0015], [0033], [0115], [0118], [0318], [0383]; EX1003, ¶ 274.

244 EX1004, [0608]; EX1003, ¶ 274.

least one N-acetylglucosamine moiety linked to each of at least three asparagine (N) residues" that "correspond to amino acid residues 200, 333 and 358 of SEQ ID NO: 3," which are unaltered in I309N-PH20$_{1-447}$.[245] Because I309N-PH20$_{1-447}$ is produced in CHO cells, each of those positions will be glycosylated.[246]

- US-275 anticipates claims 19-20 because it teaches attaching a polymer, such as dextran or PEG, to modified PH20 polypeptides, including I309N-PH20$_{1-447}$.[247]
- US-275 anticipates claims 21 and 25 because it teaches that modified PH20 polypeptides, including I309N-PH20$_{1-447}$, "can be joined to a polypeptide-encoding nucleic acid molecule … for example heterologous signal sequences, designed to facilitate protein secretion."[248]

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245 EX1004, [0015], [0033]; EX1003, ¶ 275.

246 EX1004, [0015], [0033], [0608]; EX1003, ¶ 275.

247 EX1004, [0015], [0033], [0192], [0261], [0326]-[0332], [0421]-[0434], claim 22; EX1003, ¶ 276.

248 EX1004, [0371]; *see also id.*, [0384]; EX1003, ¶ 277.

- US-275 anticipates claim 22 because it discloses that modified PH20 polypeptides, including I309N-PH20$_{1-447}$, "can be in a PH20 polypeptide that is a … chimeric polypeptide."[249]
- US-275 anticipates claim 23 because it discloses that pharmaceutical compositions can contain active modified PH20 polypeptides (such as I309N-PH20$_{1-447}$).[250] The claim imposes no requirements of said pharmaceutical compositions–any can satisfy its requirements. As such, US-275 teaches pharmaceutical compositions of I309N-PH20$_{1-447}$.

US-275 also anticipates claims 8, 10, and 12, which require use of SEQ ID NO: 35 (PH20$_{1-433}$) as the unmodified PH20 polypeptide against which sequence identity and increased activity is measured.

As discussed above, I309N-PH20$_{1-447}$, is 96.5% identical to SEQ ID NO: 35 (PH20$_{1-433}$) with 15 changes, including the substitution of N at position 309 and the addition of 14 residues to the C-terminus of SEQ ID NO: 35.[251] Further, US-275 explicitly discloses (or, at a minimum, demonstrates necessarily and inevitably)

[249] EX1004, [0261]; EX1003, ¶ 278.

[250] EX1003, ¶ 279; EX1004, [0036], [0040], [0045], [0434]-[0544].

[251] EX1003, ¶ 272.

that I309N-PH20$_{1-447}$ has increased activity compared to SEQ ID NO: 35's PH20$_{1-433}$. In Example 4, US-275 discloses that I309N-PH20$_{1-447}$ exhibited 3.11-fold (*i.e.*, 311%) compared to the wildtype PH20$_{1-447}$ (SEQ ID NO: 3).[252] US-457,[253] which is expressly incorporated-by-reference into US-275,[254] likewise establishes that SEQ ID NO: 3 (PH20$_{1-447}$) has increased activity compared to unmodified SEQ ID NO: 35 (PH20$_{1-433}$).[255] For example, the table below compares the hyaluronidase activity at pH 7.4 (1) disclosed in US-457 for SPAM1-IDAF (SEQ ID NO: 84), which has the same amino acid sequence as SEQ ID NO: 35 of US-275 and the '656 Patent, (2) disclosed in US-457 for SPAM1-QIFY (SEQ ID NO: 70), which

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

253 EX1105, US2010/0143457 ("US-457").

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

255 *See Arbutus Biopharma Corp. v. ModernaTX, Inc.*, 65 F.4th 656, 662–63 (Fed. Cir. 2023) (quoting *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000) ("When a reference or material from various documents is incorporated, they are effectively part of the host document as if they were explicitly contained therein.") (internal quotations omitted)).

has the same amino acid sequence as SEQ ID NO: 3 of US-275 and the '656 Patent, and (3) disclosed in US-275 for I309N-PH20$_{1-447}$.[256]

Mutant	pH 7.4 Activity Units/ml	Activity Normalized to PH20$_{1-447}$
PH20$_{1-433}$	0.5625	27.7%
PH20$_{1-447}$	2.03175	100%
I309N PH20$_{1-447}$	-	311%

Thus, as shown above, US-275 establishes that I309N-PH20$_{1-447}$ has increased activity (over 11-fold) compared to SEQ ID NO: 35. From this data, a POSA would have readily understood that the I309N substitution confers increased activity reported relative to unmodified PH20$_{1-447}$ (SEQ ID NO: 3) and PH20$_{1-433}$ (SEQ ID NO: 35).[257] US-275's I309N-PH20$_{1-447}$ therefore anticipates claim 8, 10, and 12.

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256 EX1105, [0362] (Table 6), p. 48; EX1003, ¶ 272.

257 EX1003, ¶ 272. If Patentee contends the claims 8-10 and 12-13 require that *all* observed increase in hyaluronidase activity relative to unmodified SEQ ID NO: 35 (claims 8, 10, and 12) or SEQ ID NO: 32 (claims 9 and 13) be attributable *solely* to the position 309 replacement, there is no § 112 support for the claims at least because the disclosure reports only single-substitution mutants of PH20$_{1-447}$, and does not show possession of any other truncated forms of PH20 with amino acid replacements at any position (including

For similar reasons, US-275 anticipates claims 9 and 13, which require use of SEQ ID NO: 32 ($PH20_{1-430}$) as the unmodified PH20 polypeptide against which sequence identity and increased activity is measured.[258]

I309N-$PH20_{1-447}$ is 95.8% identical to SEQ ID NO: 32 ($PH20_{1-430}$) with 18 changes (1.00-18/430=0.958), including the substitution position 309 and the addition of 17 residues to the C-terminus of SEQ ID NO: 32 (position 430).[259]

Further, US-275 explicitly discloses (or, at a minimum, demonstrates necessarily and inevitably) that I309N-$PH20_{1-447}$ has increased activity compared to SEQ ID NO: 32's $PH20_{1-430}$. Incorporated-by-reference US-457 establishes that SEQ ID NO: 3 ($PH20_{1-447}$) has increased activity compared to unmodified SEQ ID NO: 32 ($PH20_{1-433}$).[260] For example, the table below compares the hyaluronidase activity at pH 7.4 (1) disclosed in US-457 for SPAM1-IDAF (SEQ ID NO: 87),

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$PH20_{1-433}$ or $PH20_{1-430}$ with a position 309 replacement) or provide any means for predicting the effect a position 309 replacement would have in such other truncated forms. EX1003, ¶¶ 230-235.

258 EX1003, ¶ 273.

259 EX1003, ¶ 273; EX1004, [0626] (Table 9), p. 133.

260 *See Arbutus Biopharma Corp.*, 65 F.4th at 662–63 (quoting *Advanced Display Sys., Inc.* 212 F.3d at 1282.

which has the same amino acid sequence as SEQ ID NO: 32 ($PH20_{1-430}$) of US-275 and the '656 Patent, (2) disclosed in US-457 for SPAM1-QIFY (SEQ ID NO: 70), which has the same sequence as SEQ ID NO: 3 ($PH20_{1-447}$) of US-275 and the '656 Patent, and (3) disclosed in US-275 for I309N-$PH20_{1-447}$.[261]

Mutant	pH 7.4 Activity Units/ml	Activity Normalized to $PH20_{1-447}$
$PH20_{1-430}$	0.441	21.7%
$PH20_{1-447}$	2.03175	100%
I309N $PH20_{1-447}$	-	311%

Thus, as shown above, US-275's I309N-$PH20_{1-447}$ has increased activity (over 14-fold) compared to SEQ ID NO: 32 ($PH20_{1-430}$). This data establishes, and a POSA would have readily understood, that the I309N replacement confers increased activity reported relative to unmodified $PH20_{1-447}$ and $PH20_{1-430}$.[262] US-275's I309N-$PH20_{1-447}$ therefore anticipates claims 9 and 13.

All claims are therefore anticipated by US-275.

VII. Conclusion

For the foregoing reasons, the challenged claims are unpatentable.

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Respectfully Submitted,

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[261] EX1105, [0362] Table 6, p. 48; EX1003, ¶ 273.

[262] EX1003, ¶ 273; *supra* n.257.

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EXHIBIT LIST

EXHIBIT #	REFERENCE NAME
1001	U.S. Patent No. 11,066,656
1002	File History of U.S. Patent No. 11,066,656
1003	Declaration of Dr. James Naismith
1004	United States Patent Publication No. 2013/0302275
1005	U.S. Patent No. 7,767,429
1006	Chao et al., "Structure of Human Hyaluronidase-1, a Hyaluronan Hydrolyzing Enzyme Involved in Tumor Growth and Angiogenesis," Biochemistry, 46:6911-6920 (2007)
1007	WO 2010/077297, published 8 July 2010
1008	Stern et al., "Hyaluronidases: Their Genomics, Structures, and Mechanisms of Action," Chem. Rev. 106:818-839 (2006)
1009	Jedzrejas et al., "Structures of Vertebrate Hyaluronidases and Their Unique Enzymatic Mechanism of Hydrolysis," Proteins: Structure, Function and Bioinformatics, 61:227-238 (2005)
1010	Zhang et al., "Hyaluronidase Activity of Human Hyal1 Requires Active Site Acidic and Tyrosine Residues," J. Biol. Chem., 284(14):9433-9442 (2009)
1011	Arming et al., "In vitro mutagenesis of PH-20 hyaluronidase from human sperm," Eur. J. Biochem., 247:810-814 (1997)
1012	Bordoli et al., "Protein structure homology modeling using SWISSMODEL workspace," Nature Protocols, 4(1):1-13 (2008)
1013	Frost, "Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration," Expert Opinion on Drug Delivery, 4(4):427-440 (2007)
1014	Branden & Tooze, "Introduction to Protein Structure," Second Ed., Chapters 1-6, 11-12, 17-18 (1999)
1015	Table Associating Citations from the '656 Patent (EX1001) to Corresponding Citations in the '731 Application (EX1026) and US-275 (EX1004)

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

EXHIBIT #	REFERENCE NAME
1029	Gmachl et al., "The human sperm protein PH-20 has hyaluronidase activity," FEBS Letters, 3:545-548 (1993)
1030	Sills, "Retraction," Science, 319:569 (2008)
1031	Yue et al., "Loss of Protein Structure Stability as a Major Causative Factor in Monogenic Disease," J. Mol. Biol., 353:459-473 (2005)
1032	Wang & Moult, "SNPs, Protein Structure, and Disease," Hum. Mutation, 17:263-270 (2001)
1033	Marković-Housley et al., "Crystal Structure of Hyaluronidase, a Major Allergen of Bee Venom," Structure, 8:1025-1035 (2000)
1034	"Negative Results," Nature: Editorials, 453:258 (2008)
1035	[Reserved]
1036	Hayden, "Chemistry: Designer Debacle," Nature, 453:275-278 (2008)
1037-1038	[Reserved]
1039	Alberts, "Molecular Biology of the Cell," Fifth Edition, Chapter 3 (2007)
1040	He et al., "NMR Structures of Two Designed Proteins with High Sequence Identity but Different Fold and Function," PNAS, 105:14412-14417 (2008)
1041	Alexander et al., "A Minimal Sequence Code for Switching Protein Structure and Function," PNAS, 106:21149-21154 (2009)
1042	Ruan et al., "Design and Characterization of a Protein Fold Switching Network," Nature Comm., 14 (2023)
1043-1044	[Reserved]
1045	Redline Comparison of the '731 Application and '656 Patent Specifications
1046	Beasley & Hecht, "Protein Design: The Choice of de Novo 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)

EXHIBIT #	**REFERENCE NAME**
1048	Hayden, "Key Protein-Design Papers Challenged," Nature, 461:859 (2009)
1049-1050	[Reserved]
1051	U.S. Patent Application No. 61/631,313
1052	U.S. Patent Application No. 61/796,208
1053-1058	[Reserved]
1059	Leisola & Turunen, "Protein Engineering: Opportunities and Challenges," Appl. Microbiol. Biotechnol. 75:1225-1232 (2007)
1060	[Reserved]
1061	Rosengren et al., "Clinical Immunogenicity of rHuPH20, a Hyaluronidase Enabling Subcutaneous Drug Administration," AAPS J. 5:1144-56 (2015)
1062-1065	[Reserved]
1066	Collection of SWISS-MODEL Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20110519141121/http://swissmodel.expasy.org/?pid=smh01&uid=&token=
1067	[Reserved]
1068	Declaration of Jeffrey P. Kushan
1069-1078	[Reserved]
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 Enhanced Interstitial Transport of Therapeutics," J. Controlled Release, 114:230-241 (2006)
1081	Goldberg, "Protein degradation and protection against misfolded or damaged proteins," Nature, 426:895-899 (2003)
1082-1086	[Reserved]

EXHIBIT #	REFERENCE NAME
1087	Vembar & Brodsky, "One Step at a Time: Endoplasmic Reticulum-Associated Degradation," Nature, 9:944-958 (2008)
1088-1104	[Reserved]
1105	United States Patent Publication No. 2010/0143457
1106-1111	[Reserved]
1112	Primakoff, P., et al., "Fully effective contraception in male and female guinea pigs immunized with the sperm protein PH-20," Nature 335:543-546 (October 6, 1988)
1113-1125	[Reserved]
1126	Im, S. et al., "Cryo-EM Structure of Human Hyaluronidase PH20," Proteins: Structure, Function, and Bioinformatics 93:10671073 (2025)
1127-1129	[Reserved]
1130	Melanie Ann Simpson, Ph.D. Deposition Transcript
1131	Gregory Petsko, Ph.D. Deposition Transcript
1132-1134	[Reserved]
1135	Dr. Naismith Analysis Spreadsheet
1136	Dobson, "Principles of protein folding, misfolding and aggregation" Semin. Cell. Dev. Biol. 15(1):3-16 (2004)
1137	Dobson, "Protein folding and misfolding" Nature. 18;426(6968):884-90 (2003)
1138	Dobson, "Experimental investigation of protein folding and misfolding" Methods 34(1):4-14 (2004)
1139	Chiti & Dobson, "Protein Misfolding, Functional Amyloid, and Human Disease" Annu. Rev. Biochem. 75:333–66 (2006)
1140	Dobson, "Protein misfolding, evolution and Disease" Trends Biochem. Sci. (9):329-32 (1999)
1141	Goldsmith & Tawfik, "Directed enzyme evolution: beyond the low-hanging fruit" Curr. Opin. Struct. Biol. 22(4):406-12 (2012)
1142-43	[Reserved]

EXHIBIT #	REFERENCE NAME
1144	Ochoa-Leyva et al., "Protein Design through Systematic Catalytic Loop Exchange in the (beta/alpha)8 Fold" J. Mol. Biol. 387(4):949-64 (2009)
1145	[Reserved]
1146	Pal et al., "Comprehensive and Quantitative Mapping of Energy Landscapes for Protein-Protein Interactions by Rapid Combinatorial Scanning" J. Biol. Chem. 4;281(31):22378-22385 (2006)
1147	van Rossum et al., "Reporter-based screening and selection of enzymes" FEBS J. 280:2979-96 (2013)
1148	Reed et al., "Use of Coefficient of Variation in Assessing Variability of Quantitative Assays" Clin. Diagn. Lab Immunol. 9(6):1235-9 (2002)
1149	Ten Have et al., "Cloning and characterization of the cDNA encoding the PH20 protein in the European red fox Vulpes" Reprod. Fertil. Dev. 10(2):165-72 (1998)
1150	Chowpongpang et al., "Cloning and characterization of the bovine testicular PH-20 hyaluronidase core domain" Biotechnol. Lett. 26(15):1247-52 (2004)
1151	Fowler et al., "High-resolution mapping of protein sequence function relationships" Nature Methods 7, 741–746 (2010)
1152	Ringe & Petsko, "Q&A: What are pharmacological chaperones and why are they interesting?" J. Biol. 8:80 (2009)
1153-1154	[Reserved]
1155	Calloni et al., "Investigating the Effects of Mutations on Protein Aggregation in the Cell" J. Biol. Chem. 10607-13 (2005)
1156	Chiti et al., "Studies of aggregation of mutant proteins in vitro provided insights into genetics of amyloid diseases" PNAS 99:16419-26 (2002)
1157	Chiti et al., "Rationalization of the effects of mutations on peptide and protein aggregation rates" Nature, 424:805-808 (2003)
1158	Wang et al., "Immunogenicity of protein aggregates-Concerns and Realities" Int. J. Pharmaceutics 431:1-11, (2012)
1159	[Reserved]

EXHIBIT #	**REFERENCE NAME**
1160	Poelwijk, Frank J., et al., "Empirical fitness landscapes reveal accessible evolutionary paths" Nature 445.7126 (2007): 383-386
1161-1188	[Reserved]
1189	Martin-Deleon, P., "Epididymal SPAM1 and its Impact on Sperm Function," Molecular and Cellular Endocrinology 250:114-121 (2006)
1190-1205	[Reserved]
1206	U.S. Food and Drug Administration, Medical Review: Hylenex, App. No. 21-859 (2005)
1207	[Reserved]
1208	Redline of the '731 App. and US-275 Publication
1209	Petsko & Ringe, Protein Structure and Function, New Science Press (2004)
1210	Nelson & Cox, Lehninger Principles of Biochemistry, W.H. Freeman, 4th ed. (2005)
1211	Halozyme Therapeutics, Inc., Hylenex Label, U.S. Food and Drug Administration: AccessData (2005)
-	Declaration of Gregory A. Petsko, PGR2025-00003 (U.S. Patent No. 11,952,600), EX2070 (Sept. 22, 2025)

CERTIFICATE OF COMPLIANCE

I hereby certify that this brief complies with the type-volume limitations of 37 C.F.R. § 42.24, because it contains 13,740 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.

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CERTIFICATE OF SERVICE

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

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