Paper No. 1
Filed: May 7, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyme Inc.,
Patent Owner.

Case No. PGR2025-00050
U.S. Patent No. 12,077,791

PETITION FOR POST GRANT REVIEW

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I. Introduction

Petitioner Merck Sharp & Dohme LLC ("Merck") requests post grant review of U.S. Patent No. 12,077,791 ("'791 Patent").

Claims 1-10 of the '791 Patent define modified human PH20 polypeptides that (i) ***must have*** one amino acid substitution at position 309, and (ii) ***may have*** up to 20 additional substitutions at ***any*** of 432 other positions, and to ***any*** of 19 other amino acids. These parameters capture between 10^{49} and 10^{60} distinct PH20 polypeptides, a scale that is unfathomable—the collective weight of one molecule of each polypeptide in the smallest set exceeds the weight of the Earth, and simply making and testing each set per the patent's methodology would require lifetimes of "making and testing" experiments.

Critically, every claim requires the modified PH20 polypeptides to "exhibit[] increased hyaluronidase activity" compared to the unmodified 447 residue PH20 polypeptide in SEQ ID NO: 3 ($PH20_{1-447}$). The number of such "active mutant" polypeptides within the massive sets of modified PH20 polypeptide sequences defined by the claims' parameters, however, is undisclosed and unknown, as are the numbers of such polypeptides that (i) exhibit lower hyaluronidase activity than unmodified $PH20_{1-447}$, (ii) are "soluble," (iii) are properly folded but are inactive, or (iv) do not fold or cannot be produced (have no utility).

These immensely broad claims are unpatentable for two independent reasons, both of which are linked to their extreme breadth. Specifically, when measured against the common disclosure of the '791 Patent and its ultimate parent '731 Application,[1] each utterly fails the written description and enablement requirements of § 112(a). That also precludes the claims from being entitled to a valid § 120 benefit claim to the '731 Application, the only non-provisional application filed before March 16, 2013, thus making the '791 Patent PGR eligible.

Regarding written description, the common disclosure makes no effort to identify (and never contends there is) a common structure shared by all multiply-modified PH20 polypeptides meeting the claims' parameters that exhibit increased hyaluronidase activity. The disclosed examples also are not representative of the claimed "increased activity" modified PH20 polypeptides. Instead, each example is a modified PH20 polypeptide with only ***one*** amino acid substitution within ***one*** PH20 sequence: the 447 residue $PH20_{1-447}$ sequence of SEQ ID NO:3. By contrast, the claims encompass PH20 polypeptides with myriad, ***undescribed*** combinations of 5, 10, 15, or 20+ substitutions anywhere within a different PH20 reference sequence (*i.e.*, the 433 residue PH20 sequence of SEQ ID NO:35). And the common disclosure nowhere connects the variables of the claims: "increased

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

activity" modified PH20 polypeptides with 433 (rather than 447) residues, particular substitutions at position 309, and between 17 and 20 additional substitutions.

Regarding enablement, equally fatal problems exist: the disclosure identifies ***no*** enzymatically active modified PH20 polypeptide with 2 or more substitutions, much less affirmatively guides the selection of ***which*** of the 10^{49}+ combinations of substitutions will yield enzymes that are active and exhibit ***increased*** activity. The only process it discloses for making multiply-substituted active mutants is a prophetic "trial-and-error discovery" experiment that must be repeated innumerable times until between 10^{49} and 10^{60} unique proteins have been made and tested to determine which are active mutants within the claim scope. That is far more than undue experimentation—it is impossible. Indeed, the Supreme Court found comparable claims non-enabled due to the necessity of performing analogous "trial and error discovery" experiments to discover a much smaller genus of claimed proteins.[2]

Patentee's recent conduct in other members of the patent family that includes the '791 patent reflects even its recognition that the challenged claims are fatally defective. Specifically, each time Petitioner challenged comparable claims

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

requiring increased hyaluronidase activity or solubility in another member of this patent family for lack of written description or non-enablement, Patentee responded by statutorily disclaiming those challenged claims, instead of attempting to defend them.[3] Halozyme's actions speak volumes.

For the reasons set forth in this petition, each claim of the '791 Patent lacks sufficient written description in and is not enabled by the disclosure of any application to which it claims priority or benefit, as well as by the application that issued as the '791 Patent. Because each claim is unpatentable, the Board should institute trial.

II. Compliance with PGR Requirements

A. Certification of Standing

Petitioner certifies this Petition is filed within 9 months of the '791 Patent's issuance. Petitioner certifies it is not barred or estopped from requesting this PGR. Petitioner and its privies have not filed a civil action challenging the validity of any claim of the '791 Patent.

The '791 Patent is eligible for post-grant review because at least one of its claims is not entitled to an effective filing date prior to March 16, 2013.

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

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

Only one of the applications to which the '791 Patent claims benefit under 35 U.S.C. § 120 and/or § 121—U.S. Application No. 13/694,731 (the '731 Application)—was filed before March 16, 2013. That application, issued as U.S. Patent No. 9,447,401 (EX1025), claims priority to two provisional applications (61/631,313, filed November 1, 2012 and 61/796,208, filed December 30, 2011) and WO 01/3087 ("WO087"). The '731 Application, however, alters several

passages of the provisional disclosures, adds new examples and tested mutants and makes other changes.[4]

The ’731 Application (including subject matter incorporated by reference from the two provisional applications) does not provide written description support for and does not enable any claim of the ’791 Patent (§§ V.A, V.B). The same is true for the ’791 Patent, whose disclosure relative to the claims is generally the same as the ’731 Application.[5] The ’791 Patent is PGR eligible as at least one of its claims does not comply with § 112(a) based on the ’731 Application filed before March 16, 2013 for the reasons set forth in §§ V.A and V.B, *infra*,.

B. Mandatory Notices

1. Real Party-in-Interest

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

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

[5] “Common disclosure” refers to the shared disclosure of the ’791 Patent and the ’731 Application (EX1026). Citations are to the ’791 Patent; EX1015 correlates citations to the ’731 Application. The disclosures are highly similar but not identical. *See* EX1068, ¶ 6.

2. Related Proceedings

PGR2025-00003, PGR2025-00004, PGR2025-00006, PGR2025-00009, PGR2025-00017, PGR2025-00024, PGR2025-00030, PGR2025-00033, PGR2025-00039, PGR2025-00042, and PGR2025-00046 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 '791 Patent.

3. Counsel and Service Information

Lead Counsel	Backup Counsel	Backup Counsel
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Petitioner consents to service via e-mail at the email addresses listed above and at HalozymePGRs@sidley.com.

III. Grounds

The grounds advanced in this Petition are:

(a) Claims 1-10 are unpatentable under 35 U.S.C. § 112 as lacking adequate written description.

(b) Claims 1-10 are unpatentable under 35 U.S.C. § 112 as not being enabled.

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

"PH20" refers to the human PH20 hyaluronidase protein. The full-length PH20 protein (SEQ ID NO: 6) includes a 35 amino acid signal sequence, and mature forms of PH20 differ from SEQ ID NO: 6 by 35 residues.[6] "$PH20_{1\text{-}n}$" 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 '791 Patent

A. Field of the Patent

The '791 Patent concerns the human PH20 hyaluronidase enzyme and making structurally altered forms of that protein that retain enzymatic activity.[7]

1. Protein Structures

Proteins are comprised of sequences of amino acids. A protein's activity, however, derives from its unique, three-dimensional shape—its structure.[8] That is dictated by specific and often characteristic patterns of amino acids in its sequence, which induce formation and maintenance of various secondary structures and

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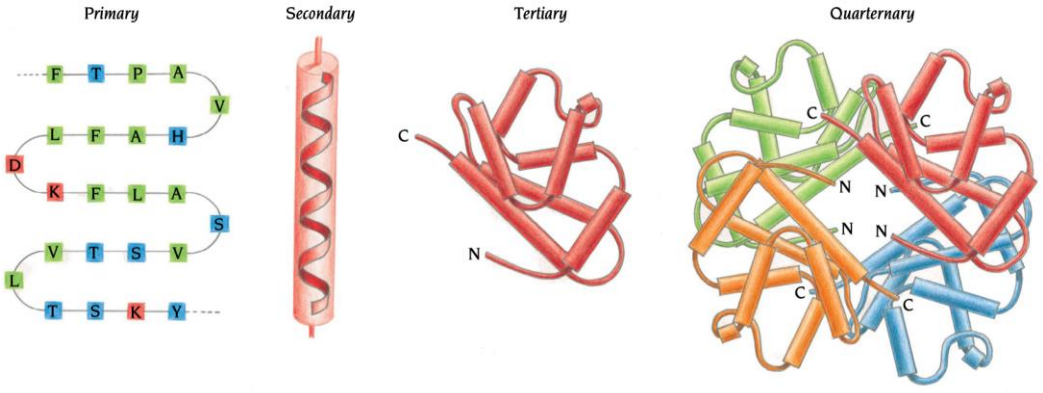
6 EX1003, ¶ 15.

7 EX1001, 2:44-47.

8 EX1003, ¶ 36.

structural motifs, which are packed into compact domains that define the protein's overall structure (tertiary structure).[9]



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

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

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

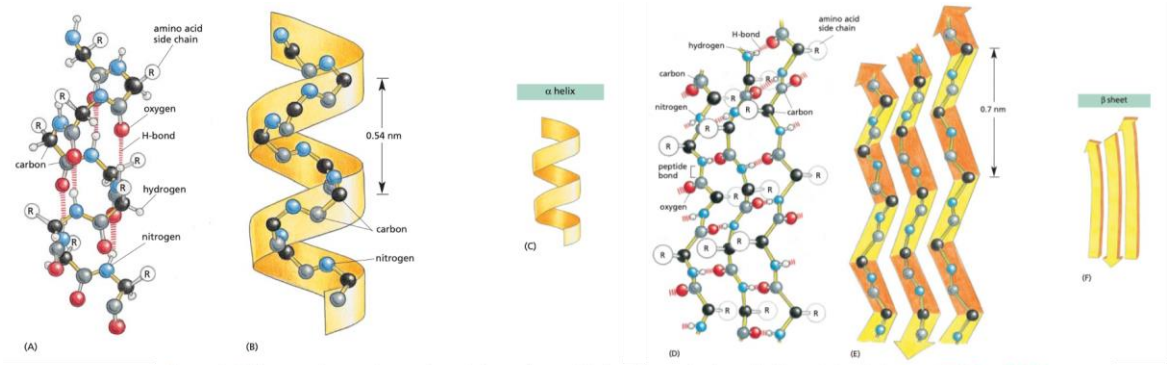


Figure 3–7 The regular conformation of the polypeptide backbone in the α helix and the β sheet. <GTAG> <TGCT> (A, B, and C) The α helix. The N–H of every peptide bond is hydrogen-bonded to the C=O of a neighboring peptide bond located four peptide bonds away in the same chain. Note that all of the N–H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

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

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

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

[11] EX1003, ¶¶ 44-46; EX1014, 21-22.

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

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

2. Hyaluronidase Enzymes

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

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13 EX1003, ¶ 163.

14 EX1003, ¶¶ 55-56, 143; EX1047, 6349; EX1046, 2034; *see also* EX1040, 14412-13; EX1041, 21149-50; EX1042, 1-3.

15 EX1003, ¶¶ 57-59.

16 EX1003, ¶¶ 50, 163, 200, 240; EX1004, ¶¶ 151-153; EX1027 at 8-11.

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

breaks down hyaluronan ("HA") by selectively hydrolyzing glycosidic linkages.[18] PH20 exists naturally as a GPI anchored protein; deletion of its GPI-anchoring sequence yields a soluble, neutral active enzyme.[19]

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

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

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18 EX1003, ¶ 77; EX1008, 819.

19 EX1005, 2:40-61, 87:52-88:24; EX1013, 430-32, Figure 2; EX1003, ¶¶ 92, 208; EX1029, 546, Figure 1.

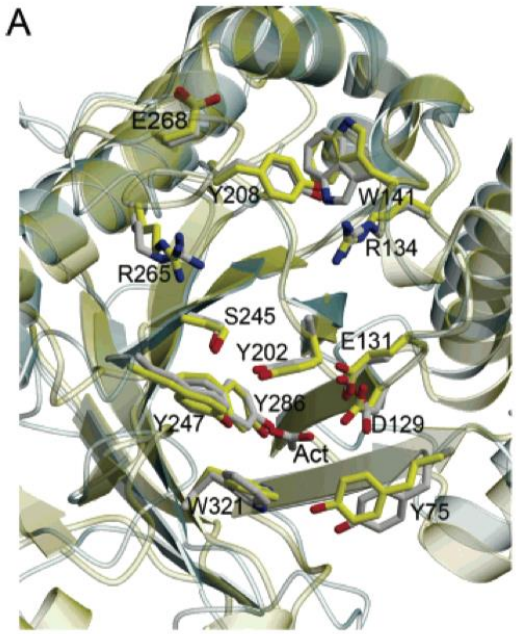
20 EX1006, 6914-16, Figure 3; EX1007, 35:28-36:10; EX1011, 810-14; EX1008, 824-25; EX1009, 6912-17.

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

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

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

illustrate shared secondary structures and conserved residues in these proteins.[24] Using its experimental structure and sequence analysis, an earlier structure of bee venom hyaluronidase, and a computer model of the protein structures, Chao showed that human and non-human hyaluronidases share a highly conserved active site and identified residues that interact with HA, *inter alia*, by superimposing HYAL1 and bee venom hyaluronidase structures.[25]



[24] EX1006, 6914-18.

[25] EX1006, 6912-6913, 6916-18 (Figure 4A); *see also id.* at 6914-16, Figure 2C; EX1033, 1028-29, 1035; Figure 1; EX1010, 9434, 9436, Figure 1; EX1004, ¶¶ 89-91; EX1003, ¶¶ 81-82.

The ’429 Patent likewise used the bee venom hyaluronidase structure to identify critical residues in PH20,[26] and taught that hyaluronidase domains share similarity among species, including residues necessary for enzymatic activity.[27] It did not, however, include a PH20 or other human hyaluronidase structural model in its disclosure.

Chao also identified predicted secondary structures (*e.g.*, β-sheets, α-helices) within human PH20 and the four other human hyaluronidases (Figure 3, below), as well as invariant conserved positions (blue), residues involved in catalysis (red), conserved cysteines that form disulfide bonds (gold) and conserved asparagine residues that are glycosylated (turquoise).[28]

[26] EX1005, 4:12-22, 86:49-53, 88:14-24.

[27] EX1005, 2:6-67, 4:11-22.

[28] EX1006, 6916; EX1003, ¶¶ 83, 222; EX1004, ¶ 92.

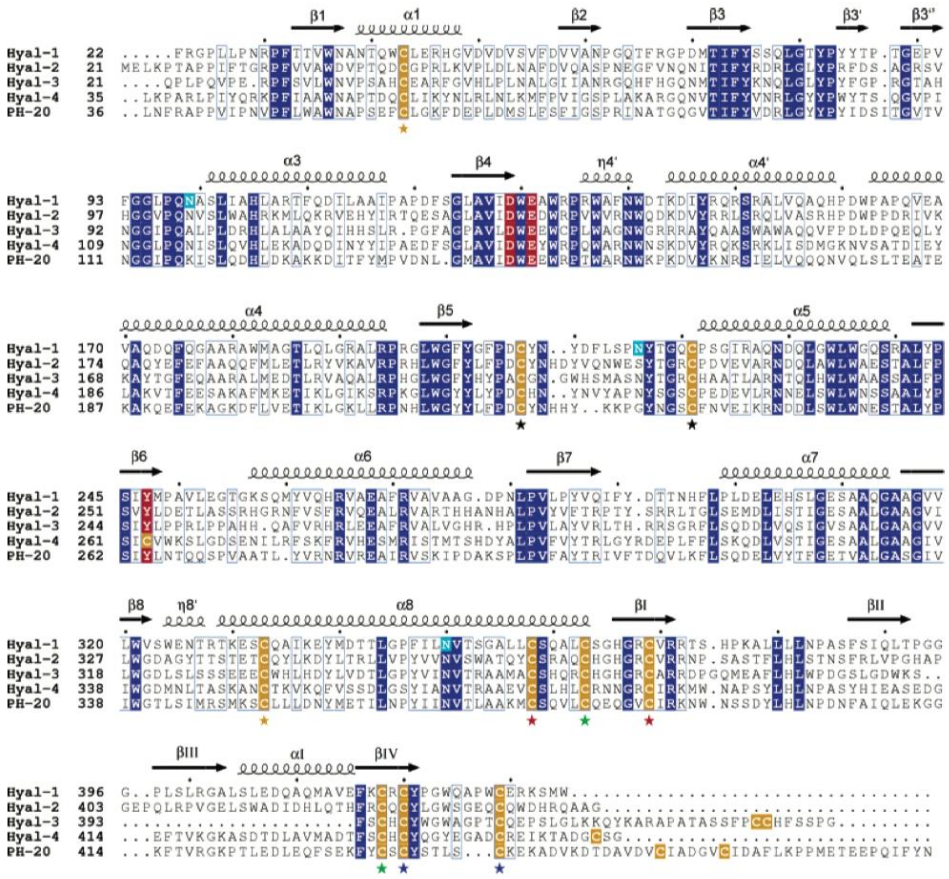


FIGURE 3: Structure-based sequence alignment of human hyaluronidases. Invariant residues are shown in blue except for three key catalytic residues that are colored red. Cysteine residues are colored yellow. The hHyal-1 N-glycosylated asparagines residues are colored turquoise. Residues exhibiting conservative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

Among Chao's findings was that human hyaluronidases (including PH20) contain a unique structure—"a novel, EGF-like domain" in the C-terminal region of human hyaluronidases[29]—that was "closely associated" with the catalytic

[29] EX1006, 6911 ("a novel, EGF-like domain, characteristic of involvement in protein-protein interactions and regulatory processes"); 6917 ("Now that the 3D structure of hHyal-1 has revealed the presence of a novel HyalEGF-like domain, a search for partners and characterization of their interactions are

domain.[30] It identified a characteristic pattern for this "Hyal-EGF" domain, which in PH20 is at positions 337-409.[31]

3. Protein Engineering

There are two general approaches used to engineer changes into proteins.[32] In "rational design," skilled artisans employed computational tools—sequence alignments and protein structure models—to study the protein and then select where and what changes to introduce.[33] For example, a "multiple-sequence alignment" ("MSA")[34] produced by aligning known sequences of homologous, naturally occurring proteins identifies positions with no or little amino acid

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timely."), 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, 6916-6918, Figures 2A, 2D, 4B; EX1010, 9434, 9436; EX1003, ¶¶ 84-86.

30 EX1006, 6911, 6913, 6914, 6917, 6918; EX1003, ¶¶ 84-86.

31 EX1006, 6911-6912; Figure 3; EX1004, ¶¶ 97-98; EX1003, ¶¶ 84-86.

32 EX1003, ¶ 47.

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

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

variation ("conserved" / "essential" residues) and positions where different amino acids occur ("non-conserved" / "non-essential" residues).[35] A structural model using the protein's sequence but based on a known structure of a homologous protein enabled assessment of interactions between amino acids at a particular positions.[36] Using rational design techniques, a skilled artisan could assess, with varying effort, effects of changing one or a few amino acids, but could not use those techniques to predict the effects of many concurrent changes, given the escalating complexity of numerous, interrelated interactions (which exponentially increase with the number of changes) and the limits of protein modeling tools.[37] Indeed, computer-based systems for predicting protein structures from amino acid sequences did not reach levels of accuracy comparable to experimentally determined structure until the 2018-2020 time frame (below).[38]

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35 EX1003, ¶¶ 225-226; EX1004, ¶¶ 21-22, 25, 30-31; EX1016, 181-84; EX1017, 224-25; EX1014, 351.

36 EX1017, 228-30; EX1031, 461, 463, 469-71; EX1014, 351-52; EX1032, 265-66; EX1004, ¶ 37; *also id.* 33-36; EX1003, ¶¶ 235-237.

37 EX1003, ¶¶ 50, 163; EX1004, ¶¶ 151-153.

38 EX1027, 6-11, Figure 6; EX1003, ¶ 163.

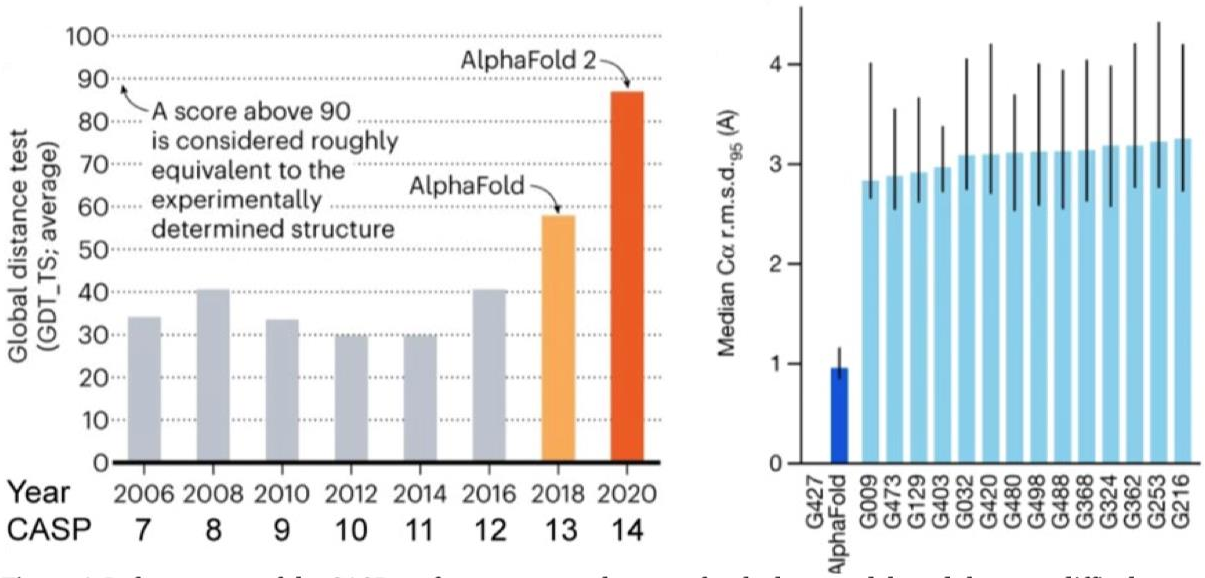

Figure 6. Left: progress of the CASP performance over the years for the best models and the most difficult targets.[38] Right: performance of AlphaFold2 relative to the top 15 entries by other groups in CASP14. Data are the median coordinate error and the 95% confidence interval of the median, estimated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

"Directed evolution" techniques arose due to the limits of rational design.[39] 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.[40] Importantly, until a desired mutant is made, found, and tested, whether it exists and its sequence are unknown.[41] Sophisticated assays that rapidly and precisely identify mutants with desired properties are critical, given the scale

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

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

41 EX1003, ¶ 194.

of experimentation this approach requires.[42] The '791 Patent embodies this approach.[43]

B. Person of Ordinary Skill in the Art

While the '791 Patent claims priority to provisional applications dating to December 30, 2011 and benefit to the '731 Application filed December 28, 2012, none of those earlier-filed applications when each was filed supported the claims as required by § 112(a). *See* §§ II.A, V.A, V.B.

In several post-grant review petitions challenging related patents in the family of the '791 Patent, Merck included obviousness grounds.[44] In support of those obviousness grounds, opinions were provided from Drs. Hecht and Park that described the knowledge and perspectives of a skilled artisan just prior to the earliest of the priority dates claimed by the patent at issue (*i.e.*, December 2011).[45]

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42 EX1003, ¶¶ 52-53.

43 EX1003, ¶¶ 146, 183, 193, 197.

44 *See, e.g.*, PGR2025-00003, Paper 1, page 7.

45 *See, e.g.*, PGR2025-00003, Paper 1, 16 (explaining '600 Patent claims "…are not entitled to those dates [2011 provisional application filing] or the filing date of the '731 Application (December 28, 2012), as they are not supported as § 112(a) requires by those earlier-filed applications" and noting "[t]he prior

In this petition, Merck is only advancing grounds based on inadequate written description and lack of enablement.

A person of ordinary skill in the art would have had an undergraduate degree, a Ph.D., and post-doctoral experience in scientific fields relevant to study of protein structure and function (*e.g.*, chemistry, biochemistry, biology, biophysics). From training and experience, the person would have been familiar with factors influencing protein structure, folding and activity, production of modified proteins using recombinant DNA techniques, and use of biological assays to characterize protein function, as well with techniques used to analyze protein structure (*i.e.*, sequence searching and alignments, protein modeling software, etc.).[46]

C. Prosecution History

During examination, the claims were rejected on several grounds (indefiniteness, anticipation, and double-patenting) that are not relevant to the

art of the grounds, however, was published by December 2011, and the obviousness grounds thus use that date to assess the knowledge and perspectives of the skilled artisan.")

[46] EX1003, ¶ 13.

currently presented grounds.[47] These rejections were traversed with claim amendments, cancellation of claims, and terminal disclaimers.[48] Enablement grounds were not considered during examination.

After initially rejecting the then-pending claims for lack of written description,[49] the Examiner withdrew the rejection without explanation in response to Patentee's claim amendments that added an "increased hyaluronidase activity" requirement to all claims.[50] The written description rejections did not advance the same reasoning as and were not supported by evidence that is used in the present grounds. Moreover, the Examiner erred by not rejecting the amended claims that required >100% hyaluronidase activity for lack of written description and enablement.

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47 EX1002, 508-531, 594-595, 620, 626.

48 EX1002, 555, 569-573.

49 EX1002, 509-515.

50 EX1002, 636, 670-671, 674.

To the extent Patentee contends discretionary denial is warranted, Petitioner reserves the right to respond separately pursuant to the Acting Director's March 26, 2025 Memorandum.[51]

D. The Challenged Claims

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

A clear understanding of the ***breadth*** of the claims, however, is important—each captures a genus of mutants with increased hyaluronidase activity from within a massive number of structurally distinct mutant PH20 polypeptides which is neither adequately described in nor enabled by the common disclosure of the '731 Application and the '791 Patent.

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

The claims define an incredibly broad and diverse genus of "modified PH20 polypeptides," which the common disclosure defines as "a PH20 polypeptide that

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

contains at least one amino acid modification, such as at least one amino acid replacement … in its sequence of amino acids compared to a reference unmodified PH20 polypeptide."[52]

Claim 1 defines the genus as containing modified PH20 polypeptides that:

- ***must*** contain ***one*** amino acid replacement at position 309 selected from substitution to one of ten amino acids (E, G, H, L M, N, Q, R, S, and T); and
- ***may*** contain ***additional*** modifications, provided each polypeptide retains ***at least 95% sequence identity*** to SEQ ID NO: 35, which has a length of 433 residues.

Claim 1 further requires that the modified PH20 polypeptide "exhibits increased hyaluronidase activity compared to the hyaluronidase activity of the polypeptide of SEQ ID NO: 3 measured under identical conditions," but the claim does not indicate which polypeptides meeting the two parameters above will meet this activity condition.

Certain dependent claims further restrict the parameters of claim 1:

(i) claims 2 and 3 require the substitution at position 309 to be to asparagine (N),

[52] EX1001, 47:3-8.

(ii) claim 3 also requires 96% sequence identity with SEQ ID NO: 35, and

(iii) claims 4-5 add further functional requirements to claim 1 (*e.g.*, "at least 120% of the hyaluronidase activity" of SEQ ID NO: 3 or solubility).

Claims 6-10 depend from claim 1 but do not alter its parameters governing the number of PH20 polypeptides. Claims 6-8 specify additional features of the PH20 polypeptides while claim 9 recites pharmaceutical compositions with the polypeptides of claim 1. Claim 10 recites a method of manufacturing the polypeptides of claim 1.

The specification explains that "sequence identity can be determined by standard alignment algorithm programs …"[53] and provides an example, explaining a polypeptide that is "'at least 90% identical to' refers to percent identities from 90 to 100% relative to the reference polypeptide" where "no more than 10% (*i.e.*, 10 out of 100) of amino acids [] in the test polypeptide [] differs from that of the reference polypeptides."[54]

It further explains that "differences can be represented as point mutations randomly distributed over the entire length of an amino acid sequence" and that

[53] EX1001, 58:33-35.

[54] EX1001, 59:1-10.

"[d]ifferences are defined as [] amino acid substitutions, insertions or deletions."[55] Also, "amino acids selected to replace the target positions on the particular protein being optimized can be either all of the remaining 19 amino acids, or a more restricted group containing only selected amino acids" (*e.g.*, 10-18 of the 19 alternative amino acids).[56] Except for position 309, no language in the claims restricts ***where*** substitutions can occur within the modified PH20 sequence, or ***which*** of 19 other amino acids can be substituted at those positions.

The sequence identity parameters capture immense numbers of modified PH20 polypeptides, each with a unique amino acid sequence (below).[57]

Claims	Max Length	Seq. Id. %	Max Changes	Pos. 309 Choices	# of Distinct Polypeptides
1, 4-10	433	95	21	10	5.08×10^{60}
2	433	95	21	1	5.08×10^{59}
3	433	96	17	1	1.53×10^{49}

55 EX1001, 59:11-19; *see also id.* at 3:29-30, 46:7-11, 21-23.

56 EX1001, 135:53-60; *see also id.* at 141:4-6.

57 EX1003, ¶¶ 129-131; EX1004, ¶¶ 159-163, Appendix F.

2. The Claim Language Restricts Them to "Active Mutants"

When a specification discloses alternative embodiments, the claim language may limit the claims to one.[58] That is unquestionably true here: the specification describes two mutually exclusive categories of "modified PH20 polypeptides" (*i.e.*, "active mutants" vs. "inactive mutants"), but the claims are expressly limited to one (*i.e.*, "active mutants," and in particular to active mutants with "increased hyaluronidase activity")).

First, the common disclosure clearly identifies two mutually exclusive categories of modified PH20 polypeptides:

- "***Active mutants***" are modified PH20 polypeptides "whereby the polypeptides exhibit at least 40% of the hyaluronidase activity of the corresponding PH20 polypeptide not containing the amino acid modification (*e.g.*, amino acid replacement)."[59]

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[58] *TIP Sys., LLC v. Phillips & Brooks/Gladwin, Inc.*, 529 F.3d 1364, 1375 (Fed. Cir. 2008).

[59] EX1001, 73:64-74:2; *see also id.* at 77:46-50 ("active mutants" "can exhibit 40% to 5000% of the hyaluronidase activity of a wildtype or reference PH20 polypeptide …"); *id.* at 77:43-46.

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

It also classifies mutants into tables of "active" or "inactive" mutants using the >40% threshold (Tables 3 and 9) or <20% threshold (Tables 5 and 10).[61] There are no examples in the common disclosure of an "active mutant" modified PH20 polypeptide with two or more specific substitutions,[62] much less one with: (i) a first substitution listed in Tables 3 or 9 ***plus*** (ii) a second substitution listed in Tables 5 and 10.

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[60] EX1001, 117:41-50. *See also id*. at 255:42-46 (mutants with <20% activity "were rescreened to confirm that the dead mutants are inactive" in Table 10).

[61] EX1001, 232:49-51 ("Active mutants were selected whereby ***at least one duplicate sample*** exhibited greater than 40% of wildtype activity …"); *id.* at 232:57-61 (Table 9 "…sets forth the ***average hyaluronidase activity*** of tested duplicates…"); *id.* at 79:10-80:18, 232:50-52, 118:43-67, 256:53-56 ("reconfirmed inactive mutants are set forth in Table 10."); EX1003 ¶¶ 101, 103-104, 116.

[62] *E.g.*, EX1003, ¶¶ 148, 184.

The common disclosure also portrays "active" and "inactive" mutants as having distinct utilities with mutually exclusive properties. "Active mutants" are portrayed as having a variety of therapeutic uses ***because they possess hyaluronidase activity***."[63] However, it identifies only one (implausible) utility for "inactive mutants"—"as antigens in contraception vaccines" (*see* § V.C).[64]

Second, the claim language expressly requires each modified PH20 polypeptide being claimed to have greater hyaluronidase activity than unmodified $PH20_{1-447}$ (SEQ ID NO: 3). As claim 1 states:

> …wherein the modified PH20 polypeptide ***exhibits increased hyaluronidase activity*** compared to the hyaluronidase

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63 EX1001, 179:55-61; *see also id*. at 2:61-64, 71:50-64, 179:55-193:14, 156:3-5. EX1003, ¶ 117.

64 EX1001, 74:6-8 ("Also provided are modified PH20 polypeptides that are inactive, ***and*** that can be used, for example, as antigens in contraception vaccines."); *see also id.* at 193:15-16, 71:10-12, 193:14-33 (for "contraception" "the modified PH20 polypeptides can be inactive enzymes, such as any described in Sections C.2."); EX1003, ¶ 118; EX1001, 156:4-17; EX1060, 1711.

> activity of the polypeptide of SEQ ID NO: 3, measured under identical conditions.[65]

Dependent claim 4 further requires the modified PH20 polypeptides of claim 1 to have "at least 120% of the hyaluronidase activity" relative to an unmodified $PH20_{1-447}$, reinforcing that all modified PH20 polypeptides in claim 1 are "active mutants."[66] The claim language thus compels the conclusion that every PH20 polypeptide in the scope of the claims must possess at least 100% of the activity of $PH20_{1-447}$, and expressly excludes "inactive mutants."

Additionally, all claims require modified PH20 polypeptides to have a single substitution at 309 to one or more of the following: I309E, I309G, I309H, I309L, I309M, I309N, I309Q, I309R, I309S, or I309T. The common disclosure reports that $PH20_{1-447}$ polypeptides with these substitutions are "Active Mutants" and

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65 EX1001, 307:16-19 (emphasis added). The common disclosure likewise explains that "increased activity" "means that, when tested under the same conditions, the modified PH20 hyaluronidase exhibits greater hyaluronidase activity…".

66 EX1001, 51:5-11, 132:52-133:4, 178:43-46, 300:21-301:42.

exhibit >100% activity, with 4 others (I309D, I309K, I309V, I309W) exhibiting >40% activity.[67]

TABLE 8-continued

PH20 Variants	
I309D	GAT
I309E	GAG
I309G	GGT
I309H	CAT
I309K	AAG
I309L	CTG
I309M	ATG
I309N	AAT
I309Q	CAG
I309R	CGT
I309S	AGT
I309T	ACT
I309V	GTG
I309W	TGG
I309Y	TAT

EX1001, 217

TABLE 9-continued

ACTIVE MUTANTS		
I309D		0.72
I309E	576	1.99
I309G	577	1.44
I303D		0.34
I309H	578	1.30
I309K		0.98
I309L	579	1.72
I309M	580	1.47
I309N	581	3.11
I309Q	582	1.64
I309R	583	2.27
I309S	584	1.16
I309T	585	2.09
I309V	586	0.60
I309W		0.88

EX1001, 234

The specification also defines a "modified PH20 polypeptide" as "a PH20 polypeptide that contains at least one amino acid modification," but explains it can "have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide ***exhibits hyaluronidase activity.***"[68] The claim language thus aligns

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[67] EX1001, 86 (Table 3), 234 (Table 9), 99:34-46; EX1003, ¶¶ 135-138. Table 9 confusingly lists two entries for I309D, one with 72% and the other 34% relative activity).

[68] EX1001, 47:3-18; *see also id*. at 46:26-30, 74:22-25, 75:17-24, 79:18-80:18; EX1003, ¶ 139.

with the specification's prophetic methodology for discovering PH20 polypeptides with multiple changes, which selects "active mutants" with one substitution, randomly introduces another, and then screens to find "double mutants" that ***retained*** hyaluronidase activity.[69]

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

Claims 1-10 are unpatentable because each claims enzymatically active modified PH20 polypeptides that lack written description in and were not enabled by the common disclosure.

Per § IV.D.1, the claim parameters capture between 10^{49} and 10^{60} distinct PH20 polypeptides. To practice the claims' full scope of multiply-modified PH20 mutants with increased hyaluronidase activity (and, for that matter, to weed out the "inactive" and inoperative mutants captured by the claims' sequence identity parameters) requires a skilled artisan to make-and-test at least ~10^{49} mutants.[70] Simply producing one molecule of each mutant in the smallest set—required to know if each is active, inactive, can be produced or will fold—would consume an aggregate mass (~1.37 x 10^{27} kg) that exceeds the mass of the Earth (~6 x 10^{24}

[69] EX1001, 140:38-49; *see also id*. at 41:10-17; EX1003, ¶ 139.

[70] EX1003, ¶¶ 194-196.

kg).[71] Testing every polypeptide within the claims' scope in search of "active mutants" is impossible—literally.

Relative to that broad scope, the '791 Patent and the '731 Application provide only a meager disclosure: ***singly***-modified PH20 polypeptides and a prophetic, make-and-test research plan to discover multiply-modified ones. It nowhere demonstrates possession of the vast remainder of enzymatically active multiply-modified polypeptides within each claim's scope, nor does it enable a skilled artisan to practice that full-range of active mutants having increased hyaluronidase activity without undue experimentation.

These ***omissions*** in the common disclosure cause fatal § 112(a) deficiencies for the claims:

(i) the absence of any description of numerous distinct types of species of modified PH20 polypeptides within the claimed genus (*e.g.*, those with multiple substitutions, those incorporating substitutions that render the enzyme inactive and those with significant C-terminal truncations) coupled with the absence of an identified common structure shared by all PH20 polypeptides with increased

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

hyaluronidase activity, renders the claims unpatentable due to inadequate written description, and

(ii) the absence of any examples of multiply-modified modified PH20 polypeptides with increased hyaluronidase activity, coupled with the disclosure's dependence on a single, prophetic method of producing them that requires making and testing 10^{49}+ different PH20 polypeptides to discover which exhibit increased hyaluronidase activity, renders the claims unpatentable as being non-enabled.

For these and other reasons explained, *infra*, every claim is unpatentable under § 112(a).

Finally, as noted above, in the face of comparable § 112(a) challenges in other patents in the family that includes the '791 Patent, Patentee statutorily disclaimed claims requiring enzymatically active modified PH20 polypeptides: those requiring 100% or 120% hyaluronidase activity, increased stability or that required the modified PH20 polypeptides to be soluble.[72] Patentee's conduct speaks volumes here.

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

A. All Claims Lack Written Description

The written description analysis focuses on the four corners of the patent disclosure.[73] "To fulfill the written description requirement, a patent owner must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and demonstrate that by disclosure in the specification of the patent."[74] If the claims define a genus, the written description must "show that one has truly invented a genus …," "[o]therwise, one has only a research plan, leaving it to others to explore the unknown contours of the claimed genus."[75]

"[A] genus can be sufficiently disclosed by either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can visualize or recognize the

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

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

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

members of the genus."[76] "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."[77]

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).[78] "[M]erely drawing a fence around the outer limits of a purported genus" is insufficient.[79] Instead, "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."[80]

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

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

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

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

80 *Id.* at 1349. *In re Entresto,* 125 F.4th 1090, 1097-99 (Fed. Cir. 2025) found sufficient written description of a pharmaceutical composition of two known active ingredients even though it did not disclose that they formed a particular

Four cases are especially probative here.

First, in *Novozymes et al., v. DuPont Nutrition Biosciences et al*., 723 F.3d 1336 (Fed. Cir. 2013), the Federal Circuit held invalid for lack of written description genus claims to modified enzymes. Similar to the structure of the presently challenged claims, the Novozyme claims defined a genus of modified enzymes that required: (i) one amino acid substitution, (ii) 90% sequence identity to a reference enzyme sequence, and (iii) increased enzyme activity ("increased thermostability") relative to the parent enzyme.[81]

The Court started by rejecting the premise that written description of a genus of enzymes can be established by combining individual attributes of the enzymes reported in the specification (*i.e.*, "[i]n particular, BSG alpha-amylase, amino acid position 239 and improved thermostability…").[82] Instead, the disclosure must describe the specific enzymes that possess those combinations of attributes:

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complex. Unlike *Entresto*, there is no disclosure of the vast majority of mutant species within the claimed genera here.

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

82 *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.").

> While the 2000 application provides formal textual support for each individual limitation recited in the claims of the '23 patent, ***it nowhere describes the actual functioning, thermostable alpha-amylase variants that those limitations together define***. Taking each claim—as we must—as an integrated whole rather than as a collection of independent limitations, one searches the 2000 application in vain for the disclosure of even a single species that falls within the claims or for any "blaze marks" that would lead an ordinarily skilled investigator toward such a species among a slew of competing possibilities. "Working backward from a knowledge of [the claims], that is by hindsight," Novozymes seeks to derive written description support from an amalgam of disclosures plucked selectively from the 2000 application.[83]

The Court also rejected the idea that because written description can be established if one can perform experiments that might discover additional species of mutated enzymes within the genus:

> Novozymes nonetheless maintains that one of ordinary skill in the art directed to position 239 would have known how to test every possible variant at that position and thus would have found the claimed variants as a matter of course. That argument misses the point, however. The question before us

[83] *Novozymes*, 723 F.3d 1336, 1349 (emphasis added, citations omitted).

> is not whether one of ordinary skill in the art presented with the 2000 application would have been enabled to take those final steps, but whether the 2000 application "discloses the [variants] to him, specifically, as something appellants actually invented.[84]

As the Court concluded:

> In this case, to actually possess the variant enzymes claimed in the '23 patent would have required Novozymes to confirm its predictions by actually making and testing individual variants or at least identifying subclasses of variants that could be expected to possess the claimed properties, which it did not do before filing the 2000 application. At best, the 2000 application describes a roadmap for producing candidate alpha-amylase variants and then determining which might exhibit enhanced thermostability. A patent, however, "is not a reward for the search, but compensation for its successful conclusion." Ariad, 598 F.3d at 1353 (quoting University of Rochester, 358 F.3d at 930 n. 10). For that reason, the written description requirement prohibits a patentee from "leaving it to the ... industry to complete an unfinished invention."[85]

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

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

Second, in *AbbVie*, the Federal Circuit found a disclosure of 300 examples to not be representative of a genus of particular IL-12 antibodies:

> Although the number of the described species appears high quantitatively, the described species are all of the similar type and do not qualitatively represent other types of antibodies encompassed by the genus.[86]

It also criticized the prophetic description as being "only a research plan, leaving it to others to explore the unknown contours of the claimed genus" and a "trial and error approach."[87]

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").[88] The court criticized the specification's failure to indicate which of the thousands of compounds would be effective, and found that "provid[ing] lists or examples of supposedly effective nucleosides," without "explain[ing] what makes them effective, or why" deprives a skilled artisan "of any meaningful

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86 *AbbVie*, 59 F.3d at 1300-1301.

87 *Id.*

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

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."[89]

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 "broad genus of amino acid sequence homologues" but which (like claim 1 here) imposed no restrictions where particular replacements could be made, thereby causing the claim "to cover, at minimum, thousands of amino acid sequences."[90] Citing dependent claim 12, the Board found fatal to claim 1 the specification's failure to "explain what, if any, structural features exist (*e.g.*, remain) in sequences that vary by as much as 10% that allow them to retain the antigenic characteristics referenced in the Specification" (*i.e.*, the same property that would be required of "inactive mutant" contraceptive PH20 polypeptides contemplated by the disclosure here).[91] As it observed, the homology limitation

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89 *Id.* at 1164.

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

91 *Boehringer*, at 35; EX1001, 71:10-12.

"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).[92]

The deficiencies of the present claims dwarf those in these cases. They capture much larger, much less predictable, and much more diverse sub-genera, and the common disclosure is far more limited. Because the common disclosure neither discloses a representative number of species of modified PH20 polypeptides with increased enzymatic activity meeting the claim requirements, nor identifies sufficient structural features common to such modified PH20 polypeptides, it fails to demonstrate possession of the full scope of the claims of the '791 Patent.

1. Claims 1-4 Lack Written Description

The claims encompass ***all*** enzymatically active PH20 polypeptides exhibiting increased hyaluronidase activity relative to the unmodified $PH20_{1-447}$ enzyme and that meet the sequence identity parameters of the claims. But the common disclosure does not identify ***which*** of the 10^{49}+ polypeptides within the scope of the claims are those increased activity mutants, much less demonstrates possession of all of them. And simply reciting a ***desired*** hyaluronidase activity

92 *Boehringer*, at 35-36.

(*i.e.*, >100% or >120%) does not identify ***which*** of the 10^{49} to 10^{60} modified PH20 polypeptides with 95% sequence identity to SEQ ID NO: 35 and a specified replacement at position 309 will exhibit those functional properties.[93]

First, the handful of $PH20_{1-447}$ polypeptides with only one substitution at position 309 that are disclosed in the common disclosure and that exhibited the claimed levels of hyaluronidase activity are not representative of each claim's genus, which includes 10^{49} to 10^{60} additional PH20 polypeptides with up to 17 or 20 additional substitutions and/or truncations.[94] Critically, there are ***no examples*** (prophetic or actual) of any multiply-modified PH20 polypeptide with 433 residues that included the required position 309 substitution.[95]

Second, the common disclosure identifies no common structural feature shared by all multiply-modified PH20 polypeptides (if any) within the claims' parameters exhibiting increased activity or >120% of the activity of unmodified $PH20_{1-447}$.[96] The presence of a single position 309 substitution does not demonstrate that all multiply-modified PH20 polypeptides with that substitution

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93 EX1003, ¶¶ 195, 202-204.

94 EX1001, 234 (Table 9); EX1003, ¶¶ 202-204.

95 EX1003, ¶ 71; *see* § V.A.1.c.ii.

96 EX1003, ¶¶ 162, 195, 201.

will exhibit increased activity, and the common disclosure does not contend otherwise.[97]

Third, the common disclosure makes no connection between modified PH20 polypeptides with "increased activity" that have 433 residues (SEQ ID NO:35) and particular substitutions at position 309, and up to 17 or 21 additional substitutions. This connection is only made in the claims presented in the '791 Patent, which thereby attempt to claim a specific subgenus of modified PH20 polypeptides not described in the common disclosure.

Fourth, the claims include in their scope modified PH20 polypeptides with mutations that the common disclosure indicates will be inactive and should be avoided in enzymatically active forms of PH20. By claiming modified PH20 polypeptides with such mutations, the claims are additionally unpatentable for lack of written description.

Finally, as noted previously, when faced with PGR petitions challenging claims requiring >100% or >120% activity on written description grounds,

[97] EX1003, ¶¶ 151, 172, 195.

Patentee has consistently filed statutory disclaimers disavowing those claims rather than defend their patentability.[98]

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

Claims 1-4 encompass modified PH20 polypeptides based on SEQ ID NO: 35 (*i.e.*, residues 1-433) that are not only immense in number but are structurally and functionally diverse. They include mutants with between 2-21 substitutions for the broadest claims (*e.g.* claims 1-2) to 2-17 for the narrowest (claim 3). The optional sets of substitutions can be anywhere in the sequence (*i.e.*, clustered in a narrow region, spaced apart in groups, or spread randomly throughout the sequence), to any of 19 other amino acids, and arranged in any manner.[99] The claims thus capture a mutant with 5 substituted hydrophobic residues clustered in a small region, as well as one with 21 or 17 substitutions that mix polar, charged, aliphatic, and aromatic amino acids in any manner.[100]

Each claim also encompasses substitutions within C-terminally truncated forms of PH20, which, via the claims' sequence identity language, capture PH20

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

99 EX1003, ¶ 128; EX1001, 59:11-18, 46:7-11, 46:21-23, 40:32-38.

100 EX1003, ¶¶ 128-129.

polypeptides terminating at positions well before 430. For example, the sequence identity parameters in claims 1 and 2 when applied to SEQ ID NO: 35 (433 residues in length) permit up to 21 changes (with any mixture of insertions, deletions and substitutions), thus capturing PH20s terminating at position 416. But removing so many residues from the C-terminus of PH20 can render it inactive, and the disclosure does not describe (or suggest) that incorporating position 309 substitutions restore (let alone increase) hyaluronidase activity.[101]

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

The claims' unconstrained sequence identity language captures not only modified PH20 polypeptides with innumerable combinations of substitutions but those with structural features a skilled artisan would understand the disclosure to be saying to avoid when making "active mutants." Multiply-modified PH20 polypeptides with these different structural features raise questions regarding whether any will possess hyaluronidase activity (let alone increased activity), but at a minimum would be viewed by a skilled artisan as being structurally distinct types of enzymatically active PH20 polypeptides as compared to singly-substituted $PH20_{1-447}$ which do not have those additional structural features.

[101] EX1003, ¶¶ 168-171.

Instead of navigating this confusing landscape, the patent simply instructs the skilled artisan "to generate a modified PH20 polypeptide containing any one or more of the described mutation, and test each for a property or activity as described herein."[102] The common disclosure thus does not describe PH20 polypeptides reflecting the structural diversity of the "active mutants" subgenus in the claims' scope, let alone the portion of it that includes modified PH20 polypeptides with >100% or >120% of the hyaluronidase activity of $PH20_{1-447}$.

(i) No Multiply-Modified "Active Mutant" PH20 Polypeptides with Substitutions that Render $PH20_{1-447}$ Inactive

The common disclosure indicates that active mutant modified PH20 polypeptides should not incorporate amino acid substitutions that as single substitutions rendered $PH20_{1-447}$ inactive, stating:

> ***To retain hyaluronidase activity***, modifications typically ***are not made*** at those positions that are less tolerant to change or required for hyaluronidase activity.[103]

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

[102] EX1001, 76:51-55; EX1003, ¶ 204.

[103] EX1001, 78:30-32 (emphases added).

and 10.[104] It does not limit this observation to single-replacement $PH20_{1-447}$ mutants, or suggest that any of these substitutions that render $PH20_{1-447}$ inactive should be included in enzymatically active, multiply-modified PH20 polypeptides (much less identifies specific combinations of substitutions including them).[105]

Instead, by stating that the substitutions listed in Tables 5 and 10 should not be included in enzymatically active multiply-modified PH20 polypeptides, it clearly conveys to the skilled artisan that enzymatically active multiply-modified PH20 polypeptides do not and should not contain these substitutions.[106] The claim language however captures active mutants that include one or more of the substitutions in Tables 5 and 10.

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

The common disclosure does not describe or provide guidance concerning "active mutant" PH20 polypeptides truncated before position 447, particularly multiply-modified PH20 mutants terminating significantly before that position.[107]

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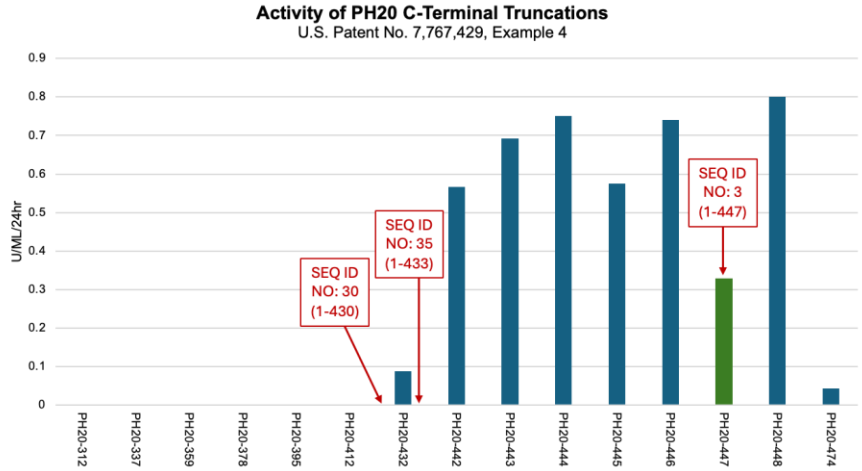
104 EX1001, 78:32-79:5.

105 EX1003, ¶¶ 156, 166-176, 173.

106 EX1003, ¶¶ 153-156, 167; EX1001, 78:30-79:5, 68:63-69:6.

107 EX1003, ¶¶ 97, 100, 171-173; EX1001, 72:26-32.

The common disclosure and prior art report that wild-type PH20 polypeptides terminating at or below position 442 have ***significantly reduced or no*** hyaluronidase activity. For example, Patentee's '429 Patent reported that PH20 mutants terminating below position 432 lacked hyaluronidase activity, while those terminating between positions 432 and 448 had widely varying activity (below):[108]



Position (w/leader)	Mutant	U/ML/24hr	Normalized to PH20(1-447)
347	PH20-312	0	0.00
372	PH20-337	0	0.00
394	PH20-359	0	0.00
413	PH20-378	0	0.00
430	PH20-395	0	0.00
447	PH20-412	0	0.00
467	**PH20-432**	**0.089**	**27.05**
477	PH20-442	0.567	172.34
478	PH20-443	0.692	210.33
479	PH20-444	0.75	227.96
480	PH20-445	0.575	174.77
481	PH20-446	0.74	224.92
482	**PH20-447**	**0.329**	**100.00**
483	PH20-448	0.8	243.16
509	PH20-474	0.044	13.37

108 EX1005, 87:52-88:24 ($PH20_{1-442}$ activity "decreased to approximately 10%"); EX1013, Figure 2, 430-32 ("[l]ess than 10% activity was recovered when constructs terminated after amino acid 467 [432] or when using the full-length PH20 cDNA"); EX1003, ¶ 94.

Patentee's '429 Patent also reported that "a very narrow range spanning … [437-447] … defined the minimally active domain" of human PH20, and observed this "minimally active" human PH20 domain contains at least residues 1-429.[109]

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

> A mature PH20 polypeptide … containing a contiguous sequence of amino acids having a C-terminal amino acid residue corresponding to amino acid residue ***464*** of SEQ ID NO: 6 [position ***429*** without signal] … ***is the minimal sequence required for hyaluronidase activity***.[110]

In 2007, Chao reported that the C-terminal region of human hyaluronidases contains a unique domain ("Hyal-EGF") linked to a characteristic pattern of sequences, which runs from positions 337-409 in PH20.[111] In 2009, Zhang showed the Hyal-EGF domain was necessary for hyaluronidase activity.[112]

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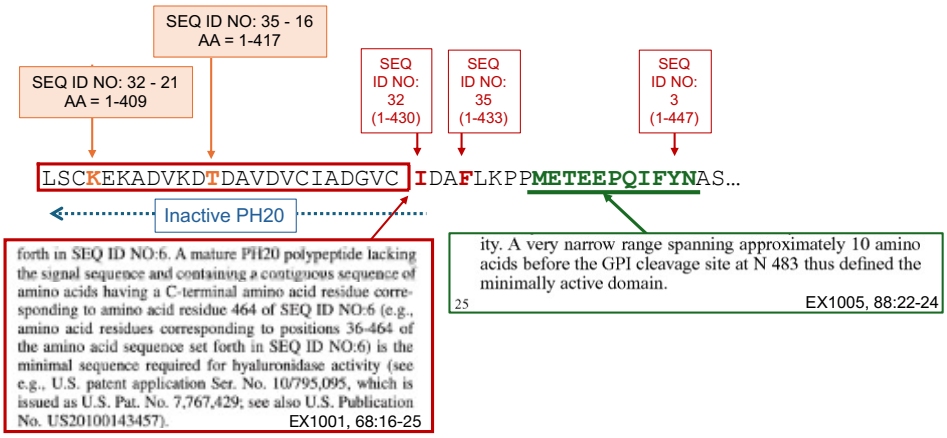
[109] EX1005, 6:65-7:7 ("… sHASEGP from amino acids 36 to Cys 464 [429] … comprise the minimally active human sHASEGP hyaluronidase domain"); EX1003, ¶ 93.

[110] EX1001, 68:16-25 (emphases added); *also* EX1003, ¶¶ 96, 157.

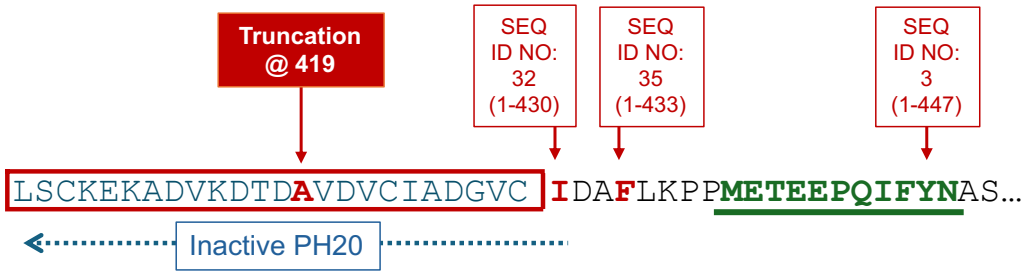
[111] EX1006, 6912-13, 6916-18; EX1004, ¶¶ 97-99; EX1003, ¶ 95.

[112] EX1010, 9438; EX1003, ¶ 89.

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



So, for example, a skilled artisan would have believed a PH20 polypeptide terminating at position 419 would be inactive based on the common disclosure and information published before 2011.[113]



[113] EX1003, ¶¶ 95-98, 169-172.

The common disclosure provides no examples of (or guidance concerning) enzymatically active multiply-substituted PH20 mutants (or ones with greater activity than unmodified $PH20_{1-447}$) truncated to positions between 418 and 447 (including to 433).[114] The claims (which each permit 17-21 total changes from the 433-length reference sequence) nonetheless capture such mutants.[115]

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

The empirical results in the common disclosure do not provide any guidance to a skilled artisan about the structural features of multiply-modified PH20 polypeptides with enzymatic activity much less increased activity.

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

The common disclosure reports results from testing a portion of a library of ~6,753 single-replacement $PH20_{1-447}$ polypeptide sequences.[116] The mutants were produced using a library of CHO cells transfected with a plasmid encoding mutagenized $PH20_{1-447}$ sequences where one of 447 positions in the sequence "was

[114] EX1003, ¶¶ 95-98, 98, 100.

[115] EX1003, ¶¶ 168-170.

[116] EX1001, 133:5-16, 200:32-34, 200:12-18.

changed to one of about 15 amino acid residues, such that each member contained a single amino change."[117] Results for ~5,917 of the mutants are reported.[118]

The common disclosure classifies more than half (~57%) of the tested mutants as "inactive mutants" and ~30% as having less activity than unmodified $PH20_{1-447}$ (20%-100%).[119] In other words, it portrays ~87% of the 5,917 single-replacement $PH20_{1-447}$ polypeptides that were made and tested as having ***less*** activity than unmodified $PH20_{1-447}$. Relevant to the claims here, these experimental results also show that only ~13% of singly-substituted mutants exhibited more than 100% activity relative to unmodified $PH20_{1-447}$.

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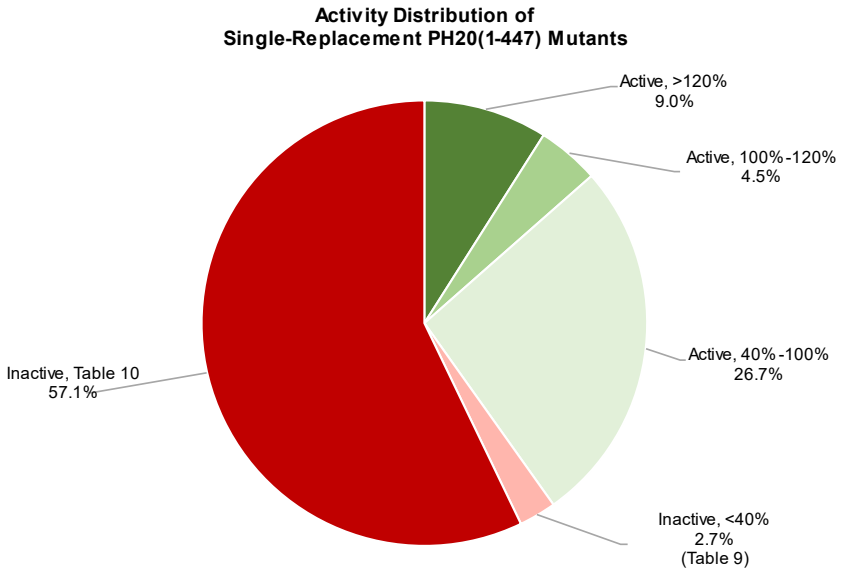
117 EX1001, 200:12-21.

118 EX1003, ¶¶ 111-112, 114. 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.

119 EX1003, ¶ 108, 114-115.

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



Notably, the data is not analyzed in the common disclosure—it is simply presented. No attempt is made to assess the impact of any single substitution on the protein's structure, much less extrapolate these results to PH20 polypeptides with multiple substitutions.[120]

120 EX1003, ¶¶ 146-148.

The data's quality is also questionable: no control values or statistical assessments are provided for these activity results, nor are the individual measured values from testing mutants.[121] The common disclosure also does not report the hyaluronidase activity measured for 3,380 inactive mutants, and provides no information on 836 other single substitution $PH20_{1-447}$ mutants that were made and tested, or classify them as "active" or "inactive" mutants. *See* § V.C.

The data reveal no trends or correlations even for single-replacement $PH20_{1-447}$ polypeptides.[122] For example, different substitutions at the same position in $PH20_{1-447}$ yielded active and inactive mutants, with >800 unclassified mutants.[123]

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

[121] EX1003, ¶¶ 107-108, 111-112, 115.

[122] EX1003, ¶¶ 146-150.

[123] EX1001, Table 8, 9, 10.

Changing multiple residues in PH20 polypeptides can cause unpredictable interactions within the protein's structure and resulting function that do not occur in single-substitution mutants.[124] The empirical test results for single substitution mutants do not identify to a skilled artisan which of the 10^{49}+ PH20 mutants with a 309 substitution and 1-20 (or 1-16) additional substitutions are enzymatically active or have increased activity (or for that matter, are inactive or cannot be made and are useless).[125] Instead, all it shows is that ***most*** single-substitutions impaired or eliminated hyaluronidase activity.[126]

(ii) Purported Stability Data Is Not Reliable or Probative

The common disclosure reports results testing ~409 single-replacement $PH20_{1-447}$ polypeptides in "stability" assays.[127] Table 11 reports hyaluronidase activities of the mutants at 4° C and 37° C, and with a "phenolic preservative" (m-cresol).[128] Table 12 reports relative hyaluronidase activities of those mutants.[129]

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124 EX1003, ¶¶ 54-58, 240.

125 EX1003, ¶¶ 147, 149, 204.

126 EX1003, ¶ 114.

127 EX1001, Tables 11-12.

128 EX1001, 269:45-276:21 (Table 11).

129 EX1001, 276:22-287:28 (Table 12).

The "stability" data provides no meaningful insights.[130] Unsurprisingly, many single-replacement $PH20_{1-447}$ polypeptides showed more activity at 37° C than at 4° C.[131] And testing with m-cresol showed only a few mutants resisted denaturation.[132] With one exception, the measured activity data cannot be attributed to improved stability of PH20.[133] The data are also largely meaningless—many measured activity values are within the activity ranges reported for the positive control.[134]

Positive Control ("PC") (OHO)	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
PC1	94.998	5.230	4.970	96.871	8.456	8.190
PC2	105.798	4.480	4.740	108.066	5.246	5.670
PC3	100.000	3.330	3.330	82.778	3.759	4.590
PC4	94.762	19.070	18.070	109.539	16.529	18.110
PC5	142.024	4.480	6.360	130.947	5.595	7.330
PC6	45.115	20.770	9.370	68.017	11.035	7.510
PC7	53.324	21.950	11.710	74.253	9.960	7.400
PC8	59.581	25.240	15.040	75.872	16.231	12.310
PC9	91.844	19.050	17.500	80.371	13.977	11.230
PC10	93.828	13.470	12.630	96.630	19.454	18.800
PC11	57.773	17.040	9.850	83.536	17.573	14.680
PC12	100.000	18.560	18.560	148.226	16.239	24.070
PC13	74.325	18.290	13.600	61.119	9.286	5.680
PC14	98.132	8.480	8.320	87.677	10.006	8.770
PC15	93.817	9.620	9.020	102.223	9.745	9.960
PC16	96.922	8.560	8.300	87.993	9.064	7.980
PC17	96.648	9.910	9.580	86.891	9.938	8.630

KEY
Coloration of Percent (%) Activity Values
n/a
>120
between 100 and 120
between 80 and 100
between 40 and 80
between 20 and 40
between 10 and 20
between 0 and < 10

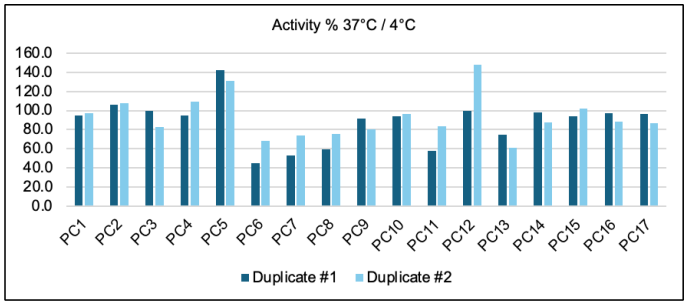
130 EX1003, ¶ 76.

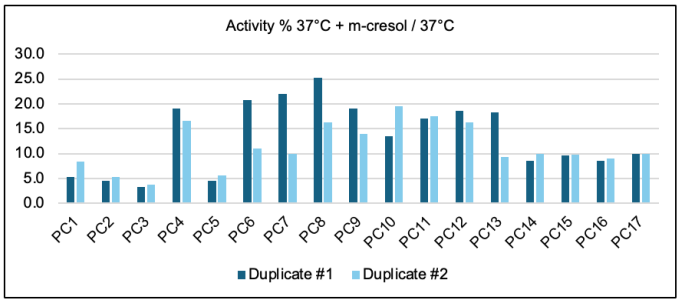
131 EX1003, ¶ 73; EX1001, 176:32-41.

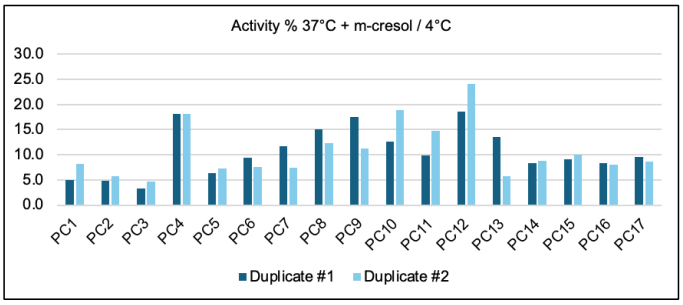
132 EX1003, ¶ 69.

133 EX1003, ¶ 69.

134 EX1003, ¶ 71, Appendix A-7, A-8; EX1001, 287:1-28 (Table 12).







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

As Dr. Hecht observes, this significant variation "raises serious doubts about how probative or instructive the values of individual tested mutants are that fall within the range of variability observed for the control."[135]

Importantly, the common disclosure does not identify any—let alone ***which***—combinations of substitutions in a multiply-modified PH20 improve

[135] EX1003, ¶¶ 70-72; *see also* EX1001, 287:34-58 (positive control also varied).

stability.[136] The common disclosure thus does not describe or provide meaningful guidance concerning which of the 10^{49}+ multiply-modified PH20 polypeptides that may have increased stability (or any other functional attribute, such as increased hyaluronidase activity).[137]

(d) The Common Disclosure's Research Plan Does Not Identify Any Singly- or Multiply-Modified Enzymatically Active PH20 Polypeptides Terminating at Position 433

The common disclosure has two notable omissions: (i) it describes no example of a modified PH20 polypeptide having residues 1-433 (SEQ NO: 35) and a substitution at position 309, and (ii) it does not describe ***any*** multiply-modified PH20 polypeptides (including those that are "active mutants" with increased hyaluronidase activity, and which contain a position 309 substitution).[138] Instead, it simply presents ***the idea*** that multiply-modified PH20 polypeptides can be made that may have enzymatic activity (or increased activity).[139]

First, it observes that "[a] modified PH20 polypeptide can have up to 150 amino acid replacements," "[t]ypically" contains between 1 and 50 amino acid

136 EX1003, ¶¶ 69, 76.

137 EX1003, ¶ 151.

138 EX1003, ¶¶ 100, 140-141, 151-152.

139 EX1003, ¶ 182.

replacements and "can include any one or more other modifications, in addition to at least one amino acid replacement as described herein."[140] 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)."[141]

None of these statements ***identify*** any actual multiply-modified PH20 polypeptides (*i.e.*, PH20 polypeptides with specific sets of 2 or more amino acid substitutions). They simply draw boundaries around immense numbers of PH20 polypeptides that may be enzymatically active.

The common disclosure also describes no multiply-modified, enzymatically active PH20 polypeptides that were made and tested.[142] Instead, it provides only a prophetic research plan requiring "iterative" make-and-test experiments that ***might discover*** such PH20 polypeptides, stating they "***can be*** modified or further

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140 EX1001, 47:8-18.

141 EX1001, 98:53-67 (emphasis added).

142 EX1003, ¶ 182.

modified" and "***can be*** identified."[143] This research plan does not identify ***which*** multiply-modified PH20 polypeptides can be made or ***are*** active mutants.[144]

Alternatively, it proposes mutations that ***can be*** "targeted near" "critical residues" which supposedly "***can be*** identified because, when mutated, a normal activity of the protein is ablated or reduced."[145] But Tables 5 and 10 report at least one substitution at each of 405 positions between positions 1 and 444 of $PH20_{1\text{-}447}$ resulted in an inactive mutant.[146] This guidance to target locations "near" ~90% of the amino acids in $PH20_{1\text{-}447}$ is no different than targeting ***every residue***.[147]

These prophetic research plans, based entirely on unfocused, iterative "make-and-test" experiments, do not identify to a skilled artisan which of the 10^{49}+ multiply-modified PH20 polypeptides within the claims' scope ***are*** enzymatically

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143 EX1001, 140:37-49 (emphases added); *see also id.* at 41:10-17, 133:51-56; EX1003, ¶¶ 183-187.

144 EX1003, ¶¶ 183, 194-195, 198; EX1001, 42:30-32; *see generally id.*, 133:5-50, 133:59-135:34, 135:62-140:36.

145 EX1001, 140:50-141:8; EX1003, ¶¶ 188-189.

146 EX1003, ¶ 190, Appendix A-3.

147 EX1003, ¶ 190.

active.[148] Instead, they require a skilled artisan to perform repeated cycles of mutagenesis, screening and selection until 10^{49} to 10^{60} modified PH20 polypeptides are made and tested.[149] That in no way demonstrates possession of ***all*** "active mutant" modified PH20 polypeptides in the scope of the claims, much less the subset of such multiply-modified PH20 polypeptides with increased activity within those claims' scope.

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

The common disclosure does not identify the structural significance of any of the ~2,500 mutations that yielded single residue "active mutant" $PH20_{1-447}$ polypeptides (or the ~3,400 inactive mutants or ~830 mutants that were uncharacterized).[150] For example, it does not identify the effect of any replacement on any domain structure, any structural motif(s) or even the local secondary structure at the site of the substitution in the PH20 polypeptide, nor does it identify how any such (possible) structural change(s) is/are responsible for the measured

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148 EX1003, ¶ 201.

149 EX1003, ¶¶ 185-187, 198-199; EX1001, 135:42-47, 135:35-60, 138:55-59, 139:3-8, 139:25-39.

150 EX1003, ¶¶ 156, 162.

change in hyaluronidase activity.[151] Instead, it simply lists ***single*** replacements to random amino acids that yielded "active mutants."[152]

The common disclosure also does not identify any ***sets*** of specific amino acid replacements within a single PH20 polypeptide that correlate to changes in structural domains or motifs that positively or negatively influence hyaluronidase activity, much less ***predictably*** increase activity to defined thresholds.[153]

The common disclosure's empirically identified examples of "active mutant" single-replacement $PH20_{1-447}$ mutants do not ***by themselves*** identify any "structure-function" relationship between "active mutants" and the set of single-replacement modified $PH20_{1-447}$ polypeptides.[154] Nor do they do so for the unknown number of multiply-modified active mutant PH20 polypeptides of varying lengths with between 2 and 21 substitutions.[155]

The common disclosure ***does not even contend*** that a particular amino acid replacement at a particular position (*e.g.*, 309) that makes $PH20_{1-447}$ an "active

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151 EX1003, ¶¶ 146-147, 156.

152 EX1001, 232:50-234:6; EX1003, ¶¶ 146-147.

153 EX1003, ¶¶ 55, 149-150.

154 EX1003, ¶¶ 61, 150, 162, 164.

155 EX1003, ¶ 162.

mutant" will make any other modified PH20 polypeptide with that replacement plus 1-20 additional substitutions an "active mutant" or a mutant with increased activity.[156] Such an assertion would have no scientific credibility—the activity of a protein such as PH20 is dictated by its overall structure, which can be influenced unpredictably by different combinations of changes to its amino acid sequence.[157] Thus, even the inventors did not view their compilation of empirical test results as identifying a structure-function relationship for 10^{49}+ multiply-modified "active mutants."[158]

The common disclosure, thus, does not identify to a skilled artisan ***any structural features*** shared by all modified PH20 polypeptides having increased hyaluronidase activity within the scope of the claims.[159]

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156 EX1003, ¶¶ 172, 202-203.

157 EX1003, ¶¶ 56-57.

158 *See, e.g.*, EX1001, 77:43-80:20, 99:1-63.

159 EX1003, ¶ 162.

(f) The Common Disclosure Does Not Describe a Representative Number of Multiply-Modified PH20 Polypeptides with Enzymatic Activity or Increased Activity

The ~2,500 active mutant single-replacement $PH20_{1-447}$ polypeptides in the disclosure are not representative of multiply-modified mutant PH20 polypeptides with increased hyaluronidase activity encompassed by the claims.[160]

First, single-replacement $PH20_{1-447}$ examples are not representative of the 10^{49}+ $PH20_{1-447}$ polypeptides having ***2 to 20 additional substitutions*** to any of 19 other amino acids at any of hundreds of positions within the protein.[161] The latter group includes a massive number of structurally distinct proteins (*e.g.*, distinct sequences, distinct secondary structures, distinct structural motifs, etc.) that form when PH20 sequences with multiple amino acid substitutions successfully fold.[162] None of them are described in the common disclosure.[163]

Multiple substitutions made to a protein can cause different interactions between neighboring residues relative to those caused by single substitutions.[164]

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160 EX1003, ¶¶ 61, 150, 160, 164.

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

162 EX1003, ¶¶ 58-63.

163 EX1003, ¶ 166.

164 EX1003, ¶¶ 55-56, 58, 60, 161, 164.

For example, a first amino acid substitution can affect the neighbors of the replaced amino acid by (i) introducing a stabilizing interaction, (ii) removing a stabilizing interaction, and/or (iii) introducing a conflicting interaction (*e.g.*, adverse charge or hydrophobicity interactions).[165] A second substitution in that region may reverse those interactions (or not), and a third substitution may do the same, and so on up to 17 rounds permitted by the narrowest claim, each potentially causing different interactions.[166]

The common disclosure, however, does not identify effects of any single substitution on the various domains, secondary structures and structural motifs within any PH20 polypeptides within the scope of the claims.[167] And the activity of a protein with multiple substitutions is rarely dictated by only one of the substitutions—it is dictated by the unique structure that reflects ***the totality*** of effects of those many substitutions.[168] The common disclosure provides no information on structural effects of multiple substitutions.[169]

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165 EX1003, ¶¶ 56-58.

166 EX1003, ¶¶ 58-60, 149.

167 EX1003, ¶¶ 162-163, 240.

168 EX1003, ¶¶ 61, 148.

169 EX1003, ¶ 162.

The single-replacement active mutant $PH20_{1-447}$ polypeptides in the disclosure thus are not representative of the unidentified number of undisclosed enzymatically active multiply-substituted PH20 mutants within the claims' scope (particularly those with increased hyaluronidase activity), which comprise myriad combinations of substitutions that each can uniquely impact the structures and properties of the mutated protein and may (or may not) result in a mutant with increased hyaluronidase activity.[170]

Enzymatically active single-replacement $PH20_{1-447}$ polypeptides also are not representative of multiply modified PH20 polypeptides that incorporate changes that render wild-type PH20 inactive (*e.g.*, truncations terminating below position 429, or single substitutions that rendered $PH20_{1-447}$ inactive).[171] Such single-replacement active mutants do not contain the additional and distinct structural features that rendered the latter PH20 polypeptides enzymatically ***inactive***.[172] For example, the I309N $PH20_{1-447}$ polypeptide would not be considered representative of a PH20 terminating at position 419 with that I309N substitution, as the former omits the structural feature (the C-terminal truncation) that rendered the latter

[170] EX1003, ¶¶ 150, 164.

[171] EX1003, ¶¶ 166, 168.

[172] EX1003, ¶ 171.

inactive.[173] The common disclosure does not teach—and a skilled artisan could not have predicted from the examples of single-replacement $PH20_{1-447}$ mutants—which single substitutions in a truncated inactive PH20 mutant would not only restore but restore increased enzymatic activity, much less identifies the precise combinations that do.[174]

The common disclosure thus provides a very narrow set of working examples relative to the diversity of increased activity modified PH20 polypeptides being claimed.[175] The examples are restricted to ***one type of change*** (a single amino acid replacement) in ***one type of PH20 polypeptide*** (SEQ ID NO: 3).[176] By contrast, the claims encompass changes to a 433-residue PH20 sequence (none of which were not tested), and include, in addition to a replacement at position 309, up to 20 (claims 1-2, 4-10), or 16 (claim 3) additional changes.[177]

Consequently, a skilled artisan would not have viewed the examples of single amino acid replacements in $PH20_{1-447}$ in the common disclosure to be

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173 EX1003, ¶¶ 170-173.

174 EX1003, ¶ 172.

175 EX1003, ¶ 160.

176 EX1003, ¶¶ 100, 102, 106, 111-112.

177 EX1003, ¶¶ 125-129.

representative of the diversity of increased activity modified PH20 polypeptides encompassed by the claims.[178]

(g) The Common Disclosure's Disparate and Generic Disclosures Regarding SEQ ID NO: 35, Position 309 and Increased Activity Do Not Describe the Claimed Genus

The common disclosure also fails to provide § 112(a) support under rationale of *Tronzo v. Biomet, Inc.* and similar Federal Circuit precedent, each of which rejected attempts to claim particular embodiments of a putative invention that were not disclosed or described in the disclosure by combining in the claims disparate and generic disclosures found in the specification.[179]

In *Tronzo*, the court held claims which captured multiple shapes of cups to not be adequately supported by a specification that described the invention as a cup having a conical shape, and where the specification's "only reference… to different shapes is a recitation of the prior art."[180] More recently, in *Novozymes*, the Federal Circuit reiterated the "fundamental concepts" of its § 112 precedents that dictate claims (such as those at issue here) are invalid "where a patent's written description disclosed certain subject matter in terms of a broad genus but

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178 EX1003, ¶ 150.

179 *Tronzo*, 156 F.3d 1154, 1158-60 (Fed. Cir. 1998).

180 *Id.* 1158-59.

its claims specified a particular subgenus or species contained therein."[181] For example, in *Novozymes* the Court, explained (citing *Ruschig*) that "a claim to a specific drug molecule" lacked written description where the specification "disclosed only a generic structure that could yield the claimed molecule given the proper selections at several variable positions," which "failed to provide 'sufficient blaze marks' to guide a reader through the forest of disclosed possibilities toward the claimed compound, which resided among the myriad others that also could have been made."[182] Likewise, in *Boston Scientific*, claims requiring drug-eluting stents to incorporate "a macrocyclic triene analog" of a particular drug were found invalid or lack of written description because the specification only "made passing reference to the term 'macrocyclic triene" and gave no indication that they "might be of special interest," such that there was no evidence the inventors "were in possession of the claimed invention."[183] Finally, in *Purdue Pharma*., claims to an extended-release formulation requiring a particular blood concentration ratio were

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181 *Novozymes*, 723 F.3d at 1346.

182 *Novozymes*, 723 F.3d at 1346 (citing *In re Ruschig*, 379 F.2d 990, 993-95 (1967)).

183 *Novozymes*, 723 F.3d at 1346 (citing *Boston Scientific Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1367-69 (Fed. Cir. 2011)).

not supported by two examples that "could be shown to meet the claimed limitation by piecing together the disclose data" but where the specification did not "in any way emphasize the [claimed] ratio."[184]

The "fundamental concepts" illustrated in these decisions confirm the lack of written description support for the '791 Patent's claims, all of which (unlike other patents in this extended family) require every modified PH20 polypeptide to have 95% or 96% sequence identity relative to one reference sequence: SEQ ID NO:35 that consists of residues 1-433 of the unmodified PH20 protein. But the common disclosure makes only "passing reference" to this particular reference sequence, does not identify it as having any particular significance or special interest, and does not include ***any*** examples of mutant polypeptides made from this reference sequence (whether with a position 309 substitution or with any other change or combination of changes).[185] Rather, every mutant made and tested by the inventors used a different reference sequence (NO:3) having 447 residues, and the

[184] *Novozymes*, 723 F.3d at 1346-47 (citing *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323-26 (Fed. Cir. 2000)).

[185] *See, e.g.*, EX1001, 3:61-4:19, 79:11-19; EX1003, ¶¶ 100, 127, 171.

inventors provided no particular reason to make mutants using a 433-length sequence instead.[186]

In fact, the common disclosure, referencing experimental work reported in an earlier Halozyme patent (the '429 Patent)(EX1005), states that significant C-terminal truncations abolished activity of the native PH20 enzyme—it reports that truncations terminating before position 429 are inactive.[187] There is no data reported in the '791 Patent (or the prior art) from testing the activity of an unmodified PH20 polypeptide with the SEQ ID NO: 35 sequence, much less one with a substitution at position 309 plus up to 17 or 20 additional substitutions or deletions. The most similar truncation mutant for which such data was publicly disclosed is the 1-432 residue native sequence PH20 truncation mutant (SEQ ID NO:34), which was reported to have ***only 27%*** of the activity of the 1-447 length PH20 ($PH20_{1-447}$)(below).[188] The common disclosure does not reconcile the data indicating truncation mutants terminating at or below position 433 exhibit ***reduced***

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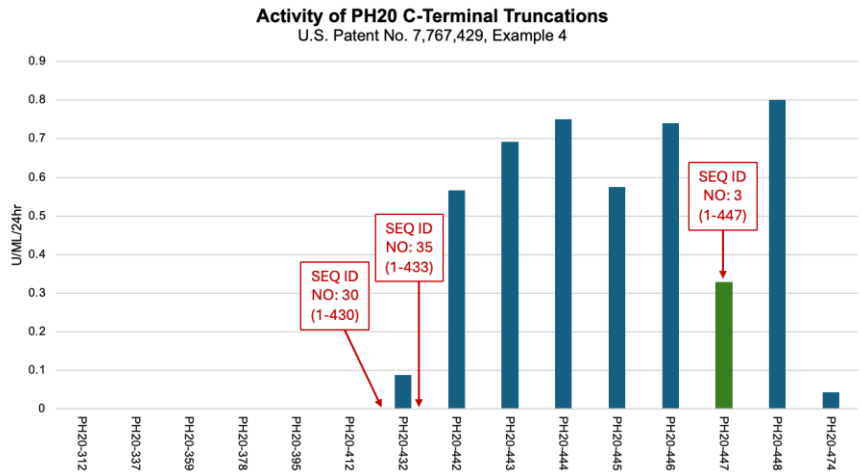
186 *See, e.g.*, EX1001, 200:12-34, Table 8; EX1003, ¶¶ 102, 106, 171.

187 EX1001, 68:16-25. *Also* EX1005 ('429 Patent), 87:52-88:24; EX1003, ¶¶ 94-96, 157-159.

188 EX1005, 87:52-88:24; EX1013, 432, Figure 2; EX1003, ¶¶ 94-96, 157-159, 171.

or no hyaluronidase activity and the claim language requiring such mutants to exhibit ***greater hyaluronidase activity*** than unmodified $PH20_{1-447}$, much less provide specific examples of modified PH20 polypeptides with such increased activity levels.[189]



Position (w/signal)	Mutant (mature #)	U/ML/24hr	Normalized to PH20(1-447)
347	PH20-312	0	0.00
372	PH20-337	0	0.00
394	PH20-359	0	0.00
413	PH20-378	0	0.00
430	PH20-395	0	0.00
447	PH20-412	0	0.00
467	**PH20-432**	**0.089**	**27.05**
477	PH20-442	0.567	172.34
478	PH20-443	0.692	210.33
479	PH20-444	0.75	227.96
480	PH20-445	0.575	174.77
481	PH20-446	0.74	224.92
482	**PH20-447**	**0.329**	**100.00**
483	PH20-448	0.8	243.16
509	PH20-474	0.044	13.37

The common disclosure does not describe modified PH20 polypeptides with ***increased*** activity relative to unmodified $PH20_{1-447}$ and have a position 309 substitution and up to 20 (or 16) additional changes relative to SEQ ID NO:35. That omission from the common disclosure cannot be rectified by "piecing together" desired combinations of properties and traits of modified PH20 polypeptides from the disparate and generic disclosures in the common disclosure. That disclosure does not guide a skilled artisan through its recitation of countless combinations of reference sequences and possible substitutions, deletions, or

189 EX1003, ¶¶ 171-173.

additions and desired activity levels to the particular (yet still enormous) genus of mutants being claimed by the ’791 Patent.

(h) The Claims Capture Multiply-Modified PH20 Polypeptides the Disclosure Excludes from the Class of Enzymatically Active PH20 Proteins

The claims require enzymatically active PH20 polypeptides. *See* § IV.D.2. The claim language also permits the claimed modified PH20 polypeptides, in addition to a position 309 substitution, to contain up to 20 additional substitutions to any other amino acid at any position in SEQ ID NO:35.

The common disclosure, however, 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).[190] It also provides no guidance on incorporating substitutions in an inactive mutant having one of the substitutions in Tables 5 or 10 that would restore increased enzymatic activity to that mutant.[191] Yet the claims capture such enzymatically active multiply modified PH20 polypeptides having changes the disclosure says to omit from “active mutants.”[192]

190 EX1001, 78:30-79:5; EX1003, ¶¶ 156, 166-167, 173.

191 EX1003, ¶ 166.

192 EX1003, ¶¶ 156, 166.

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. Dependent Claims 5-10 Lack Written Description

(a) Claim 5

Claim 5 requires the modified PH20 polypeptide to be "soluble."

Claim 5 lacks written description support for the same reasons identified for claim 1.

In addition, claim 5 lacks written description because it encompasses modified PH20 polypeptides that the common disclosure suggests will be insoluble and thus will lack enzymatic activity. It explains that "a soluble PH20 lacks all or a portion of a glycophosphatidyl anchor (GPI) attachment sequence," which was known to be hydrophobic,[193] and identifies position 456 as the first residue of the GPI sequence in PH20 (position 491 in SEQ ID NO: 6).[194] It also states that a

[193] EX1001, 44:59-61, 70:25-26, 49-61, 72:43-55; EX1005, 86:18-22; EX1003, ¶¶ 92-94.

[194] EX1001, 70:49-61.

soluble PH20 "is a polypeptide that is truncated after amino acid 482 of … SEQ ID NO: 6" (*i.e.*, 447 in SEQ ID NO:3).[195] The common disclosure thus suggests that human PH20 sequences that terminate below position 448 are soluble while those terminating above position 456 are insoluble.[196] For modified PH20 polypeptides that terminate between positions 448 and 456, it provides no guidance and provides no examples demonstrating any are soluble as the claims require.[197]

Claim 5 encompasses PH20 polypeptides which terminate at positions up to position 453 (one required substitution at position 309 plus 20 additions to SEQ ID NO: 35 (433 residues in length). Patentee may contend that some unidentified number of modified PH20 polypeptides that terminate at positions between 448 and 453 ***may*** be soluble. For example, the common disclosure suggests that between 1-10 residues within the GPI anchor "can be retained, provided the polypeptide is soluble."[198] But the common disclosure does not identify ***which*** modified PH20 polypeptides terminating above position 448 ***are*** soluble, whether any that incorporate substitutions at positions 448 to 453 are, and critically

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195 EX1001, 73:33-35; EX1005, 3:57-62.

196 EX1003, ¶¶ 92-93.

197 EX1003, ¶ 100.

198 EX1001, 72:36-42.

provides no examples of soluble PH20 mutants terminating at those positions.[199] It also provides no reason to expect that many modified PH20 polypeptides within the claim's scope are soluble.[200]

Claim 5 is unpatentable for these additional, independent reasons.

Finally, as noted above, when faced with PGR petitions challenging claims requiring solubility on written description grounds, Patentee has consistently disclaimed rather than defend such claims.[201]

(b) Claims 6-10

Dependent claims 6-10 do not alter the structure of PH20 polypeptides in the genus of claim 1. They instead specify additional features (claims 6-8), pharmaceutical compositions (9), or methods of manufacture (10) that reference the genus of claim 1. They lack written description for the same reasons explained in § V.A.1.[202]

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199 EX1003, ¶ 100, 106.

200 EX1003, ¶¶ 92-94, 100.

201 *E.g.*, PGR2025-00003 (claim 7), PGR2025-00006 (claim 7), PGR2025-00009 (claims 5, 15).

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

B. All Challenged Claims Are Not Enabled

All challenged claims are also unpatentable for lack of enablement.

"If a patent claims an entire class of … compositions of matter, the patent's specification must enable a person skilled in the art to make and use the ***entire*** class," *i.e.*, "the ***full scope*** of the invention," and so the "more one claims, the more one must enable."[203] "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."[204] "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."[205]

Although not required, enablement may be assessed using the *Wands* factors, which consider: "(1) the quantity of experimentation necessary; (2) how routine any necessary experimentation is in the relevant field; (3) whether the patent discloses specific working examples of the claimed invention; (4) the

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

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

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

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."[206]

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."[207]

"It is well established that the enablement requirement of § 112 incorporates the utility requirement of § 101."[208] A claimed invention must be ***presently useful***—stating a hypothesis and proposing testing to determine its accuracy is insufficient.[209] Further, if a claim encompasses significant numbers of inoperative

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

207 *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).

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

209 *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 skilled artisan must engage in undue experimentation to identify the operative ones, that renders the claims non-enabled.[210]

Here, the common disclosure utterly fails to enable the immense genus of modified PH20 polypeptides claimed. Using the disclosure and knowledge in the prior art, the skilled artisan would have to make and test 10^{49}+ different PH20 polypeptides having (i) a position 309 substitution and (ii) up to 17 to 20 more substitutions and/or deletions to determine which are useful because they are "active mutants" with increased hyaluronidase activity, which are "inactive mutants" that the disclosure implausibly contends are useful as a contraceptive antigen, and, finally, which are those mutants will not fold or be expressed, and which thus have no utility at all.[211]

1. Claims 1-4 Are Not Enabled

This case is a textbook example of claims that are not enabled under the reasoning articulated by the Supreme Court in *Amgen*. An analysis of the common disclosure under the Federal Circuit's framework for assessing undue

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

[211] EX1003, ¶¶ 180-182, 201.

experimentation using the factors in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) compels the same conclusion.

(a) Extreme Scope of the Claims

As explained in § IV.D.1, claims 1-4 capture between 10^{49} and 10^{60} modified PH20 polypeptides that have (i) particular substitution(s) at position 309, and (ii) 1 to 20 additional substitutions to any other amino acid anywhere in a PH20 polypeptide sequence 433 residues in length. Within these immense sets of PH20 polypeptides are unknown numbers of "active mutant" PH20 polypeptides with unknown sequences that have >100% or >120% of the activity of unmodified $PH20_{1-447}$.

Practicing the full scope of either of these "active mutant" subgenera within the claims requires navigating substantial scientific questions left unanswered by the common disclosure. Indeed, other than by making and testing ~10^{49} to 10^{60} multiply modified PH20 polypeptides using the prophetic, iterative procedure described it discloses, the common disclosure does not explain how to determine ***which*** combinations of substitutions (in addition to position 309) will yield enzymatically active mutants, particularly ones with the required thresholds of increased hyaluronidase activity.

There are also many types of PH20 mutants that the common disclosure would lead a skilled artisan to believe will ***not*** be enzymatically active, but which are nonetheless captured by the claim language, including those that:

(i) have substitutions the disclosure instructs to not include in an enzymatically active modified PH20 polypeptide because they rendered $PH20_{1-447}$ an inactive mutant;[212]

(ii) terminate before position 429, which the disclosure reports will eliminate activity in unmodified PH20 proteins;[213] and

(iii) include substitutions at positions that the common disclosure instructs "are less tolerant to change or required for hyaluronidase activity."[214]

Whether there are any (and how many of) such "active mutant" PH20 polypeptides within the scope of the claims is unknown, but the common disclosure identifies ***none***.[215]

The common disclosure also does not provide any guidance that a skilled artisan could use to identify which of the 10^{49}-10^{60} modified PH20 polypeptides

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212 EX1001, 78:30-32.

213 EX1001, 68:16-25; EX1003, ¶¶ 96, 157-159, 168-170.

214 EX1001, 75:62-76:7.

215 EX1003, ¶ 171.

with a position 309 substitution and 1-20 additional substitutions are ***inactive*** (and therefore, according to the common disclosure, allegedly useful as a contraceptive antigen), or ***cannot fold or be produced*** and thus have no utility at all [216]

In short, the claims capture a massive number of multiply-modified PH20 polypeptides that have ***unknowable*** properties absent the skilled artisan producing and testing 10^{49} and 10^{60} distinct mutants pursuant to the common disclosure's prophetic "make and test" methodology.[217]

Claims that capture a massive and diverse sets of proteins such as those here have routinely been found non-enabled. For example, the claims in *Amgen* covered "millions" of different, untested antibodies,[218] while in *Idenix*, the court found that a skilled artisan would "understand that 'billions and billions' of compounds literally meet the structural limitations of the claim."[219] In both cases (as here), the enormous claim scope was contrasted to limited working examples in the patent, the field of technology was unpredictable, and an immense quantity of experimentation was required to practice the claims' full scope (*Wands* Factors 1,

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216 EX1003, ¶¶ 112-113, 122, 144, 201.

217 EX1003, ¶¶ 161-163, 173.

218 598 U.S. at 603.

219 941 F.3d at 1157.

3, 4, and 7). Importantly, as the *Idenix* court also observed, it is improper to rely on the knowledge and efforts of a skilled artisan to try to "fill the gaps in the specification" regarding which of the "many, many thousands" of possible compounds should be selected for screening, and which in this case is impossible.[220]

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

The common disclosure provides an extremely narrow set of working examples: ~5,917 randomly generated single-replacement $PH20_{1-447}$ polypeptides, of which ~2500 were "active mutants" (with ~ 800 of that set exhibiting over >100% activity), ~3380 were "inactive mutants" and ~830 mutants that are only characterized by the single substitution each incorporates; these latter modified PH20 polypeptides are not classified as either "active" or "inactive" mutants.[221] Combined, those examples constitute a tiny fraction of the 10^{49} to 10^{60} modified PH20 polypeptides covered by the claims, and provide no insights into the effects of combining 5, 10, 15, or 20+ substitutions in one PH20 polypeptide.[222]

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220 *Id.* at 1159.

221 EX1003, ¶¶ 111-112.

222 EX1003, ¶¶ 160-164, 171.

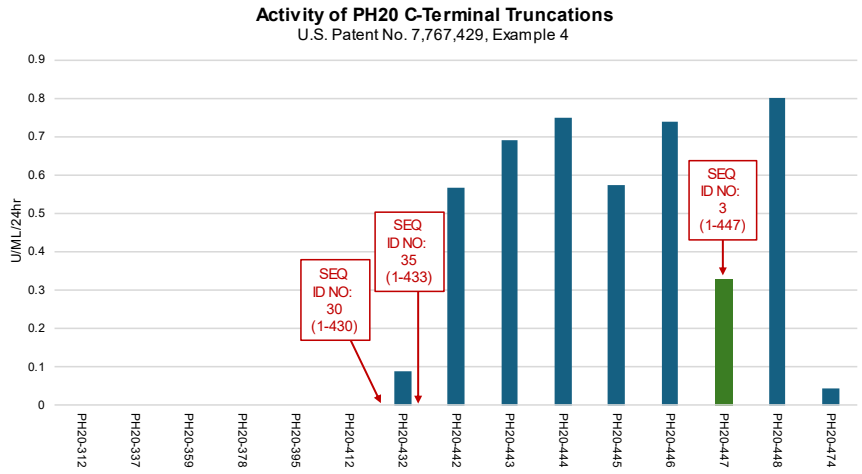
Notably, ***none*** of the exemplified PH20 polypeptides is based on a PH20 polypeptide truncated before position 447—there are ***zero*** examples of a modified PH20 polypeptide with the length required by every claim (*i.e.*, positions 1 to 433 (SEQ ID NO: 35)), ***plus*** a position 309 substitution and ***also*** between 2 and 21 additional substitutions.[223] In fact, the common disclosure does not even report the hyaluronidase activity of the reference ***unmodified*** $PH20_{1-433}$ polypeptide sequence (SEQ ID NO: 35).[224] The only truncated PH20 polypeptide with a comparable length was the 1-432 PH20 sequence characterized in Patentee's '429 Patent and other prior art, which reported that $PH20_{1-432}$ polypeptide exhibited ***only 27%*** of the activity of the $PH20_{1-447}$ sequence (SEQ ID NO: 3)(below).[225] The common disclosure provides no guidance about how one might modify $PH20_{1-433}$ to cause it to have greater hyaluronidase activity than unmodified $PH20_{1-447}$, let alone a form

[223] EX1003, ¶¶ 160-164, 171.

[224] EX1001, 200:12-34, Table 9 (describing generation of single substitution mutants based on $PH20_{1-447}$ and reporting activity only of those mutants).

[225] EX1005 ('429 Patent), 87:52-88:24; EX1013 (Frost), 430-432, Fig. 2; EX1003, ¶¶ 95-97.

of $PH20_{1-433}$ that includes a position 309 substitution plus 2 to 20 additional substitutions.[226]



Position (w/signal)	Mutant (mature #)	U/ML/24hr	Normalized to PH20(1-447)
347	PH20-312	0	0.00
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394	PH20-359	0	0.00
413	PH20-378	0	0.00
430	PH20-395	0	0.00
447	PH20-412	0	0.00
467	**PH20-432**	**0.089**	**27.05**
477	PH20-442	0.567	172.34
478	PH20-443	0.692	210.33
479	PH20-444	0.75	227.96
480	PH20-445	0.575	174.77
481	PH20-446	0.74	224.92
482	**PH20-447**	**0.329**	**100.00**
483	PH20-448	0.8	243.16
509	PH20-474	0.044	13.37

The working examples in the common disclosure thus provide no credible guidance on practicing the full scope of the claims, particularly multiply-modified, enzymatically active PH20 polypeptides truncated to position 433.[227]

The remainder of the common disclosure does not provide this guidance either. The only guidance it provides for producing multiply-modified PH20 polypeptides is a prophetic and "iterative" "make and test" process for ***discovering*** active mutant PH20 polypeptides. *See* § V.A.1.d. But this research plan requires a skilled artisan to engage in undue experimentation to practice the full scope of the claims.

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226 EX1003, ¶¶ 94-97, 100, 171.

227 EX1003, ¶¶ 141, 147.

First, the prophetic method described in the common disclosure requires performing iterative rounds of ***randomized*** mutations (up to 20 rounds per starting molecule under the broadest claims) to ***discover*** which of the 10^{49}+ possible modified PH20 polypeptides the claims encompass might possess increased hyaluronidase activity.[228]

Second, the common disclosure provides no meaningful guidance or information that a skilled artisan could use to implement the prophetic procedure it discloses for making and discovering "active mutant" modified PH20 polypeptides 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 "active mutants" or those with increased activity;

[228] EX1003, ¶¶ 189-191; *see also* EX1018, 382 ("combinatorial randomization of only five residues generates a library of 205 possibilities (3.2×10^6 mutants), too large a number for manual screening"). Chica credited a "ground-breaking" predictive molecular modeling technique that was later shown to be false. EX1018, 384, 382; EX1030, 569; EX1034, 258; EX1036, 275, 277; EX1048, 859.

(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.[229]

Instead, the common disclosure requires the skilled artisan to iteratively repeat its prophetic research plan to make and test 10^{49}+ multiply-modified PH20 polypeptides to discover which are enzymatically active and will exhibit increased activity.[230]

Regardless whether individual rounds of "iterative" production and testing of PH20 mutants might be considered "routine," the aggregate scale of experimentation required to practice the full scope of the claims goes far beyond undue—it is impossible. Simply put, the common disclosure's prophetic, iterative and labor-intensive process requires making and screening an immense number of modified PH20 polypeptides, before which the skilled artisan will not know which

[229] EX1001, 140:51-63; EX1003, ¶¶ 151, 163, 182, 194-195.

[230] EX1003, ¶¶ 182, 196-197.

multiply-modified PH20 polypeptides are within the claims' scope.[231] The "***iterative***, ***trial-and-error process[es]***" the common disclosure specifies here are indistinguishable from those consistently found to not enable broad genus claims to modified proteins or other useful compounds.[232]

(c) Making Multiple Changes to PH20 Polypeptides Was Unpredictable

Like any protein, the activity of PH20 can be unpredictably influenced by changes to its amino acid sequence.[233] Introducing changes can alter the local structure of the protein where the change is made, which may disrupt secondary structures or structural motifs within the protein that are important to its biological activity (*e.g.*, catalysis, ligand binding, etc.) and/or stability.[234]

By 2011, skilled artisans could have assessed whether certain ***single*** amino acid substitutions at certain positions would be tolerated within the PH20 protein structure with a reasonable (though not absolute) expectation of success. [235]

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231 EX1003, ¶¶ 176, 193-195, 202.

232 *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.

233 EX1003, ¶ 61.

234 EX1003, ¶¶ 61, 202-203.

235 EX1003, ¶ 205, 240.

However, before the advances in computer-based protein structure prediction that occurred in the 2018-2020 time frame,[236] skilled artisans could ***not*** have predicted the effects of making more than a few concurrent amino acid replacements within a PH20 polypeptide, particularly when they were within a particular region of the protein.[237]

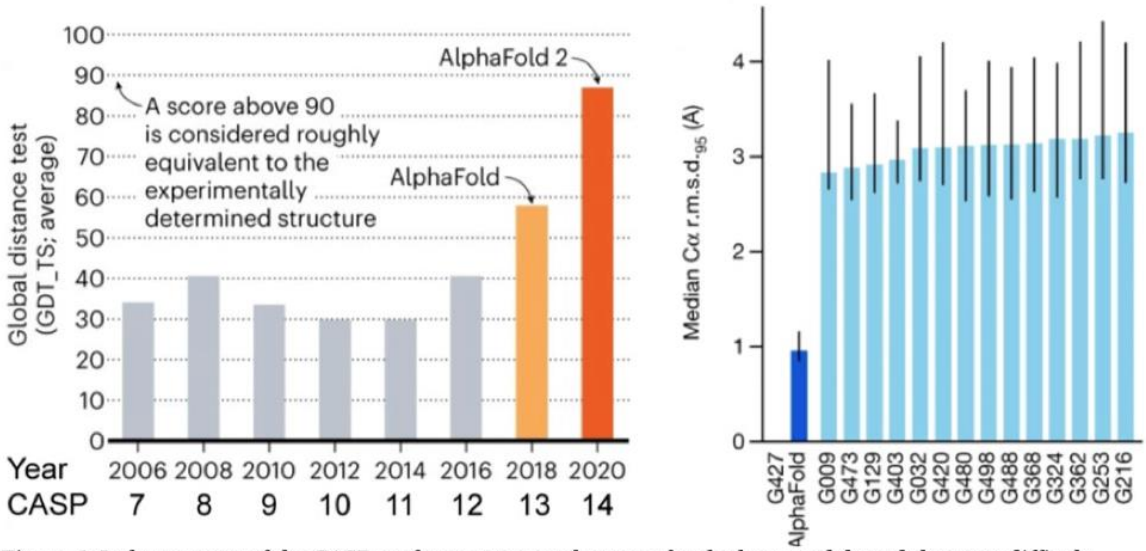

Figure 6. Left: progress of the CASP performance over the years for the best models and the most difficult targets.[38] Right: performance of AlphaFold2 relative to the top 15 entries by other groups in CASP14. Data are the median coordinate error and the 95% confidence interval of the median, estimated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

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

236 EX1003, ¶¶ 6, 206, 240.

237 EX1003, ¶¶ 163, 240; EX1027, 6-11, Figure 6.

and can even introduce new ones into the protein.[238] Replacing multiple amino acids thus can introduce an immense number of simultaneous influences on a protein's structure that cannot be predicted, particularly whether the resulting protein would have the required threshold hyaluronidase activity—be it >100% or >120%—of hyaluronidase activity of unmodified $PH20_{1-447}$.[239]

The cumulative effects of multiple changes also would have rapidly exceeded the capacity of computer-based, rational design protein engineering techniques to reliably predict the effects of each change on the protein's structure.[240] For example, the further away the modeled amino acid sequence gets from an actual naturally occurring sequence and/or the original model's structure, the less reliable that model became.[241] In addition, depending on the structural template used to produce the model, regions of the protein not supported by a corresponding structure cannot be reliably used to assess particular changes.[242]

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238 EX1003, ¶¶ 59-60, 195.

239 EX1003, ¶¶ 55, 58, 61, 205-206, 240.

240 EX1003, ¶ 163; EX1027, 6-11, Figure 6.

241 EX1003, ¶¶ 163, 201, 240; EX1004, ¶¶ 152-153.

242 EX1003, ¶¶ 163, 240; EX1004, ¶¶ 142-144; EX1012, 4, 8.

And the time required to carry out rational design techniques to "practice" the full scope of the claimed genus would be unimaginable.[243]

Consequently, a skilled artisan could not have used conventional rational design techniques to identify multiply-modified PH20 polypeptide sequences having more than a few substitutions, and certainly not 17 or 21 substitutions.[244] Moreover, using such techniques to identify even a handful of active mutant PH20 polypeptides with more than 1 substitution would have taken an extreme amount of time and effort.[245]

(d) Other Wands Factors and Conclusion

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

For example, while a skilled artisan was highly skilled, the field of protein engineering was unpredictable and tools did not exist that permitted accurate modeling of the range of multiply-changed PH20 polypeptides being claimed.[246] Likewise, while there was significant public knowledge about hyaluronidases,

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

244 EX1003, ¶¶ 50, 199.

245 EX1003, ¶¶ 163, 201.

246 EX1003, ¶¶ 163, 204-205, 240; EX1027, 6-11; EX1004, ¶¶ 149-151.

there was no experimentally-determined structure of the PH20 protein.[247] Also, the public literature generally reported on ***loss of activity*** from mutations in hyaluronidases, and did not predictably teach how to introduce changes that preserved or ***enhanced*** stability or activity of such proteins.[248]

Practicing the full scope of claims 1-4 thus would have required a skilled artisan to engage in undue experimentation, which renders those claims non-enabled.

2. Dependent Claims 5-10 Are Not Enabled

(a) Claim 5

Claim 5 requires "soluble" forms of PH20. Because claim 5 encompasses a substantial portion of the genus of claim 1, it is not enabled for the same reasons.

Additionally, as explained in § V.A.2.b, the common disclosure suggests that PH20 polypeptides extending past position 447 may be "insoluble." A skilled artisan would have expected the presence of the hydrophobic GPI sequence in a PH20 protein to cause aggregation, loss of activity, and/or reduced expression.[249]

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247 EX1004, ¶ 36.

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

249 EX1003, ¶¶ 92-93, 208, 234; EX1005, 86:18-26, 87:52-88:24; EX1013, 430-432, Fig. 2.

The common disclosure recognizes these problems, but provides no solutions to them—it discloses ***no*** examples of modified PH20 polypeptides extending past position 447 that are soluble.[250]

(b) Claims 6-10

Claims 6-10 employ the genus definition used in claim 1 and recite either further modifications to the modified polypeptides (6-8), pharmaceutical compositions (9), or methods of manufacture (10) using the claimed genus. These claims do not add requirements that limit the structure of polypeptides in the claim 1 genus and are not enabled for the same reasons.[251]

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

As explained in § IV.D.2., every claim requires modified PH20 polypeptides based on $PH20_{1-433}$ (SEQ ID NO: 35) that have (i) a specified position 309 substitution and (ii) up to between 17 and 20 additional modifications. The sequence parameters in the claims invariably capture PH20 polypeptides that exhibit less than 100% of the hyaluronidase activity of unmodified $PH20_{1-447}$, along with properly folded PH20 polypeptides that are "inactive mutants" (less

[250] EX1003, ¶¶ 96-97, 100; EX1001, 68:16-25.

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

than 20% of the activity of unmodified $PH20_{1-447}$) or cannot be produced or will not fold (and thus have no recognized utility).[252]

Despite this, the common disclosure identifies no correlation between either of the two claimed sub-genera of enzymatically active modified PH20 polypeptides (*i.e.*, those with >100% or >120% of the hyaluronidase activity of unmodified $PH20_{1-447}$) and the 10^{49}+ multiply-modified PH20 polypeptides captured by the sequence identity parameters of the claims.[253] Consequently, whether to identify the species within each sub-genera of modified PH20 polypeptides with "increased hyaluronidase activity", or to practice the full scope of each claimed subgenera will require a skilled artisan to perform trial-and-error testing of 10^{49}+ multiply-modified PH20 polypeptides to determine which are within either sub-genera, which are "inactive mutants" and which cannot be produced or will not fold and have no utility.[254]

The common disclosure also does not demonstrate that ~3,380 "inactive mutant" PH20 polypeptides folded correctly but were inactive—there is no evidence all these inactive mutants were successfully produced. The experimental

252 EX1003, ¶¶ 113, 161.

253 EX1003, ¶ 151.

254 EX1003, ¶ 195-196.

protocol instead equated the ***absence*** of hyaluronidase activity in the supernatant from each transfected cell with proof of production of an "inactive mutant."[255] But an absence of hyaluronidase activity in the supernatant would also be observed if the cell did not secrete the mutant or if the secreted mutant did not fold.[256]

The common disclosure also does not report the measured hyaluronidase activity values of the 3,380 mutants labeled "inactive mutants" or ~830 (12%) unclassified mutants, even though it did so for the thousands of "active mutants" in Table 9.[257] It is thus impossible to determine from the common disclosure which of the ~ 4,180 mutants made 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.[258]

These deficiencies are significant in assessing both enablement and written description (or lack thereof) of the claims because, even if a fraction of a percent of the 10^{49}+ multiply-modified PH20 polypeptides within the scope of the claims'

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255 EX1003, ¶¶ 107, 109-110.

256 EX1003, ¶¶ 108-110.

257 EX1003, ¶¶ 110-112, 114-115; EX1001, 234:7-255:41 (Table 9), 256:57-267:27 (Table 10).

258 EX1003, ¶¶ 109, 112.

sequence identity parameters cannot be produced or did not properly fold, they represent a massive absolute number of inoperative embodiments that must be identified by making and testing 10^{49}+ polypeptides.[259] Performing the scale of testing necessary to identify such inoperative species within the scope of the claims independently demonstrates a lack of enablement.[260]

The common disclosure thus presents only a "research proposal" to discover "active mutants" and, requires use of a labor and resource intensive process to sort them from any "inactive mutants" with alleged contraceptive utility as well as other mutants having no utility.[261] It does not demonstrate possession of or teach "how to make and use" all PH20 polypeptides with increased hyaluronidase activity within the claims. Thus, the claims are unpatentable under § 112(a).

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259 EX1003, ¶¶ 193-196, 200, 201.

260 EX1003, ¶¶ 122-123; *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984); *Pharm. Res., Inc. v. Roxane Labs., Inc.*, 253 F. App'x. 26, 30 (Fed. Cir. 2007).

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

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

As explained in §§ V.A to V.C, above, the specifications of the pre-AIA ’731 Application and post-AIA ’791 Patent are substantially identical, but neither supports the challenged claims as § 112(a) requires. The claims are both PGR-eligible and unpatentable under § 112(a).

The original claims of the ’731 Application provide no additional guidance demonstrating written description or enablement of the claimed genera of multiply-modified PH20 polypeptides. Those original claims claimed 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. And, while certain claims contemplated 2-3 particular combinations of amino acid replacements (from dozens listed), others encompassed substitutions at unspecified locations.[262]

More directly, none of the original claims filed in the ’731 Application or either of the provisional applications to which it claims priority include a claim that is restricted to modified PH20 polypeptides having (i) 95% sequence identity with only SEQ ID NO: 35, (ii) contain a position 309 substitution to E, G, H, L, M, N,

[262] EX1026, 335.

Q, R, S, and T, and (iii) have >100% or >120% hyaluronidase activity of unmodified $PH20_{1-447}$.[263] Such claims (if present) would not have been supported by an adequate written description in nor would have been enabled by any of the applications (or the '791 Patent disclosure), for the reasons set forth in §§ V.A to V.C.[264]

VI. Conclusion

For the foregoing reasons, the challenged claims are unpatentable.

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[263] EX1026, 335-356; EX1051 323-378; EX1052, 357-420.

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

EXHIBIT LIST

No.	Exhibit Description
1001	U.S. Patent No. 12,077,791
1002	File History of U.S. Patent No. 12,077,791
1003	Declaration of Dr. Michael Hecht
1004	Declaration of Dr. Sheldon Park
1005	U.S. Patent No. 7,767,429
1006	Chao et al., "Structure of Human Hyaluronidase-1, a Hyaluronan Hydrolyzing Enzyme Involved in Tumor Growth and Angiogenesis," Biochemistry, 46:6911-6920 (2007)
1007	WO 2010/077297, published 8 July 2010
1008	Stern et al., "The Hyaluronidases: Their Genomics, Structures, and Mechanisms of Action," 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 SWISS-MODEL 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 '791 Patent (EX1001) to Corresponding Citations in the '731 Application (EX1026)

No.	Exhibit Description
1016	Steipe, "Consensus-Based Engineering of Protein Stability: From Intrabodies to Thermostable Enzymes," 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	U.S. Patent No. 9,447,401
1026	U.S. Patent Application No. 13/694,731
1027	2024 Chemistry Nobel Prize Background
1028	[Reserved]
1029	Gmachl et al., "The human sperm protein PH-20 has hyaluronidase activity," FEBS Letters, 3:545-548 (1993)

No.	Exhibit Description
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	Lins et al., "Analysis of Accessible Surface of Residues in Proteins," Protein Sci., 12:1406-1417 (2003)
1036	Hayden, "Chemistry: Designer Debacle," Nature, 453:275-278 (2008)
1037	Benkert et al., "Toward the Estimation of the Absolute Quality of Individual Protein Structure Models," Bioinformatics, 27:343-350 (2010)
1038	Schwede et al., "SWISS-MODEL: An Automated Protein Homology-Modeling Server," Nucleic Acids Rsch., 31:3381-3385 (2003)
1039	Alberts, "Molecular Biology of the Cell," Fifth Edition, Chapter 3 (2007).
1040	He et al., "NMR Structures of Two Designed Proteins with High Sequence Identity but Different Fold and Function," PNAS, 105:14412-14417 (2008)
1041	Alexander et al., "A Minimal Sequence Code for Switching Protein Structure and Function," PNAS, 106:21149-21154 (2009)
1042	Ruan et al., "Design and Characterization of a Protein Fold Switching Network," Nature Comm., 14 (2023)
1043	Sievers et al., "Fast, Scalable Generation of High-Quality Protein Multiple Sequence Alignments Using Clustal Omega," Molecular Sys. Biology, 7.1 (2011)
1044	Mihel, "PSAIA – Protein Structure and Interaction Analyzer," BMC Structural Biology, 8:21 (2008)

No.	Exhibit Description
1045	Redline Comparison of the ’731 and ’791 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)
1048	Hayden, “Key Protein-Design Papers Challenged,” Nature, 461:859 (2009)
1049	KEGG, *DRUG: Hyaluronidase (human recombinant)*, available at: https://www.genome.jp/entry/D06604
1050	Pace & Scholtz, “A Helix Propensity Scale Based on Experimental Studies of Peptides and Proteins,” Biophysical J. 75:422-427 (1998)
1051	U.S. Patent Application No. 61/631,313
1052	U.S. Patent Application No. 61/796,208
1053	Hom_pre2011
1054	Hom_pre2011_header
1055	Hom_pre2011_header_clean
1056	Hom_pre2011.fasta
1057	Ph20_pre2011.aln-clustal_num
1058	Ph20_pre2011 Alignment html
1059	Leisola & Turunen, “Protein Engineering: Opportunities and Challenges,” Appl. Microbiol. Biotechnol. 75:1225-1232 (2007)
1060	Hecht et al., “De Novo Proteins from Designed Combinatorial Libraries,” Protein Sci., 13:1711-1723 (2004)
1061	Rosengren et al., “Clinical Immunogenicity of rHuPH20, a Hyaluronidase Enabling Subcutaneous Drug Administration,” AAPS J., 17:1144-1156 (2015)
1062	[Reserved]
1063	[Reserved]

No.	Exhibit Description
1064	Collection of BLAST Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20111022151531/http://www.clustal.org/omega/
1065	Collection of Clustal Omega Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20111022151531/http://www.clustal.org/omega/
1066	Collection of SWISS-MODEL Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20110519141121/http://swissmodel.expasy.org/?pid=smh01&uid=&token=
1067	Collection of PyMol Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20110701072314/http://pymol.org/
1068	Declaration of Jeffrey P. Kushan
1069	Swiss Model Printout of PH20 Model
1070	Swiss Model Printout of PH20 Model with I309N Mutation
1071	Swiss Model Printout of PH20 Model with I309L Mutation
1072	Swiss Model Printout of PH20 Model with I309M Mutation
1073	[Reserved]
1074	[Reserved]
1075	[Reserved]
1076	[Reserved]
1077	[Reserved]
1078	[Reserved]
1079	Hunnicutt et al., “Sperm Surface Protein PH-20 Is Bifunctional: One Activity Is a Hyaluronidase and a Second, Distinct Activity Is Required in Secondary Sperm-Zona Binding,” Biol. Reprod., 55(1):80-86 (1996)

No.	Exhibit Description
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 of against misfolded or damaged proteins," Nature, 426:895-899 (2003)

CERTIFICATE OF COMPLIANCE

I hereby certify that this brief complies with the type-volume limitations of 37 C.F.R. § 42.24, because it contains 15,872 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 7th day of May, 2025, I caused to be served a true and correct copy of the foregoing and any accompanying exhibits by FedEx on the following counsel:

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