UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,
Petitioner

v.

HALOZYME INC.,
Patent Owner

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

PATENT OWNER'S SUR-REPLY

Mail Stop "PATENT BOARD"
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

TABLE OF CONTENTS

I. INTRODUCTION 1
II. CLAIM CONSTRUCTION 1
A. Petitioner's Claim Construction Is Contrary To The Specification 1
B. The Claims Meet Section 112 3
III. THE PATENT'S MUTAGENESIS DATA MAKES MODIFYING PH20 PREDICTABLE 3
A. What the Disclosure Shows 4
B. How a POSA Would Visualize and Use the Disclosure 5
C. Drs. Petsko and Simpson Did Not Contradict the Specification 11
D. Petitioner's Theoretical Concerns About Unpredictability Contradict the Record and Are Unsupported 11
E. Testing to Confirm Active/Inactives Is Routine 14
F. Numerosity Is Not a Basis for Invalidity Under § 112 15
G. Petitioner's Experts Refused to Consider the Data And Provide No Evidence Contradicting It 17
IV. WRITTEN DESCRIPTION 18
A. The Specification Discloses Common Structural Features 18
B. Representative Species 21
V. ENABLEMENT 22

PATENT OWNER'S UPDATED EXHIBIT LIST

Exhibit No.	Description
2001	Declaration of Barbara Triggs-Raine, Ph.D. in support of Patent Owner Discretionary Denial Brief (WITHDRAWN)
2002	*Curriculum Vitae* of Barbara Triggs-Raine, Ph.D.
2003	Disclaimer in a Patent under 37 C.F.R. § 1.321(a), filed in U.S. Patent Application No. 18/659,215, July 24, 2025
2004	Sequence listing of U.S. Patent Application No. 18/659,215
2005	"2023 Pharma 50: The 50 largest pharma companies in the world," drugdiscoverytrends.com, accessible at https://www.drugdiscoverytrends.com/2023-pharma-50-largest-companies/ (last accessed April 28, 2025)
2006	"Merck Announces Fourth-Quarter and Full-Year 2024 Financial Results," Merck Press Release, February 4, 2025
2007	"Merck & Company, Inc. Common Stock (new) (MRK)," Nasdaq.com, accessible at https://www.nasdaq.com/market-activity/stocks/mrk (last accessed April 28, 2025)
2008	"Halozyme Therapeutics, Inc. Common Stock (HALO)," Nasdaq.com, accessible at https://www.nasdaq.com/market-activity/stocks/halo (last accessed April 28, 2025)
2009	"Halozyme reports full year 2024 record revenue of $1.015 billion and Exceeds its Financial Guidance for Royalty Revenue, Adjusted EBITDA and Non-GAAP Diluted EPS," Halozyme.com, accessible at https://ir.halozyme.com/news/news-details/2025/HALOZYME-REPORTS-FULL-YEAR-2024-RECORD-REVENUE-OF-1.015-BILLION-AND-EXCEEDS-ITS-FINANCIAL-GUIDANCE-FOR-ROYALTY-REVENUE-ADJUSTED-EBITDA-AND-NON-GAAP-DILUTED-EPS/default.aspx (last accessed April 28, 2025)

Exhibit No.	Description
2010	"Commercial Products," Halozyme.com, accessible at https://halozyme.com/commercial-products/ (last accessed April 28, 2025)
2011	"About Us," Halozyme.com, accessible at https://halozyme.com/about-us/#our-focus (last accessed April 28, 2025)
2012	Complaint for Patent Infringement and Declaratory Judgment of Patent Infringement, *Halozyme, Inc. v. Merck Sharp & Dohme Corp.*, Civil Action No. 2:25-cv-03179-ES (D.N.J.), filed April 24, 2025
2013	"Alteogen announces amendment to license agreement with MSD," Alteogen Press Release, February 22, 2025, accessible at https://www.alteogen.com/en/ir_1/?uid=2223&mod=document&pageid=1 (last accessed April 28, 2025)
2014	"Big Pharma's Business Model: Corporate Greed," United States Senate Health, Education, Labor, and Pensions Committee February 6, 2024
2015	"Medicare now negotiating price of drug that costs $7,100 in US vs. $900 in Canada," CNN February 6, 2024
2016	Fact Sheet: President Donald J. Trump Announces Actions to Put American Patients First by Lowering Drug Prices and Stopping Foreign Free-riding on American Pharmaceutical Innovation," The White House May 12, 2025 Last accessed August 12, 2025
2017	"Big Pharma Earnings Watch: Merck and Pfizer" February 7, 2025 The Campaign for Sustainable Rx Pricing
2018	Declaration of Tyler C. Liu *(served not filed)*
2019-2067	*Intentionally Left Blank*

Exhibit No.	Description
2068	Declaration of Melanie A. Simpson, Ph.D. in Support of Patent Owner's Response
2069	*Curriculum Vitae* of Melanie A. Simpson, Ph.D.
2070	Declaration of Gregory A. Petsko, Ph.D. in Support of Patent Owner's Response
2071	*Curriculum Vitae* of Gregory A. Petsko, Ph.D.
2072-2075	*Intentionally Left Blank*
2076	Transcript of the Deposition of Michael Hecht, Ph.D., August 26, 2025
2077	Transcript of the Deposition of Dr. Sheldon Park, August 7, 2025
2078	Transcript of the Deposition of Dr. Sheldon Park, August 21, 2025
2079	Koehl, P. et al., "Structure-based conformational preferences of amino acids," *PNAS*, 96(22):12524-12529 (October 26, 1999)
2080	Pommié, C. et al., "IMGT standardized criteria for statistical analysis of immunoglobulin V-REGION amino acid properties," *Journal of Molecular Recognition*, 17:17-32 (2004)
2081	*Intentionally Left Blank*
2082	Kyte, J. et al., "A Simple Method for Displaying the Hydropathic Character of a Protein,"*Journal of Molecular Biology*, 157:105-132 (1982)
2083	*Assay Guidance Manual*, Eli Lilly & Company and the National Center for Advancing Translational Sciences
2084	"The Central Role of Enzymes as Biological Catalysts," NCBI Bookshelf, National Institutes of Health (accessible at https://www.ncbi.nlm.nih.gov/books/NBK9921/, last accessed September 22, 2025)

Exhibit No.	Description
2085	French, S. et al., "What is a Conservative Substitution?", *Journal of Molecular Evolution*, 19:171-175 (1983)
2086	El-Safory, N. et al., "Hyaluronidases, a group of glycosidases: Current and future perspectives," *Carbohydrate Polymers*, 81:165-181 (2010)
2087	Lu, J. et al., "Hyaluronidase: structure, mechanism of action, diseases and therapeutic targets," *Molecular Biomedicine*, 6:50-77 (2025)
2088	Stern, R. et al., "Mammalian Hyaluronidases," Hyaluronan Index (2000)
2089	Gmachl, M. et al., "The human sperm protein PH-20 has hyaluronidase activity," *FEBS Letters*, 336(3):545-548 (December 1993)
2090	Gmachl, M. et al., "Bee venom hyaluronidase is homologous to a membrane protein of mammalian sperm," *PNAS USA*, 90:3569-3573 (April 1993)
2091	Davies, G. et al., "Structures and mechanisms of glycosyl hydrolases," *Current Biology*, 3:853-859 (1995)
2092	Marković-Housley, Z. et al., "Crystal Structure of Hyaluronidase, a Major Allergen of Bee Venom," *Structure*, 8:1025-1035 (October 2000)
2093	U.S. Patent No. 8,343,487 B2 to Baker et al., issued January 1, 2013
2094	Thermo Scientific Multidrop® 384 User Manual, Rev. 3.4, Thermo Fisher Scientific (October 2008)
2095	*Intentionally Left Blank*
2096	Frost, G. et al., "A Microtiter-Based Assay for Hyaluronidase Activity Not Requiring Specialized Reagents," *Analytical Biochemistry*, 251:263-269 (1997)

Exhibit No.	Description
2097	U.S. Patent Application Publication No. 2005/0260186 A1 to Bookbinder et al., published November 24, 2005
2098	Delpech, B. et al., "Enzyme-Linked Hyaluronectin: A Unique Reagent for Hyaluronan Assay and Tissue Location and for Hyaluronidase Activity Detection," *Analytical Biochemistry*, 229:35-41 (1995)
2099	Takahashi, T. et al., "A fluorimetric Morgan-Elson assay method for hyaluronidase activity," *Analytical Biochemistry*, 322:257-263 (2003)
2100-2162	*Intentionally Left Blank*
2163	National Medal of Science in Medicine Citation for Gregory Petsko, 2022 (accessible at https://nationalmedals.org/laureate/gregory-petsko/?amp=1, last accessed September 19, 2025)
2164	Petsko, G., et al., *Protein Structure and Function*, New Science Press (2004)
2165	U.S. Patent Application Publication No. 2010/0143457 A1 to Wei et al., published June 10, 2010
2166	Petsko Patent Analysis Data
2167	*Intentionally Left Blank*
2168	Profile of Gregory A. Petsko, American Academy of Arts and Sciences (accessible at https://www.amacad.org/person/gregory-petsko, last accessed September 22, 2025)
2169	"BLAST Topics," National Institutes of Health (accessible at https://blast.ncbi.nlm.nih.gov/doc/blast-topics, last accessed September 22, 2025)
2170	Chain, E. et al., "Identity of Hyaluronidase and Spreading Factor," *British Journal of Experimental Pathology*, 21(6):324-338 (1940)

Exhibit No.	Description
2171-2173	*Intentionally Left Blank*
2174	Errata from Park Deposition (introduced during Park deposition and marked by court reporter as "Park 2068")
2175	Mutational Analysis Table, 2024-11-7, Native Excel File (introduced during Park deposition and marked by court reporter as "Park 2069")
2176	Mutational Analysis Table, 2024-11-7, PDF File (introduced during Park deposition and marked by court reporter as "Park 2070")
2177	E-mail Correspondence dated August 14, 2025
2178	1LOH pdb file
2179	1FCV pdb file
2180	2PE4 pdb file
2181	8SMN pdb file
2182	I309L Swiss Model
2183	I309N Swiss Model
2184	I309E Swiss Model
2185	I309G Swiss Model
2186	I309H Swiss Model
2187	I309M Swiss Model
2188	I309Q Swiss Model
2189	I309R Swiss Model
2190	I309S Swiss Model

Exhibit No.	Description
2191	PH20 Swiss Model
2192	*Intentionally Left Blank*
2193	N47A_N219A_I309N Swiss Model
2194	N47A_N131A_I309N Swiss Model
2195	N47A_N131A_N219A_I309N Swiss Model
2196	N131A_N219A_I309N Swiss Model
2197	Orangutan_I309N Swiss Model
2198	Chimpanzee_I309N Swiss Model
2199	Gibbon_I309N Swiss Model
2200	I309T Swiss Model
2201-2213	*Intentionally Left Blank*
2214	Declaration of Zachariah Summers in Support of *Pro Hac Vice* Admission
2215	Khurana, et al., "MF59 Adjuvant Enhances Diversity and Affinity of Antibody-Mediated Immune Response to Pandemic Influenza Vaccines," Sci Transl Med. 3(85) (June 2011)
2216-2299	*Intentionally Left Blank*
2300	Errata sheet for Declaration of James Naismith, Ph.D.
2301	Transcript of the Deposition of James Naismith, Ph.D., February 6, 2026
2302	Transcript of the Deposition of Garnett H. Kelsoe, Ph.D., February 5, 2026
2303	*Intentionally Left Blank*

Exhibit No.	Description
2304	Transcript of the Deposition of James Naismith, Ph.D., June 13, 2026
2305	Declaration of Naismith (Exhibit 1003), *Merck Sharp & Dohme LLC v. Halozyme Inc.*, Case No. 1PR2026-00312 (P.T.A.B., Mar. 23, 2026)
2306-2399	*Intentionally Left Blank*
2400	Merck & Co., Inc. Form 10-Q, Securities and Exchange Commission, November 5, 2025
2401	E-mail Correspondence between Counsel for Petitioner and Patent Owner, January 6, 2026 (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2402	MERCK_PGR00006 - 30November2023 Merck 031988 Master Agreement - executed 4932-6153-3216 1_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2403	MERCK_PGR00056 - MSA - Term 4 - Dechert LLP_Signed_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2404	MERCK_PGR00467 - Mark Stewart Offer Letter_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2405	MERCK_PGR00052 - Hecht Engagement Letter (7-19)_Signed (Redacted)_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2406	MERCK_PGR00086 - Park Engagement Letter with signature - sjp (redacted)_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2407	"Executive team," MSD, accessible at http://www.msd.com/company-overview/leadership/executive-team/ (last accessed January 5, 2026)

Exhibit No.	Description
2408	"Executive team," Merck, accessible at http://www.merck.com/company-overview/leadership/executive-team/ (last accessed January 5, 2026)
2409	"Board of directors," MSD, accessible at http://www.msd.com/company-overview/leadership/board-of-directors/ (last accessed January 5, 2026)
2410	"Board of directors," Merck, accessible at http://www.merck.com/company-overview/leadership/ board-of-directors/ (last accessed January 5, 2026)
2411	"Contact us," MSD, accessible at http://www.msd.com/contact-us/ (last accessed January 5, 2026)
2412	"Contact us," Merck, accessible at http://www.merck.com/contact-us/ (last accessed January 5, 2026)
2413	"Who we are," MSD, accessible at http://www.msd.com/company-overview/ (last accessed January 5, 2026)
2414	"Who we are," Merck, accessible at http://www.merck.com/company-overview/ (last accessed January 5, 2026)
2415	Merck & Co., Inc. Form 10-K, Securities and Exchange Commission, February 25, 2025
2416	USPTO OED Practitioner Search - Mark J. Stewart, October 30, 2025
2417	Petition for *Inter Partes* Review, *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, IPR2024-00240 (P.T.A.B.), November 30, 2023
2418	Petition for *Inter Partes* Review, *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, IPR2024-00622 (P.T.A.B.), March 4, 2024

Exhibit No.	Description
2419	Petition for *Inter Partes* Review, *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, IPR2024-00623 (P.T.A.B.), March 4, 2024
2420	Petition for *Inter Partes* Review, *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, IPR2024-00624 (P.T.A.B.), March 4, 2024
2421	Petition for *Inter Partes* Review, *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, IPR2024-00625 (P.T.A.B.), March 4, 2024
2422	Petition for *Inter Partes* Review, *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, IPR2024-00647 (P.T.A.B.), March 13, 2024
2423	Petition for *Inter Partes* Review, *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, IPR2024-00648 (P.T.A.B.), March 13, 2024
2424	Petition for *Inter Partes* Review, *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, IPR2024-00649 (P.T.A.B.), March 13, 2024
2425	Petition for *Inter Partes* Review, *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, IPR2024-00650 (P.T.A.B.), March 13, 2024
2426	MERCK_PGR00035 - 20250813 Payment Remittance_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2427	MERCK_PGR00042 - Dechert T360 Halozyme - 202500327_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2428	MERCK_PGR00045 - FW_ Attn_ Accounts Receivable Dept - PAYMENT REMITTANCE DETAIL (Nov 2025)_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)

Exhibit No.	Description
2429	MERCK_PGR00049 - Halozyme - 202000447 - Invoices 5_1_2024-12_22_2025_1 of 3_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2430	MERCK_PGR00465 - Mark Stewart Payroll Statement for Dec 12 2025_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2431	MERCK_PGR00001 - Workday - Ginkel Organization Screen Shot (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2432	MERCK_PGR00002 - Workday - Lally Organization Screen Shot (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2433	MERCK_PGR00003 - Workday - Majchrzak Organization Screen Shot (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2434	MERCK_PGR00004 - Workday - Stewart Organization Screen Shot (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2435	MERCK_PGR00005 - Workday - Su Organization Screen Shot (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2436	MERCK_PGR00036 - 20250903 Payment Remittance_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2437	MERCK_PGR00037 - 20251001 Payment Remittance_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2438	MERCK_PGR00038 - 20251203 Payment Remittance_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2439	MERCK_PGR00040 - 20251215 Payment Remittance_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2440	MERCK_PGR00046 - FW_ Attn_ Accounts Receivable Dept - PAYMENT REMITTANCE DETAIL (Oct 2025)_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)

Exhibit No.	Description
2441	MERCK_PGR00047 - FW_ Attn_ Accounts Receivable Dept - PAYMENT REMITTANCE DETAIL (Sept 2025)_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2442	MERCK_PGR00048 - Halozyme - 202000447 - Invoice IN00125072310 Review History (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2443	MERCK_PGR00050 - Halozyme - 202000447 - Invoices 5_1_2024-12_22_2025_2 of 3_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2444	MERCK_PGR00051 - Halozyme - 202000447 - Invoices 5_1_2024-12_22_2025_3 of 3_Redacted (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
2445	By-Laws of Merck & Co., Inc., Effective as of November 19, 2024
2446	U.S. Supreme Court Amicus Curiae Brief by the Intellectual Property Owners Association, *Jack Daniel's Properties, Inc. v. VIP Products LLC*, Case No. 22-148
2447	Board of Directors – Intellectual Property Owners Association, accessible at https://ipo.org/index.php/board-of-directors (last accessed February 15, 2026)
2448	ChIPs Speaker Bio Information
2449	LinkedIn Profile Page
2450	Form PTO-158, Office of Enrollment and Discipline, United States Patent & Trademark Office
2451	Jennifer Zachary's March 16, 2018 Job Offer Letter
2452	Form 13F Cover Page, Merck & Co., Inc., September 2025
2453	Form 13F Cover Page, Merck Sharp & Dohme LLC, September 2025

Exhibit No.	Description
2454	Form 10-Q, Merck & Co. Inc., Quarterly Report for Quarter Ended June 30, 2025
2455	*Intentionally Left Blank*
2456	Exhibit 24.1 to Merck & Co. Inc.'s Form 10-K for the Fiscal Year Ended December 31, 2024
2457	Sarbanes-Oxley Act of 2002
2458	Jennifer Zachary Biography, Merck.com
2459	Rules of Professional Conduct of the New Jersey Bar
2460	Jennifer Zachary Biography, MSD.com
2461	USPTO Office of Enrollment and Discipline Practitioner Search for Mark J. Stewart, February 13, 2026
2462	Schedule 13D, Harpoon Therapeutics, Inc., January 17, 2024
2463	Schedule 14A Proxy Statement, Merck & Co., Inc., 2025
2464	Form 13F, Information Required of Institutional Investment Managers Pursuant to Section 13(f) of the Securities Exchange Act of 1934 and Rules Thereunder, accessible at https://www.sec.gov/pdf/form13f.pdf (last accessed February 15, 2026)
2465	USPTO Office of Enrollment and Discipline Practitioner Search for "Merck," February 15, 2026
2466	Form 8-K, Merck & Co. Inc., February 3, 2026
2467	Exhibit 99.1 to Form 8-K, Merck & Co. Inc., February 3, 2026
2468	Exhibit 99.2 to Form 8-K, Merck & Co. Inc., February 3, 2026

TABLE OF AUTHORITIES

Cases

Ajinomoto Co. v. Int'l Trade Comm'n,
932 F.3d 1342 (Fed. Cir. 2019) 8, 15, 20, 21

Ariad Pharms., Inc. v. Eli Lilly & Co.,
598 F.3d 1336 (Fed. Cir. 2010) 21

Cephalon, Inc. v. Watson Pharmaceuticals, Inc.,
707 F.3d 1330 (Fed. Cir. 2013) 15, 16

Invitrogen Corp. v. Clontech Lab'ys, Inc.,
429 F.3d 1052 (Fed. Cir. 2005) 11

Johns Hopkins Univ. v. CellPro, Inc.,
152 F.3d 1342 (Fed. Cir. 1998) 11, 15, 16

Phillips v. AWH Corp.,
415 F.3d 1303 (Fed. Cir. 2005) 3

PPG Industries, Inc. v. Guardian Industries Corp.,
75 F.3d 1558 (Fed. Cir. 1996) 15, 16

In re Wands,
858 F.2d 731 (Fed. Cir. 1988) 8, 14, 15, 16

Verizon Services Corp. v. Vonage Holdings Corp.,
503 F.3d 1295 (Fed. Cir. 2007) 2

Vitronics Corp. v. Conceptronic, Inc.,
90 F.3d 1576 (Fed. Cir. 1996) 3

Zoltek Corp. v. United States,
815 F.3d 1302 (Fed. Cir. 2016) 20

I. INTRODUCTION

The primary dispute between the parties is whether POSAs can predictably multiply mutate PH20 ***when using the patent's mutagenesis data***. The overwhelming evidence of record shows that POSAs can do so without undue experimentation. Petitioner ignores the patent data and raises theoretical problems with no evidence they apply to PH20—including effects its own experts called "not very common." Petitioner's claim construction errors are similarly dispositive. Petitioner's Grounds should be rejected.

II. CLAIM CONSTRUCTION

A. Petitioner's Claim Construction Is Contrary To The Specification

Petitioner asserts that the claimed modified PH20s must be "properly folded." Reply, 1-3. But the claims do not mention proper folding, and neither does the specification. The claims instead are directed to "modified PH20 polypeptides" that exhibit increased hyaluronidase activity and that have mutations at specific positions. "Modified PH20 polypeptide" is a defined term, and the definition says nothing about "folding." In fact, the words "folded," "properly folded" and "proper folding" do not appear in the specification. Petitioner itself has argued that the patent does not teach folding; in its PGR submission, Petitioner criticized the specification for allegedly providing "no evidence of proteins in supernatants or their folded state." Reply, 38.

Petitioner's "properly folded" claim construction is based solely on expert

testimony that Petitioner provides. Reply, 1-3; EX1133, ¶¶87-104. Dr. Naismith opines that the claims require "properly folded" modified PH20s, which means that the PH20s are "stably folded." *Id.* Dr. Naismith testified that modified PH20s must maintain activity following 8 hours of incubation to satisfy Petitioner's "properly folded" claim requirement. EX2301, 138:6-141:19, 180:2-184:24, 190:9-19, 200:9-16, 250:17-25. That is because, according to Dr. Naismith, "a POSA would not believe an enzyme had 'properly folded' if it did not maintain activity over a meaningful period or if it formed aggregates within a short period." EX1133, ¶59; EX2305, ¶110.

The activity assay in the patent tested for activity following 1.5 hours, not 8 hours. EX1001, Example 3. Thus, according to Dr. Naismith, the activity assay in the patent is not sufficient to establish "proper folding" because it tested for activity after 90 minutes. EX2301, 140:23-141:19; EX1133, ¶59. As a result, Dr. Naismith's "properly folded" requirement would exclude the exemplary modified PH20s disclosed in the specification from the claims, which itself shows that Petitioner's construction is wrong. *Verizon Services Corp. v. Vonage Holdings Corp.*, 503 F.3d 1295, 1305 (Fed. Cir. 2007) ("We normally do not interpret claim terms in a way that excludes disclosed examples in the specification.").

Contrary to basic tenets of claim construction, Petitioner relies on expert testimony to read a "proper folding" limitation into the claims that is reflected

nowhere in the specification and in fact is inconsistent with the specification. The Federal Circuit made clear thirty years ago that expert testimony cannot be used to construe claims contrary to the intrinsic record. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1584 (Fed. Cir. 1996) ("Indeed, where the patent documents are unambiguous, expert testimony regarding the meaning of a claim is entitled to no weight."); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1318 (Fed. Cir. 2005) ("[A] court should discount any expert testimony "that is clearly at odds with the claim construction mandated by the claims themselves, the written description, and the prosecution history, in other words, with the written record of the patent.") Petitioner's claim construction is contrary to the intrinsic record and should be rejected.

B. The Claims Meet Section 112

As PO explained in its POR and below, under its proposed construction, §112 is satisfied. POR, 33-63. A proper claim construction is essential for a proper §112 analysis. That is because PO need not enable or describe unclaimed features. Petitioner fails to apply the correct claim construction, and its § 112 analysis therefore rests on an improperly imported limitation and necessarily fails.

III. THE PATENT'S MUTAGENESIS DATA MAKES MODIFYING PH20 PREDICTABLE

Beyond claim construction, the parties' primary dispute is whether the patent data could be used to predict the effects of multiple changes in the PH20 sequence

such that the POSA could visualize and recognize the claimed genus and practice the full scope of the claims without undue experimentation.

The evidence shows a POSA could do so.

Drs. Petsko and Simpson detail what was known about PH20 ***before*** disclosure of the patent's vast mutagenesis study, including the location of catalytic and substrate binding residues, essential glycosylation cites, and effect of C-terminal truncations on activity. EX2070, ¶¶112-230; EX2068, ¶¶106-153. Additionally, all parties agree that an accurate homology model of PH20's structure, showing the distorted PH20 alpha-beta barrel fold and location of each amino acid in the structure, was available to a POSA. Pet., 11-16; EX1004, ¶¶36, 104-158; EX2077, 176:2-5; EX1130, 97:14-99:10; EX2070, ¶¶112-230, 343-434; EX2068, ¶¶91-153.

With this information, Dr. Simpson, a PH20 expert, and Dr. Petsko explained how POSAs could, ***using the patent's disclosure***, visualize and recognize the genus and predictably practice the full scope of the claims.

A. What the Disclosure Shows

The patent teaches the results of a systematic mutagenesis study in which each of 447 positions on PH20 was changed to up to 18 amino acids. EX2068, ¶192. Dr. Petsko imported the mutagenesis data into a spreadsheet (EX2166) and color coded it to show positions that tolerated:

- all tested substitutions (43 positions/9%/dark green);
- no tested substitutions (94 positions/21%/red);
- 60% or more (115 positions/26%/light green);
- 30% or less (120 positions/27%/orange).

The results are below:

Position	WT	30	61	92	123	154	185	216	247	278	309	340	371	402	433
		D	L	A	W	K	L	W	V	L	I	M	A	C	F
		E	G	K	K	Q	F	L	R	K	M	C	I	Y	L
1	L	P	Y	K	P	E	P	W	E	F	R	S	Q	S	K
2	N	L	Y	D	K	F	D	N	A	L	S	Q	L	T	P
3	F	D	P	I	D	E	C	E	I	S	M	V	E	L	P
4	R	M	Y	T	V	K	Y	S	R	Q	K	L	K	S	M
5	A	S	I	F	Y	A	N	T	V	D	S	C	G	C	E
6	P	L	D	Y	K	G	H	A	S	E	C	Q	G	K	T
7	P	F	S	M	N	K	K	L	K	L	L	E	K	E	E
8	V	S	I	P	R	D	Y	Y	I	V	L	Q	F	K	E
9	I	F	T	V	S	F	K	P	P	Y	L	G	T	A	P
10	P	I	G	D	I	L	K	K	S	D	T	V	V	D	Q
11	N	G	V	N	E	V	P	I	A	F	N	C	R	V	I
12	V	S	T	L	L	E	G	Y	K	G	Y	I	G	K	F
13	P	P	V	G	V	T	Y	L	S	E	M	R	K	D	Y
14	F	R	N	M	Q	I	N	N	P	T	E	K	P	T	
15	L	I	G	A	Q	K	G	T	L	V	T	N	Q	D	
16	W	N	G	V	Q	L	S	Q	P	V	I	W	L	A	
17	A	A	I	I	N	G	C	Q	V	L	N	H	E	V	
18	W	T	P	D	V	K	F	S	F	G	S	S	E	D	
19	N	G	Q	W	Q	L	N	P	A	A	P	S	L	V	
20	A	Q	K	E	L	L	V	V	V	S	Y	D	E	C	
21	P	G	I	E	S	R	E	A	T	G	I	Y	Q	I	
22	S	V	S	W	L	P	I	I	R	I	I	L	L	A	
23	E	T	L	R	T	N	K	T	I	V	N	H	S	D	
24	F	I	Q	P	E	H	R	L	V	W	V	L	E	G	
25	C	F	D	T	A	L	N	F	Y	W	T	N	K	V	
26	L	Y	H	W	T	W	D	V	T	G	L	P	F	C	
27	G	V	L	A	E	G	D	R	D	T	A	D	Y	I	
28	K	D	D	R	K	Y	L	N	Q	L	A	N	C	D	
29	F	R	K	N	A	Y	S	R	V	S	K	F	S	A	

The patent's disclosure provides a granular structure/function correlation that teaches, on a position-by-position basis, the effect on activity of substituting different amino acids into every position within the primary structure.

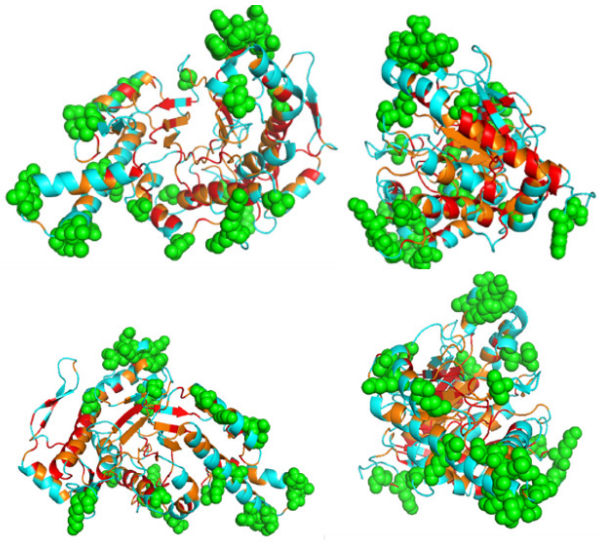
B. How a POSA Would Visualize and Use the Disclosure

To evaluate written description and enablement, Drs. Petsko and Simpson used a visualization-based assessment technique that Petitioner's experts assert can be used to predict the effects of up to five modifications, ***without the patent data***. EX1003, ¶163; EX1004, ¶153; EX1133, ¶258, fn. 287 (citing Hecht, Park for

same).

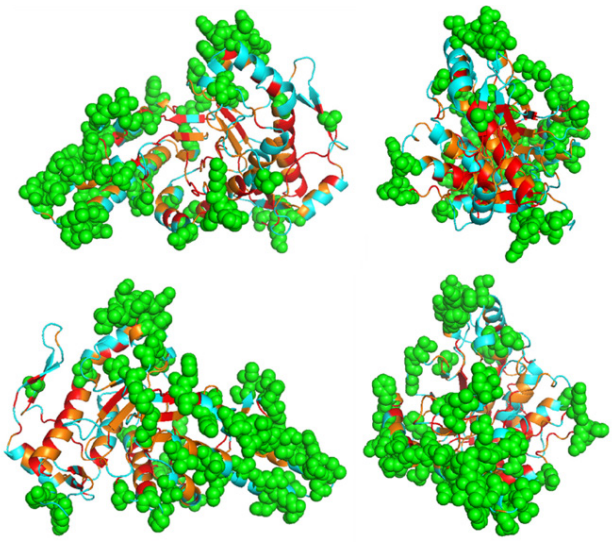
Specifically, they overlayed the tolerance data onto the same prior art PH20 model used by Petitioner's expert in order to visualize the data, as a POSA would. As Petitioner's expert, Dr. Park, explained, generating a homology model for a protein structure "allows you to look at the molecule, as opposed to imagining it in your head" and can also "help you evaluate the impact of a substitution." EX2077, 53:15-54:5.

Using this routine method, Dr. Petsko showed how a POSA would visualize, for instance, "those positions that tolerate all of the tested changes in green in the 'sphere' format":



EX2070, ¶320.

Similarly, Dr. Petsko generated figures showing positions that tolerated 90% or more of the tested changes:



EX2070, ¶321.

As Dr. Petsko testified, "[t]aken together, these figures show that there are many positions that are very tolerant of substitution on the surface of PH20 that can be targeted by the POSA seeking to generate a modified PH20 that retains hyaluronidase activity." EX2070, ¶322. As he testified at deposition based on the patent data:

> Q. So your opinion is that a POSA could use the data from testing single mutants in the patent to select 15 or 20 substitutions in the PH20 sequence, and you would be able to predict whether that mutated 15 or 20 residue-mutated PH20 will exhibit the activity that you are hoping to get?
>
> **A. My opinion is that you could do so**….
>
> ***
>
> **A POSA would have the capability of both visualizing and practicing the full scope of the claims if they needed to**. They could -- that is to say, they could look at any particular type of variant that

> fit the claim and they could make that variant and they would be able to predict beforehand what that variant might do with a -- in many cases, on a high degree of confidence.

EX1131, 111:9-19, 114:5-16; EX2070, ¶355.

Similarly, as Dr. Simpson testified, a POSA could "visualize the species within the claim" and had sufficient information to "choose … the 95% identical polypeptide that would meet those criteria," including selecting variants based on whether activity retention was desired**.** EX1130, 95:5-10, 97:14-98:10; EX2068, ¶¶27-41.

Put succinctly: "A POSA could select 23 residues to change and reasonably expect to obtain an active PH20 as those changes were based on the data in the patent." EX2070, ¶359; *see Ajinomoto*, 1358-61; *see Wands*, 737.

Moreover, Drs. Petsko and Simpson testified that a POSA's ability to practice the claims was not limited to independent changes at highly tolerated positions. Instead, POSAs could evaluate additional substitutions or "make informed decisions about making several changes close together on the protein using the data in the '791 patent regarding which substitutions were tested and the results for each, combined with an assessment of the local environment of the residues in question." EX2070, ¶324; EX1130, 97:14-98:10, 101:21-102:21, 190:12-195:25.

Notably, Dr. Park made just such an assessment of the local environment.

And Dr. Hecht admitted that using this visualization technique "you look at [a change] in the context of its physical chemical environment in the protein and in the context of its homologous environment sequence space, then you're better able to come up with an assessment of the properties of a potential mutation." EX2076, 72:15-73:6. He referred to this as a "more informed analysis of what would be the impact of such changes." EX2076, 75:10-17. It is undisputed that POSAs understand the characteristics of amino acids, such as their charge/size/polarity and propensity to be present in secondary structures, and could evaluate their replacement using routine techniques, including visualizing interactions at the atomic level. EX2070, ¶¶61-67, 343-434. As Dr. Petsko explained, a POSA can do that "for any member of the 10^49 sequences that they wish to examine." EX1131, 114:17-24. And, as Dr. Petsko confirmed, ***the patent's mutagenesis data are critical*** for this method. *Id.*, 148:1-8; *see also* 148:9-20.

This routine method allows a POSA to reliably predict the effect of mutations based on the examples in the patent, without making and testing all of them as Petitioner contends is necessary. That is because, as Dr. Petsko explains, the "information content" of the disclosed substitutions is "enormous," and "when combined with the structural information from modeling the PH20 structure, it allows you to visualize and make predictions about much more of the dataset than just what you see here." EX1131, 113:2-18.

Relatedly, and as importantly, with the patent data in hand, the POSA can avoid the billions of PH20s that will be inactivated by changes identified in the patent. Petitioner makes much of Dr. Petsko's testimony in this regard, but it mistakes its import entirely. There is no dispute that PH20s with the inactivating changes identified in the patent will stay inactive, even if further mutations are made, absent intentional "rescue" mutations. As Dr. Hecht testified, if you break a PH20, it will remain broken. EX2076, 228:1-9.

As Dr. Petsko explains, the number of inactivating mutations "does not mean PH20 is unpredictable or that making and using the claimed modified polypeptides is unpredictable." EX2070, ¶293. It means "[t]he '791 patent renders modifying PH20 predictable by identifying these areas that are particularly intolerant to mutation" while also teaching "where to make mutations to likely retain activity." *Id*.

Petitioner contends that the data on inactivating mutations should be ignored because those data do not differentiate proteins that failed to fold from those that folded but lacked activity. Reply, 37-39. This ignores structural knowledge of PH20 regarding positions essential to folding. And it does not detract from the value of these data in showing which mutations inactivate the protein.

Petitioner also contends that because Dr. Petsko could not give a precise number of properly folded active modified PH20s satisfying the claims, the claims

are invalid. Reply, 7-8. §112 imposes no such requirement.

C. Drs. Petsko and Simpson Did Not Contradict the Specification

Petitioner contends that the patent mandates a random screening approach to making multiply mutated PH20s (Reply, 40). But Petitioner misunderstands the specification. The experiment that Petitioner identifies involves testing for stability—not activity— and that approach is called out as exemplary only. EX1026, 47:11-18, 141:7-33; 150:1-26. The patent in no way mandates it.

Patentee's experts admitted it was "***very common and expected*** for a POSA to generate a model and consider the substitution in that structural context," as Patentee's experts did. EX2077, 176:2-5; EX2076, 75:10-17. Petitioner had the burden of showing that all modes are insufficient to enable the claims, and it has failed. *CellPro*, 1361; *Invitrogen*, 1071.

D. Petitioner's Theoretical Concerns About Unpredictability Contradict the Record and Are Unsupported

Petitioner insists that introducing multiple mutations into PH20 is unpredictable, raising on Reply various theoretical problems concerning protein folding, aggregation and the specter of "epistasis." But both parties' experts agree these effects are "rare" and "not very common." EX2077, 199:20-201:13. And Petitioner, unlike in other §112 cases, has a complete failure of proof in this regard: it does not point to a single example of a modified PH20 that contradicts what a POSA would predict using the data in the patent.

Petitioner's arguments about misfolding rest on teachings about the possible conformations of ***any*** amino acid sequence. But here, the claim specifies a small range of sequences highly similar to mature PH20, and Petitioner's expert admitted that if active, ***they would fold to the PH20 alpha-beta barrel fold***. EX2301, 213:10-18, 85:19-86:595:9-20, 96:16-98:20, 99:13-18, 101:11-20, 159:13-25. Similarly, when asked whether a mutation will cause a modified PH20 to adopt a different structure, Dr. Petsko responded "[t]hat would not be the case for PH20." EX1131, 41:22-42:7. Dr. Petsko further explained that misfolding due to mutation is "usually not the case for most mutations," and "it is rare." EX1131, 40:18-24; 197:6-15. When asked about the potential for mutations to cause aggregation, Dr. Petsko explained that is "not a common consequence," and more specifically, "[i]f I make, typically, 100 mutations in a protein, okay, one or two might do that. None of them might do that." *Id.*, 48:23-49:8.

Petitioner also emphasizes the alleged potential for unpredictable effects resulting from epistasis. Petitioner argues that, though one can investigate the local environment, sometimes residues far apart in the structure can affect each other surprisingly. But Dr. Park testified that such effects are "not very common." EX2077, 200:14-201:13. He further admitted that, because the effect is uncommon, POSAs can "estimate the combined effect of the two or more mutations, if necessary, and include whether the mutant would be better or worse

than wild-type." *Id.*, 201:7-13.

Similarly, Dr. Petsko explained that if two mutations "are separated from each other in the structure there is a high degree of likelihood that they will operate independently." EX1131, 195:5-10. Moreover, even for this "not very common" phenomenon, Petitioner points to ***nothing*** that suggests the effect will abrogate activity entirely.

Moreover, Dr. Naismith admitted at deposition that epistasis simply refers to the fact that multiple mutations will not necessarily be "additive" (EX2301, 129:17-130:18)—that is, that a POSA could not necessarily predict the precise activity level when combining mutations by looking at the effect on activity from individual mutations. But an exact prediction of activity level is not at issue here—particularly because Petitioner's 40% activity construction must be rejected.

Petitioner suggests the patent's disclosure shows the effect of epistasis is prevalent, pointing to the number of inactivating mutations. But as Dr. Petsko explains, the intolerant positions (and the tolerant positions) are not randomly scattered throughout the protein but rather are clustered, reflecting structural features rather than random epistastic effects. EX1131, 157:5-25; EX2070, ¶¶334-342.

Indeed, Petitioner's 112 challenge fails because it identifies no prior art or post-filing evidence showing that combining mutations, including through epistasis

or otherwise, renders visualizing, making, and using multiply-mutated PH20s unpredictable in light of the mutagenesis data. If modifying PH20 is so unpredictable, it should have been utterly trivial for them to do so. With Drs. Simpson's and Dr. Petsko's tolerance data and mappings in hand, if the patent data were as useless as Petitioner claims, Petitioner should have easily been able show multiple examples of sequences within the scope of the claims that produced results that were not predicted by the patent's disclosure of tolerance data. Instead, ***they did not submit a single example*** that contradicts what the specification's disclosure teaches.

This is a complete failure of evidence. Petitioner cannot satisfy its §112 burden with theoretical concerns alone, particularly where PO's experts show that, in light of the patent's extensive mutagenesis data, a POSA could predictably make multiple substitutions.

E. Testing to Confirm Active/Inactives Is Routine

Once a POSA has used the patent's data to select and design a modified PH20, any confirmatory testing, if necessary, is routine. *Wands*, 736–37. As Drs. Petsko and Simpson explain, it is routine for a POSA to make and test the desired polypeptides to confirm its properties. EX2070, ¶348; EX2068, ¶¶357-358, 375-387. Confirmatory testing is routine because the patent's vast disclosure allows a POSA to select variants with high expectations about activity (or lack thereof). To

the extent any results differ from those expectations, those instances would be rare, and the experimentation is not undue. *Wands*, 737-740; *CellPro*, 1360; *Cephalon*, 1336; *PPG*, 1564.

Contrary to Petitioner's argument, a POSA would not "ignore the information in the patent, generate an enormous library, and then screen billions of sequences," (EX2070, ¶349), as occurred in the *Idenix* and *Amgen* cases. Unlike those cases where the specification failed to provide "meaningful guidance" regarding which embodiments would function, thereby forcing a POSA to engage in "iterative, trial-and-error" screening, the specification here provides extensive, position-by-position mutagenesis data and a detailed structure–function correlation. That guidance enables a POSA to identify tolerated substitutions and predictably make and use singly or multiply mutated PH20 variants without resorting to blind screening or undue experimentation. *Idenix*, 1161-1162.

A POSA armed with the patent's data does not guess; the POSA predicts, then confirms. Thus POSAs could "reliably predict" activity (*Ajinomoto*) and experimentation would not be "undue" (*Wands*). Section 112 is met.

F. Numerosity Is Not a Basis for Invalidity Under § 112

Petitioner avers, without support, that experimentation for the size of the sequence space "is impossible" because of the number of possible sequences. Reply, 9-10.

First, Petitioner's argument fails as a matter of law. As *Wands* makes clear, the enablement inquiry "is not merely quantitative," and "a considerable amount of experimentation is permissible" where the experimentation is routine or guided. If the number of potential embodiments were dispositive, any claim encompassing a range and therefore effectively infinite embodiments would be categorically invalid. The law is to the contrary: the question is whether the specification provides sufficient guidance such that a POSA can practice the invention without undue experimentation. *See Cellpro*, 1360 (no undue experimentation "where the experiments involve repetition of known or commonly used techniques."); *Cephalon*, 1330 (same); *PPG*, 1558.

Second, Petitioner's argument rests on its mistaken rejection of the patent data and belief that mutating PH20 is unpredictable and thus a POSA allegedly would start on a vast screening project. But a POSA would not, as Petitioner proposes, "start by calculating the theoretical maximum number of sequences" and screening. EX1130, 98:11-99:10, 97:14-23, 98:7-10. As Dr. Petsko testified: "the POSA would not start that way at all. They would start with a much more focused program making use of the data in the patent," as set out above. EX1131, 106:21-25, 107:1-17, 113:20-114:24. That is because a POSA could "reliably predict" actives and practice the claims without "undue" experimentation.

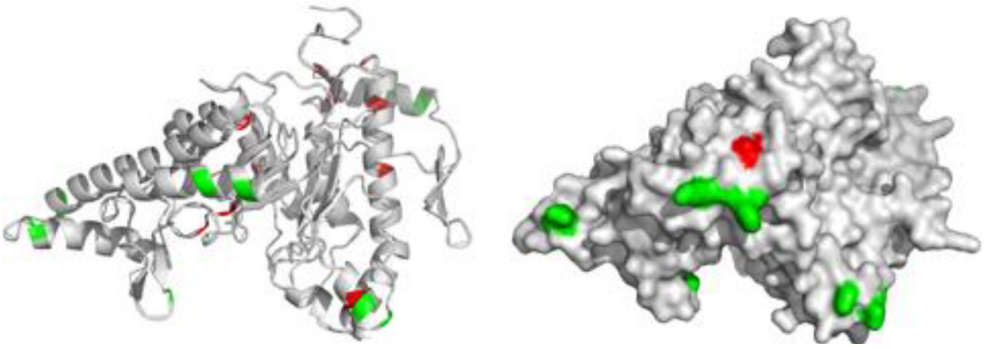
G. Petitioner's Experts Refused to Consider the Data And Provide No Evidence Contradicting It

Despite Petitioner's changing claim construction positions and invalidity theories, Petitioner has been steadfast in one thing: its refusal to actually consider the patent data.

Petitioner did not provide the patent data to Dr. Park at all.

Petitioner's expert, Dr. Hecht, then characterized the data to the Board as a scattershot experiment with random changes and randomly selected positions, concluding it was of no use to a POSA. EX1003, ¶¶146-204. When he learned at deposition the data was for every position in PH20, Dr. Hecht admitted that the patent data would in fact be useful in predicting changes in PH20. EX2076, 262:7-22, 253:9-254:12.

Petitioner then replaced Dr. Hecht with Dr. Naismith, who admitted that he had not heard of PH20 before this case. EX2301, 60:22-24. Dr. Naismith criticized assays that are common in the art, yet with which he has no familiarity (EX1133, ¶¶291-299; EX2301, 22:7-23), and dismissed the majority of the patent data by applying arbitrarily selected criteria. Thus, despite the disclosure of data for substitutions at all 447 positions in SEQ ID No. 3, he considered the data for ***only 33 of those positions***, as shown below:



EX1133, ¶¶320, 305, 316, Appendix B-3.

Dr. Naismith provides no scientific basis for the limits he applied. And he admitted at deposition that his position that the activity data is unreliable rested on his misunderstanding of a ***different assay***. EX2301, 308:2-19; 284:11-285:2, 277:7-278:4.

Evaluating written description and enablement requires evaluating the patent's actual disclosure. Petitioner has failed to offer ***any*** testimony to the Board doing so.

IV. WRITTEN DESCRIPTION

A. The Specification Discloses Common Structural Features

The record developed since Institution establishes that the specification discloses the common structural features based on that primary structure and the related mutagenesis data:

- 95% sequence identity to the primary structure of the recited SEQ ID;
- The I309E, I309G, I309H, I309L, I309M, I309N, I309Q, I309R, I309S, and I309T mutations;

- A PH20 alpha-beta barrel fold, with known catalytic and binding sites; and
- Lack of the inactivating changes identified in the disclosure.

Petitioner's primary response to this record is to argue that amino acid sequence is not in fact a structural feature. But Dr. Naismith admitted at deposition that both amino acid sequence and a particular recited residue are in fact structural features. EX2301, 57:9-60:10.

Beyond primary structure, Petitioner contends that the alpha-beta barrel motif is not a common structural feature shared by actives. But Dr. Naismith admitted at deposition that active PH20s within the scope of the claim will share the same PH20 alpha-beta barrel fold. EX2301, 213:10-18, 85:19-99:18, 101:11-20, 159:13-25.

Petitioner contends that the claimed genus is "structurally heterogeneous" (Reply, 6-7) because there can be variations in secondary structural features between actives. But the common structural features test does not require exactly identical structures. Dr. Naismith admitted that active modified PH20s will share the same alpha-beta barrel fold (EX2301, 213:10-18, 85:19-99:18, 101:11-20, 159:13-25), so any variation in structure amongst actives would not impact the fold or activity.

Petitioner makes much of the similarity in structure between human

hyaluronidases, despite functional differences, to argue the PH20 alpha-beta barrel "can be ignored" as irrelevant to distinguishing actives. Reply, 25. But the common structural features must be considered ***together***. While human hyaluronidases share an alpha-beta barrel fold, they are ***not*** 95% identical to PH20. EX2301, 215:19-217:2; EX2068, ¶¶101, 276-280. It is thus not surprising that while they share a common fold, some are not active.

Petitioner also argues that the specification does not disclose the PH20 alpha-beta barrel fold structure. But it is an inherent feature of the actives, and Petitioner acknowledges it was known in the art. EX2077, 175:18-176:5, 53:22-54:5; EX1004, ¶¶140-151, 33-52, 88-101. "[A] patentee may rely on information that is 'well-known in the art' for purposes of meeting the written description requirement, because the specification is viewed from the perspective of one of skill" in the relevant art. *Ajinomoto*, 1359; *Zoltek*, 1308. A POSA would use the prior art structure to easily visualize the actives based on the other common features, as Petitioner's experts testified.

Finally, Petitioner makes much of a "hyal-EGF" domain," which Petitioner acknowledges is common structural feature shared by actives. Petitioner contends the hyal-EGF domain is not identified by name in the specification. But the patent need not identify common structural features using Petitioner's preferred terminology (particularly given the Hyal-EGF is a misnomer). The patent expressly

reports the import of this region ("amino acid residues corresponding to positions 36-464… is the minimal sequence required for hyaluronidase activity") and incorporates by reference Arming, which Petitioner itself says "proves" the region was essential based on its teaching that a C-terminal truncation mutant ending at position 340 was not secreted or active. EX1001, 68:16-31.

B. Representative Species

As to representative species, Petitioner again relies on the numerosity, but the law is clear this is not sufficient: "[No] bright-line rules govern[ ] ... the number of species that must be disclosed to describe a genus claim, as this number necessarily changes with each invention, and it changes with progress in a field." *Ariad*, 1351; *Ajinomoto*, 1359.

There is no dispute that there are several highly active representative species disclosed in the specification. Moreover, Petitioner's new expert admitted that all actives within the genus fold to the same PH20 alpha-beta barrel fold with catalytic and binding residues properly positioned, just as in the representative species. EX2301, 213:10-18, 85:19-99:18, 101:11-20, 159:13-25.

Petitioner thus only contests the reliability of the patent's disclosure of structure/function correlation that makes the disclosed variants representative of further the sub-variants. PO addressed this issue in Section III.G above, and Petitioner's attempt to disregard the mutagenesis data or diminish its predictive

value should be rejected for the same reasons.

V. ENABLEMENT

The specification provides a detailed structure-function correlation that enables POSAs to predictably generate claimed PH20 variants with single or multiple amino acid substitutions and test them for activity using routine techniques. Petitioner never meaningfully engages with PO's showing that the specification's extensive mutagenesis data, considered as a whole, identifies the "general quality" required under *Amgen* to reliably enable a POSA to make and use the claimed invention. POR, 53.

Petitioner challenges only the predictability of determining active modified PH20s with five or more changes—not the routine nature of making and testing them. For the same reasons addressed in Section III, these challenges fail. But PO addresses the new arguments Petitioner raises below.

First, Petitioner focuses on the size of the "sequence space" encompassed by the claims. But, as set out above, this is not a case where a POSA would need to engage in a massive screening exercise to find, for instance, proteins capable of binding to a target. As Dr. Simpson explained at deposition, POSAs would be able to practice the full scope of the claims despite Petitioner's "sequence space": "no POSA would start with the theoretical maximum number of potential sequence

variants as a starting point for making a comparative analysis of what amino acids would retain activity in a PH20 polypeptide." EX1130, 93:20-24.

Instead, using the method used by Drs. Simpson and Petsko, "a POSA could determine…using the information in the disclosure, what would be reasonable locations… to make mutations such that the POSA would be able to narrow down the set of variant PH20 polypeptides to a manageable set that was fully accessible to them experimentally." EX1130, 94:18-25.

In other words, POSAs would "be able to identify residues that would likely maintain the activity of the enzyme. And that would significantly narrow the scope down from 10 to the 49th to a very small number of reasonable polypeptides that would fit that criterion." EX1130, 92:25-93:7.

Second, Petitioner also contends that a POSA cannot identify the actives using the data in the disclosure because "most single mutations were deleterious." Reply, 32. But, as addressed above, this mistakes the value of the disclosure of inactivating mutations. The patent discloses mutations at every position, including those positions essential for folding and activity. As Dr. Park explained, the importance of this data is knowing what to avoid:

> Q. Would you expect that if you tried to introduce a mutation into a position known to be important for folding, that the -- that the protein would not be able to fold correctly?
>
> A. I would expect that; **therefore, I would not try that.**

EX2077, 106:12-17.

Third, Petitioner claims that the common PH20 alpha-beta barrel fold does not add to stability or predictability. But the 2009 paper (EX1144) Petitioner cites in this regard proves the opposite. In that paper, the authors intentionally ***chose*** areas most likely to disrupt the activity of the protein (not a PH20)—those near the catalytic domain. *Id.*, 949. The authors still found the fold "surprising[ly]" robust. Here, POSAs know far more.

Fourth, as addressed in Section III.G, Petitioner also criticizes the variability of the patent data. But Dr. Simpson, who has experience with the patent's assays, explained why variability does not undermine reliability and is consistent with a POSA's expectation. EX2068, ¶¶198-199, 219-222, 178-179, 182. Petitioner, on the other hand, intentionally selected experts with absolutely ***no prior experience*** with hyaluronidases or PH20s. EX2301, 21:19-22:23; EX2077, 15:1-16:10; EX2076, 64:3-13; EX2302, 28:13-29:3.

Fifth, Dr. Naismith criticizes Dr. Petsko for evaluating what he termed "unreliable" positions on PH20. EX1133, ¶¶243-251, 284. But Dr. Park, whose

analysis Dr. Naismith agreed with, considered those exact same positions in his analysis. EX2175; EX2176; EX2301, 267:7-18.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX PLLC

/Eldora L. Ellison/

Eldora L. Ellison, Ph.D.
Registration No. 39,967
Lead Attorney for Patent Owner

Date: June 30, 2026

1101 K Street, NW, 10th Floor
Washington, DC 20005
(202) 371-2600

CERTIFICATE OF WORD COUNT (37 C.F.R. § 42.24(d))

1. This Patent Owner Sur-Reply complies with the type-volume limitation of 5,600 words, comprising 4,794 words, excluding the parts exempted by 37 C.F.R. § 42.24(a)(1).

2. This Patent Owner Sur-Reply complies with the general format requirements of 37 C.F.R. § 42.6(a) and has been prepared using Microsoft® Word in 14-point Times New Roman font.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX PLLC

/Eldora L. Ellison/

Eldora L. Ellison, Ph.D.
Registration No. 39,967
Lead Attorney for Patent Owner

Date: June 30, 2026

1101 K Street, NW, 10th Floor
Washington, DC 20005
(202) 371-2600

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

CERTIFICATE OF SERVICE (37 C.F.R. § 42.6(e))

I certify that the above-captioned **PATENT OWNER'S SUR-REPLY** and Exhibits 2215, 2300-2302, and 2304-2305 were served in their entireties on June 30, 2026, upon the following parties via electronic mail:

Jeffrey P. Kushan (Lead Counsel)	jkushan@sidley.com
Leif Peterson (Back-up Counsel)	leif.peterson@sidley.com
Sue Wang (Back-up Counsel)	sue.wang@sidley.com
Katherine A. Helm (Back-up Counsel)	khelm@dechert.com
Amy Mahan (Back-up Counsel)	Amy.mahan@sidley.com
Blaine Hackman (Back-up Counsel)	Blaine.Hackman@dechert.com
Christine M. Engen (Back-up Counsel)	christine.engen@sidley.com
Amit Bhatla (Back-up Counsel)	abhatla@sidley.com
Brian M. Goldberg (Back-up Counsel)	Brian.Goldberg@dechert.com
Mark Stewart (Back-up Counsel)	mark.stewart@merck.com
HalozymePGRs@sidley.com	
Merck-Halozyme-Dechert@dechert.com	

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX PLLC

/Eldora L. Ellison/

Eldora L. Ellison, Ph.D.
Registration No. 39,967
Lead Attorney for Patent Owner

Date: June 30, 2026

1101 K Street, NW, 10th Floor
Washington, DC 20005
(202) 371-2600

27140289