

UNITED STATES PATENT AND TRADEMARK OFFICE

---

BEFORE THE PATENT TRIAL AND APPEAL BOARD

---

MERCK SHARP & DOHME LLC,  
Petitioner

v.

HALOZYME, INC.,  
Patent Owner

---

Case PGR2025-00017  
U.S. Patent No. 12,110,520

---

**PATENT OWNER PRELIMINARY RESPONSE  
UNDER 37 C.F.R. § 42.207(a)**

***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. MERCK FAILED TO ESTABLISH PGR ELIGIBILITY BECAUSE IT FAILED TO ASSESS THE '731 PRIORITY APPLICATION AS OF ITS DECEMBER 28, 2012 FILING DATE..... 10

III. MERCK'S POSA DEFINITION OMITTS *ANY* HYALURONIDASE EXPERIENCE..... 12

IV. MERCK IGNORES THE REQUIREMENT TO IDENTIFY HOW THE CLAIMS ARE TO BE CONSTRUED AND IMPROPERLY IMPORTS A FUNCTIONAL REQUIREMENT INTO THE CLAIMS ..... 15

    A. "Modified PH20 Polypeptide" is Defined in a Purely Structural Manner .....19

    B. The Board Should Deny Trial Under 37 C.F.R. §42.204(b)(3) Because Merck Does Not Identify How the Claims Should Be Construed Or Provide Sufficient Evidence Supporting Its Claim Interpretation. ....25

    C. Merck Improperly Imports a Functional Limitation into the Claims. 28

V. CLAIMS 1-2, 6-15, AND 17-30 ARE ENTITLED TO AT LEAST THE '731 APPLICATION'S DECEMBER 28, 2012 FILING DATE..... 32

VI. GROUND 1: MERCK FAILS TO SHOW THAT IT IS MORE LIKELY THAN NOT THAT THE CLAIMS LACK WRITTEN DESCRIPTION... 33

    A. Merck's Cited Written-Description Law Concerns Functionally Defined Claims, Not Structural Claims. ....34

    B. Merck Does Not Grapple With the Common Structural Features Shared by the Claimed Polypeptides.....39

    C. Merck Ignores Disclosures of Modified PH20 Polypeptides Containing Multiple Substitutions. ....41

    D. The Claims Do Not Capture Multiply Modified PH20 Polypeptides Excluded from the Specification.....45

    E. "Modified PH20 Polypeptide" in the Remaining Claims is Also Structural. ....46

VII. GROUND 2: MERCK FAILED TO SHOW THAT IT IS MORE LIKELY THAN NOT THAT THE CLAIMS LACK ENABLEMENT..... 47

A.	Merck’s Cited Enablement Law Concerns Functionally Defined, Not Structural, Claims.....	47
B.	Merck Failed to Show Undue Experimentation Would be Required.	48
1.	Merck Failed To Establish that Making Modified PH20 Polypeptides Required Undue Experimentation.....	48
2.	Merck Fails To Demonstrate that Using Modified PH20 Polypeptides Required Undue Experimentation.....	54
C.	Merck Did Not Refute the Data Showing that PH20 Polypeptides Are Useful as Contraceptives in Guinea Pigs. ....	56
D.	The Remaining Claims Are Also Enabled. ....	60
VIII.	GROUND 3: MERCK FAILED TO SHOW THAT IT IS MORE LIKELY THAN NOT THAT THE CLAIMS WOULD HAVE BEEN OBVIOUS...	61
A.	Merck’s Art Does Not Teach All Claim Elements. ....	61
B.	Merck Failed to Establish a Reason to Combine the ’429 Patent and Chao to Arrive at the Claimed Invention. ....	64
1.	Merck Fails to Show that a POSA Would Have Been Motivated to Make an Amino Acid Substitution in Non-Essential Regions of PH20 and Identify Position 324. ....	64
2.	Merck Further Fails to Explain Why a POSA Would Have Been Motivated to Make the E324D, E324N, or E324R Modifications. ....	74
C.	Merck Failed to Establish a Reasonable Expectation of Success. ....	81
D.	Merck Relies on Hindsight.....	84
IX.	THE BOARD SHOULD GIVE HECHT’S AND PARK’S TESTIMONY LITTLE TO NO WEIGHT.....	86
X.	CONCLUSION.....	88

**PATENT OWNER'S EXHIBIT LIST**

Exhibit No.	Description
2001	Declaration of Barbara Triggs-Raine, Ph.D. in support of Patent Owner Discretionary Denial Brief
2002	<i>Curriculum Vitae</i> 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. 18/068,418, May 7, 2025
2004	“Halozyme Therapeutics to Present Data on PEGPH20 at the Upcoming 2011 EORTC-NCIASCO Annual Meeting,” Halozyme Therapeutics, Inc. Press Release, October 24, 2011
2005	LinkedIn profiles of Michael Shepard, Robert Connor, Ge (Gina) Wei, and Qiping Zhao
2006	Sequence listing of U.S. Patent Application No. 18/068,418
2007	Gifre, L., et al., “Trends in recombinant protein use in animal production,” <i>Microb Cell Fact</i> 16:40 (2017)
2008	“Recombinant Drugs,” Smithsonian Institution, accessible at <a href="https://www.si.edu/spotlight/birth-of-biotech/recombinant-drugs">https://www.si.edu/spotlight/birth-of-biotech/recombinant-drugs</a> (last accessed February 27, 2025)
2009	Naz, R., “Antisperm Contraceptive Vaccines: Where We Are and Where We Are Going?,” <i>American Journal of Reproductive Immunology</i> 66:5-12 (2011)
2010	Primakoff, P., et al., “Fully effective contraception in male and female guinea pigs immunized with the sperm protein PH-20,” <i>Nature</i> 335:543-546 (October 6, 1988)
2011	Definition of “guinea pig,” Merriam-Webster OnLine, archived by the Internet Archive on February 21, 2010, accessible at <a href="https://web.archive.org/web/20100221175034/http://www.merriam-webster.com/dictionary/guinea%20pig">https://web.archive.org/web/20100221175034/http://www.merriam-webster.com/dictionary/guinea%20pig</a> (last accessed February 27, 2025)

Exhibit No.	Description
2012	“A decade in numbers,” <i>Nature Materials</i> 11:743-744 (September 2012)
2013	Lin, Y., <i>et al.</i> , “Molecular cloning of the human and monkey sperm surface protein PH-20,” <i>Proc. Natl. Acad. Sci USA</i> 90:10071-10075 (November 1993)
2014	<i>Intentionally Left Blank</i>
2015	File History of U.S. Patent No. 7,872,107
2016	Pils, B., <i>et al.</i> , “Variation in structural location and amino acid conservation of functional sites in protein domain families,” <i>BMC Bioinformatics</i> 6 (August 25, 2005)
2017	<i>Intentionally Left Blank</i>
2018	Duterme, C., <i>et al.</i> , “Two Novel Functions of Hyaluronidase-2 (Hyal2) Are Formation of the Glycocalyx and Control of CD44-ERM Interactions,” <i>The Journal of Biological Chemistry</i> , 284(48):33495-33508 (November 27, 2009)
2019	Atmuri, V., <i>et al.</i> , “Hyaluronidase 3 ( <i>HYAL3</i> ) knockout mice do not display evidence of hyaluronan accumulation,” <i>Matrix Biology</i> 27 (2008)
2020	Hemming, R., <i>et al.</i> , “Mouse Hyal3 encodes a 45- to 56-kDa glycoprotein whose overexpression increases hyaluronidase 1 activity in cultured cells,” <i>Glycobiology</i> 18(4):280-289 (2008)
2021	Miller, A., “Hyaluronidase 2 and its intriguing role as a cell-entry receptor for oncogenic sheep retroviruses,” <i>Seminars in Cancer Biology</i> 18:296-301 (2008)
2022	Kaneiwa, T. <i>et al.</i> , “Identification of human hyaluronidase-4 as a novel chondroitin sulfate hydrolase that preferentially cleaves the galactosaminidic linkage in the trisulfated tetrasaccharide sequence,” <i>Glycobiology</i> 20(3):300-309 (March 2010)

<b>Exhibit No.</b>	<b>Description</b>
2023	Petition for Post-Grant Review, <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00004 (P.T.A.B.), November 26, 2024
2024	Petition for Post-Grant Review, <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00003 (P.T.A.B.), November 12, 2024
2025	Petition for Post-Grant Review, <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00009 (P.T.A.B.), December 27, 2024
2026	Petition for Post-Grant Review, <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00006 (P.T.A.B.), December 10, 2024
2027	Petition for Post-Grant Review, <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00030 (P.T.A.B.), February 4, 2025
2028	Petition for Post-Grant Review, <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00024 (P.T.A.B.), February 21, 2025
2029	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00004 (P.T.A.B.), November 26, 2024
2030	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00003 (P.T.A.B.), November 12, 2024
2031	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00009 (P.T.A.B.), December 27, 2024
2032	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00006 (P.T.A.B.), December 10, 2024

Exhibit No.	Description
2033	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00030 (P.T.A.B.), February 4, 2025
2034	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00024 (P.T.A.B.), February 21, 2025
2035	Lokeshwar, V., <i>et al.</i> , “Regulation of Hyaluronidase Activity by Alternative mRNA Splicing,” <i>The Journal of Biological Chemistry</i> 277(37):33654-33663 (2002)
2036	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00033 (P.T.A.B.), March 7, 2025
2037	Petition for Post-Grant Review, <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00033 (P.T.A.B.), March 7, 2025
2038	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00039 (P.T.A.B.), March 28, 2025
2039	Petition for Post-Grant Review, <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00039 (P.T.A.B.), March 28, 2025
2040-2045	<i>Intentionally Left Blank</i>
2046	“2023 Pharma 50: The 50 largest pharma companies in the world,” drugdiscoverytrends.com, accessible at <a href="https://www.drugdiscoverytrends.com/2023-pharma-50-largest-companies/">https://www.drugdiscoverytrends.com/2023-pharma-50-largest-companies/</a> (last accessed April 28, 2025)
2047	“Merck Announces Fourth-Quarter and Full-Year 2024 Financial Results,” Merck Press Release, February 4, 2025

Exhibit No.	Description
2048	“Products list,” Merck.com, accessible at <a href="https://www.merck.com/products/">https://www.merck.com/products/</a> (last accessed April 28, 2025)
2049	<i>Intentionally Left Blank</i>
2050	“Merck & Company, Inc. Common Stock (new) (MRK),” Nasdaq.com, accessible at <a href="https://www.nasdaq.com/market-activity/stocks/mrk">https://www.nasdaq.com/market-activity/stocks/mrk</a> (last accessed April 28, 2025)
2051	“Halozyme Therapeutics, Inc. Common Stock (HALO),” Nasdaq.com, accessible at <a href="https://www.nasdaq.com/market-activity/stocks/halo">https://www.nasdaq.com/market-activity/stocks/halo</a> (last accessed April 28, 2025)
2052	“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 <a href="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">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</a> (last accessed April 28, 2025)
2053	“Commercial Products,” Halozyme.com, accessible at <a href="https://halozyme.com/commercial-products/">https://halozyme.com/commercial-products/</a> (last accessed April 28, 2025)
2054	“About Us,” Halozyme.com, accessible at <a href="https://halozyme.com/about-us/#our-focus">https://halozyme.com/about-us/#our-focus</a> (last accessed April 28, 2025)
2055	Second Declaration of Barbara Triggs-Raine, Ph.D. in Support of Patent Owner’s Preliminary Response
2056	Petition for Post-Grant Review, <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00042 (P.T.A.B.), April 15, 2025

<b>Exhibit No.</b>	<b>Description</b>
2057	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00042 (P.T.A.B.), April 15, 2025
2058	Complaint for Patent Infringement and Declaratory Judgment of Patent Infringement, <i>Halozyme, Inc. v. Merck Sharp &amp; Dohme Corp.</i> , Civil Action No. 2:25-cv-03179-ES (D.N.J.), filed April 24, 2025
2059	“Alteogen announces amendment to license agreement with MSD,” Alteogen Press Release, February 22, 2025, accessible at <a href="https://www.alteogen.com/en/ir_1/?uid=2223&amp;mod=document&amp;p_ageid=1">https://www.alteogen.com/en/ir_1/?uid=2223&amp;mod=document&amp;p_ageid=1</a> (last accessed April 28, 2025)
2060	Petition for Post-Grant Review, <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00046 (P.T.A.B.), April 29, 2025
2061	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00046 (P.T.A.B.), April 29, 2025
2062	Petition for Post-Grant Review, <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00050 (P.T.A.B.), May 7, 2025
2063	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00050 (P.T.A.B.), May 7, 2025
2064	Petition for Post-Grant Review, <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00053 (P.T.A.B.), June 6, 2025
2065	Declaration of Michael Hecht, Ph.D. (Exhibit 1003), <i>Merck Sharp &amp; Dohme LLC v. Halozyme Inc.</i> , Case No. PGR2025-00053 (P.T.A.B.), June 6, 2025

**TABLE OF AUTHORITIES**

	<b>Page(s)</b>
<b>Cases</b>	
<i>Adapt v. Teva</i> , 25 F.4th 1354 (Fed. Cir. 2022) .....	75
<i>Alcon v. Barr</i> , 745 F.3d 1180 (Fed. Cir. 2014) .....	43, 56
<i>Alnylam v. Moderna</i> , No. 23-2357 (Fed. Cir. June 4, 2025) .....	19, 20
<i>Am. Med. Sys. v. Biolitec</i> , 618 F.3d 1354 (Fed. Cir. 2010) .....	24
<i>Amgen v. Sanofi</i> , 598 U.S. 594 (2023) .....	47, 51
<i>Arendi v. Apple</i> , 832 F.3d 1355 (Fed. Cir. 2018) .....	62, 63
<i>Ariad v. Eli Lilly</i> , 598 F.3d 1336 (Fed. Cir. 2010) .....	<i>passim</i>
<i>AT&amp;T Services v. Innovative Sonic</i> , IPR2024-01143, Paper 15 (P.T.A.B. Feb. 11, 2025) .....	65, 75, 77
<i>Avail v. Teladoc</i> , IPR2022-00444, Paper 10 (P.T.A.B. July 21, 2022) .....	88
<i>Ex parte Bandman</i> , No. 2004-2319, Decision on Appeal (B.P.A.I. Jan. 6, 2005) .....	38
<i>Baxalta v. Genentech</i> , 81 F.4th 1362 (Fed. Cir. 2023) .....	47, 48, 51
<i>Belden v. Berk-Tek</i> , 805 F.3d 1064 (Fed. Cir. 2015) .....	65
<i>Boehringer v. Kansas State</i> , PGR2020-00076, Paper 42 (P.T.A.B. Jan. 31, 2022) .....	35

<i>Boehringer v. Kansas State</i> , PGR2022-00021, Paper 11 (P.T.A.B. Feb. 24, 2023) .....	<i>passim</i>
<i>Boehringer</i> , PGR2022-00021, Paper 9 (P.T.A.B. July 15, 2022) .....	23, 36
<i>Bradium Techs. v. Iancu</i> , 923 F.3d 1032 (Fed. Cir. 2019) .....	30
<i>In re Brana</i> , 51 F.3d 1560 (Fed. Cir. 1995) .....	60
<i>Cephalon v. Watson</i> , 707 F.3d 1330 (Fed. Cir. 2013) .....	50, 51
<i>Chiron v. Genentech</i> , 363 F.3d 1247 (Fed. Cir. 2004) .....	11
<i>Cordis v. Medtronic</i> , 339 F.3d 1352 (Fed. Cir. 2003) .....	44
<i>Corephotonics v. Apple</i> , 84 F.4th 990 (Fed. Cir. 2023) .....	81
<i>Deeper v. Vexilar</i> , IPR2018-01310, Paper 7 (P.T.A.B. Jan. 24, 2019) .....	27
<i>DSS v. Apple</i> , 885 F.3d 1367 (Fed. Cir. 2018) .....	64
<i>Eli Lilly v. Teva</i> , 8 F.4th 1331 (Fed. Cir. 2021) .....	84
<i>In re Entresto</i> , 125 F.4th 1090 (Fed. Cir. 2025) .....	<i>passim</i>
<i>Envtl. Designs v. Union Oil Co. of Cal.</i> , 713 F.2d 693 (Fed. Cir. 1983) .....	13
<i>Falko-Gunter v. Inglis</i> , 448 F.3d 1357 (Fed. Cir. 2006) .....	39

*Ex parte Friedberg et al.*,  
No. 2004-2314, Decision on Appeal (B.P.A.I. Nov. 17, 2004) .....*passim*

*Gillette v. Sphere USA*,  
PGR2022-00030, Paper 31 (P.T.A.B. Sept. 19, 2023).....9

*GlaxoSmithKline v. Banner Pharmacaps*,  
744 F.3d 725 (Fed. Cir. 2014) .....23, 37

*Google v. Headwater Research*,  
IPR2024-00944, Paper 17 (P.T.A.B. Dec. 4, 2024) .....9

*In re Google*,  
56 F.4th 1363 (Fed. Cir. 2023) .....64

*Harmonic v. Avid*,  
815 F.3d 1356 (Fed. Cir. 2016) .....46

*Idenix v. Gilead*,  
941 F.3d 1149 (Fed. Cir. 2019) .....34, 35, 47

*Invitrogen v. Clontech*,  
429 F.3d 1052 (Fed. Cir. 2005) .....17, 28

*Jack Guttman v. Kpykake Enterprises*,  
302 F.3d 1352 (Fed. Cir. 2002) .....18

*Ex parte Joo-Eun Bae*,  
No. 2009-013469, Decision on Appeal (B.P.A.I. Apr. 5, 2010) .....41

*KSR v. Teleflex*,  
550 U.S. 398 (2007).....76

*Kyocera Senco Industrial Tools v. ITC*,  
22 F.4th 1369 (Fed. Cir. 2022) .....19, 88

*Lenovo v. LiTL*,  
IPR2021-00800, Paper 7 (P.T.A.B. Nov. 2, 2021).....61

*Medichem v. Rolabo*,  
437 F.3d 1157 (Fed. Cir. 2006) .....83

*Merck v. Wyeth*,  
PGR2017-00016, Paper 9 (P.T.A.B. Oct. 20, 2017) .....10, 47

*Oatey v. IPS*,  
514 F.3d 1271 (Fed. Cir. 2008) .....29

*Okajima v. Bourdeau*,  
261 F.3d 1350 (Fed. Cir. 2001) .....13, 14

*Orthopediatrics v. K2M*,  
IPR2018-01548, Paper 9 (P.T.A.B. Mar. 1, 2019) .....25, 26

*Osseo v. Planmeca*,  
116 F.4th 1335 (Fed. Cir. 2024) .....88

*PAR Pharmaceutical v. TWI Pharmaceuticals*,  
773 F.3d 1186 (Fed. Cir. 2014) .....62

*ParkerVision v. Vidal*,  
88 F.4th 969 (Fed. Cir. 2023) .....19, 27, 37

*In re Payne*,  
606 F.2d 303 (C.C.P.A. 1979) .....17

*Phillips. Head Sport v. Vermont Safety Developments*,  
IPR2024-01099, Paper 15 (P.T.A.B. Jan. 15, 2025) .....28, 30, 31

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

*Ex parte Porro*,  
No. 2008-0184, Decision on Appeal (B.P.A.I. Mar. 11, 2008).....41

*Qualcomm v. UNM*,  
IPR2021-00375, Paper 14 (P.T.A.B. July 19, 2021).....76

*Rasmusson v. SmithKline*,  
413 F.3d 1318 (Fed. Cir. 2005) .....56

*Reiffin v. Microsoft*,  
214 F.3d 1342 (Fed. Cir. 2000) .....1, 11, 32

*RiceTec v. BASF SE*,  
PGR2021-00113, Paper 35 (P.T.A.B. Mar. 8, 2023) .....44

*Samsung v. Cobblestone*,  
IPR2024-00319, Paper 16 (P.T.A.B. June 24, 2024) .....*passim*

*SanDisk v. Memorex Prods.*,  
415 F.3d 1278 (Fed. Cir. 2005) .....21

*Sandoz v. Biogen*,  
PGR2022-00054, Paper 16 (P.T.A.B. Feb. 2, 2023) ..... 10

*Seachange Int’l v. C-Cor*,  
413 F.3d 1361 (Fed. Cir. 2005) .....31

*In re Stepan*,  
868 F.3d 1342 (Fed. Cir. 2017) .....84, 85, 87

*Syngenta Crop Protection AG v. UPL*,  
PGR2023-00017, Paper 58 (P.T.A.B. July 26, 2024) ..... 13, 16

*Thorner v. Sony Computer Entm’t Am. LLC*,  
669 F.3d 1362 (Fed. Cir. 2012) ..... 19

*TIP Sys. v. Phillips & Brooks/Gladwin*,  
529 F.3d 1364 (Fed. Cir. 2008) .....29

*TQ Delta v. Cisco*,  
942 F.3d 1352 (Fed. Cir. 2019) .....75

*Union Carbide v. Shell*,  
308 F.3d 1167 (Fed. Cir. 2002) ..... 11

*United Services Automobile v. PNC Bank*,  
IPR2021-01248, Paper 27 (P.T.A.B. Jan. 3, 2023) .....31

*In re Vaeck*,  
947 F.2d 488 (Fed. Cir. 1991) .....84

*Virtek v. Assembly*,  
97 F.4th 882 (Fed. Cir. 2024) .....70

*Volkswagen Group of America v. Michigan Motor Techs.*,  
IPR2020-00229, Paper 13 (P.T.A.B. Jul. 6, 2020) .....18, 26

*In re Wands*,  
858 F.2d 731 (Fed. Cir. 1988) .....48, 51, 53, 54

*Wyeth v. Abbott*,  
720 F.3d 1380 (Fed. Cir. 2013) .....48

*Xerox v. Bytemark*,  
IPR2022-00624, Paper 12 (P.T.A.B. Feb. 10, 2023).....4, 27, 44

**Statutes**

35 U.S.C. §324(a) ..... 10

**Other Authorities**

37 C.F.R. §§42.6(a)(3) .....62

37 C.F.R. §42.22(a)(2) .....61

37 C.F.R. §42.65 .....44

37 C.F.R. §42.65(a).....77

37 C.F.R. §42.65(b) .....9, 82

37 C.F.R. §42.65(b)(2).....76, 77, 82

37 C.F.R. §42.65(b)(3).....82

37 C.F.R. §42.104(b)(3).....18

37 C.F.R. §§42.104(b)(4)–(5) .....61

37 C.F.R. §42.204(b)(3).....25, 26, 28

37 C.F.R. §§42.204(b)(3)-(4).....2, 4, 17

37 C.F.R. §42.207(e).....9

37 CFR §42.65(b)(4).....82

## I. INTRODUCTION

Merck's petition challenging Halozyme's U.S. Patent No. 12,110,520 suffers from multiple flaws warranting denial.

*First*, Merck failed to establish that the '520 patent is PGR-eligible. The '520 patent claims priority to a series of applications, including provisionals filed December 30, 2011; and November 1, 2012; and a nonprovisional ("the '731 Application") (EX1026) filed December 28, 2012, before the PGR-eligibility cutoff of March 16, 2013. Merck and its declarants, however, only applied the 2011 date, and failed to analyze written-description or enablement of the pre-AIA '731 Application as of its 2012 filing date. *Reiffin v. Microsoft*, 214 F.3d 1342, 1345 (Fed. Cir. 2000) ("the sufficiency [of a disclosure] under §112, first paragraph *must be judged as of its filing date.*"); Pet., 11-15, 27, 40, 56, 73-78, 82, 88-90, 93-96, 102-103, 107-109; EX1003, ¶¶11-14; EX1004, ¶¶10-14. Merck failed to meet its burden to show that the challenged claims are not entitled to the benefit of the 2012 filing date of the '731 Application. As such, Merck failed to establish PGR eligibility. Institution should be denied for this dispositive reason alone.

*Second*, the Board should deny institution because, although Merck offers no actual claim construction, it improperly imports a functional requirement, *viz.* hyaluronidase activity, into the claims. Merck's improper backdoor attempt to

import a functional requirement into the claims is not without consequence, because it is central to Merck’s written-description and enablement Grounds. Merck’s gambit—to incorrectly *read in* a functional requirement—is an unsubtle effort to shoehorn the facts in this case into the law Merck cites, all of which relates to claims containing a functional requirement. Section IV.

Another problem for Merck is that it never performs a claim construction analysis of *any* claim term and offered no expert testimony on claim construction. Neither of Merck’s declarants evinces any understanding of the concept of claim construction, and neither declarant addresses claim construction principles at all, let alone applies them.

Yet, without basis, Merck incorrectly treats the claims as requiring hyaluronidase activity—in direct contrast to the specification’s disclosure. Merck’s petition therefore violates 37 C.F.R. §§42.204(b)(3)-(4). Here, where Merck failed to even educate its declarants on claim construction principles, refused to construe or identify the plain and ordinary meaning of any term, and imported into the claim a requirement for hyaluronidase activity—the lynchpin of Merck’s §112 challenges—Merck has not provided a sufficient basis for its claim interpretation and thus not demonstrated that any claim is more likely than not unpatentable. *Samsung v. Cobblestone*, IPR2024-00319, Paper 16 at 20-21 (P.T.A.B. June 24, 2024) (“Petitioner has failed to set forth a sufficient basis to support the claim

construction it relies on and, consequently has failed to establish a reasonable likelihood that its unpatentability arguments, which are based on that construction, have merit.”).

Here, the patent expressly defines the term “modified PH20 polypeptide” by its *structure*, i.e., amino acid sequence, and not by function. EX1001, 48:38-43. As such, a person of ordinary skill in the art (“POSA”) would have understood that this term does not require hyaluronidase activity. Patent Owner’s expert, Barbara Triggs-Raine, Ph.D., the former Head of the Department of Biochemistry and Medical Genetics at Max Rady College of Medicine and a leading expert in the hyaluronidase field, supports this construction of the term “modified PH20 polypeptide.” EX2055, ¶¶9-19. Unlike Merck’s declarants, Dr. Triggs-Raine actually engaged in a claim construction analysis, and Halozyme offers a well-supported basis for its claim interpretation. *Phillips v. AWH*, 415 F.3d 1303, 1313-1315 (Fed. Cir. 2005).

Rather than apply the specification’s express definition of “modified PH20 polypeptide,” Merck—based solely on attorney argument—argues that the claims are limited to “active mutants,” completely discounting the specification’s disclosure that “modified PH20 polypeptides” includes “inactive” and other less active mutants. To the extent Merck alleges that its arguments are supported by expert testimony, Merck is wrong because its declarants were never even informed

about claim construction principles and made no effort to apply them. So, any testimony that the claims are limited to active mutants should be given no weight. *Xerox v. Bytemark*, IPR2022-00624, Paper 12 (P.T.A.B. Feb. 10, 2023). Merck's petition contains no arguments applying the correct claim construction. As such, Merck fails to meet its burden to show that it is more likely than not that at least one *construed claim* is unpatentable. 37 C.F.R. §§42.204(b)(3)-(4).

*Third*, the Board should deny institution because Merck's written-description challenge lacks merit as it hinges on importing into the claims a requirement for hyaluronidase activity. Merck repeatedly insists that the claims are limited to only "active mutants," but Merck fails to establish lack of written description for the claims as properly construed. Merck cannot credibly deny that Halozyme's claims specifying "at least 91%" sequence identity to the disclosed amino acid sequences (SEQ ID Nos: 3, 7 and 32-66) allow POSAs to visualize or recognize the identity of all members of the structurally defined genus.

Additionally, Merck ignores the specification's disclosures of various modified PH20 polypeptides containing multiple amino acid substitutions encompassed by the claims. Merck failed to identify any authority supporting its written-description challenge of claims reciting purely structural modified PH20 polypeptides. Thus, Merck's written-description challenge fails.

*Fourth*, the Board should deny institution because Merck fails to show that

making and using the claimed polypeptides would require undue experimentation.

Here again, Merck improperly relies on importing into the claims a requirement for hyaluronidase activity. *Boehringer v. Kansas State*, PGR2022-00021, Paper 11 at 5-6 (P.T.A.B. Feb. 24, 2023) (Director Vidal finding “the Board was correct to focus on whether the claims themselves were enabled and *to find inapposite Petitioner’s arguments as to whether functional language*—appearing only in the specification—was *enabled.*”).<sup>1</sup> Even so, Merck cannot credibly deny that, once a POSA is equipped with the guidance in the specification, making and using the claimed polypeptides would have required only routine, commonly used techniques, not undue experimentation. Indeed, Merck does not dispute that the disclosed “active mutant” PH20 polypeptides are useful because they possess hyaluronidase activity and can be used, e.g., “for treating a hyaluronan-associated disease or condition” or to “increas[e] delivery of a therapeutic agent to a subject.” EX1001, 39:5-15, 25-28; 174:38-39; 175:39-187:37. And though Merck alleges that inactive PH20 polypeptides are not useful, Merck does not substantively address disclosures teaching that PH20 polypeptides are useful as contraceptives. Moreover, Merck’s declarants’ testimony disputing PH20’s usefulness for contraception should be given little to no weight because (i) neither of Merck’s

---

<sup>1</sup> Emphasis is added throughout, unless specified.

declarants has *any* hyaluronidase experience, and (ii) neither disputes that PH20 was known to be useful as a contraceptive in guinea pigs. Additionally, Merck cites post-filing data (EX1024, EX1061) from 2015 and 2018 in an attempt to undercut a contraceptive utility, but these later-published studies could not inform a POSA's understanding in 2012. Pet., 82. Merck's enablement challenge fails.

*Fifth*, the Board should deny institution because Merck falls far short of its burden to demonstrate that a POSA would have had a reason to combine the '429 Patent and Chao to arrive at the claimed polypeptides having a E324D, E324N, and E324R mutation with a reasonable expectation of success. Notably, Merck does not identify any prior art disclosing an E324D, E324N, and E324R mutation in PH20. Indeed, Merck fails to establish that a POSA would have even had a *reason* to modify PH20's sequence. Merck merely relies on art stating that substitutions "*can be*" made without "altering the biological activity." Yet, Merck fails to provide a *reason* a POSA would have expended resources to make such substitutions, particularly if doing so was expected not to "alter[] the biological activity." EX2055, ¶171; EX1005, 16:14-22.

Unable to find an E324D, E324N, and E324R mutation in the art, Merck relies on Park's declaration to allege that a POSA would have undertaken approximately *thirty* steps to depart from the disclosures in the '429 Patent and Chao and arrive at the claimed invention. Pet., 93-99. Yet, Merck does not

establish that a POSA would have had a *reason* to perform these many steps or that doing so would have led a POSA to select residue E324 for modification. Even by Merck's own analysis, there were ~370 *other* so-called "non-essential" residues beyond residue E324. Similarly, Dr. Hecht never gives a reason to select residue E324 for modification; he relies solely on Park's testimony. And Park's only reason for selecting residue E324 was because he had been "asked by counsel to report [his] conclusions with respect to position 324." EX1004, ¶103. This is the very definition of hindsight.

Merck also uses hindsight when arguing that it would have been obvious to replace glutamic acid (E) at position 324 with aspartic acid (D), asparagine (N), or arginine (R). Merck first argues that a POSA would pick aspartic acid (D), asparagine (N), and arginine (R) because aspartic acid (D) was the most prevalent amino acid found at position 324 and asparagine (N) and arginine (R) appeared in some of the 88 different hyaluronidases when Merck aligned PH20's sequence with the sequences of multiple, other hyaluronidases. But Park's alignment included multiple different types of hyaluronidases having different substrate targets and different enzymatic functions. EX1056. As such, these divergent, non-PH20 hyaluronidases would not have informed POSAs of the most prevalent amino acid at residue 324 *in PH20*. And, *none* of the PH20 sequences Park analyzed contained D at residue 324 and only four PH20 sequences contained

either N or R, undermining Merck's obviousness theory. EX2055, ¶¶205-211.

Merck also argues a POSA would have selected D, N, or R as obvious choices because “many different amino acids occur in homologous hyaluronidase enzymes corresponding to position 324” and that this fact “would have suggested to the skilled artisan that many different amino acids can be tolerated at position 324 in PH20, including amino acids with low helix propensity.” Pet., 98-99. But, Merck never explains why a POSA would have specifically chosen D, N, or R. Merck further argues that a POSA would have picked D, N, or R because they are hydrophilic amino acids that would be obvious choices to replace hydrophilic glutamic acid at position 324. Pet., 99. Again, Merck provides no reason why a POSA would have chosen D, N, or R when there were other more hydrophilic amino acids. EX1014, 245; EX2055, ¶217. Merck's hindsight bias is further revealed through Merck's eleven related PGRs challenging Halozyme patents claiming PH20 polypeptides having modifications at other residues. In these eleven other petitions, Merck applies the *same* prior art and reasoning used here to work backwards from the claims to devise an obviousness theory. Section VIII.D.

In assessing reasonable expectation of success, Merck again—through Hecht—relies on Park's declaration and its discussion of an additional *fifty*-step analysis that Park alleges a POSA would have performed. Pet., 100-109. Merck and its declarants do not assert that any combination of the '429 Patent and Chao

discloses this fifty-step analysis or that a POSA would have had a reason to carry out these fifty steps. Nor do Merck's declarants adequately explain how and why the analysis and data were used, generated, or regarded in the art as 37 C.F.R. §42.65(b) requires.

Claims 3-5, 16, and 31-35 of the '520 patent have been statutorily disclaimed, leaving only claims 1-2, 6-15, and 17-30 (the "challenged claims") as the remaining claims challenged by the Petition<sup>2</sup>. EX2003. The Board may not institute a post-grant review proceeding based on disclaimed claims, and the Petition fails to demonstrate that it is more likely than not that any of claims 1-2, 6-15, and 17-30 is unpatentable. *Google v. Headwater Research*, IPR2024-00944, Paper 17 at 2 (P.T.A.B. Dec. 4, 2024) ("Because those claims have been disclaimed, we may not institute *inter partes* review on those claims. 37 C.F.R. §42.107(c) (2023). Accordingly, we treat the Petition as only challenging claims [that] have not been disclaimed.").

The Board should deny trial because Merck never even applies the correct application filing date to establish PGR eligibility, which is a dispositive threshold matter that must be resolved before the Board has jurisdiction to proceed. *Gillette*

---

<sup>2</sup> 37 C.F.R. §42.207(e) ("No post-grant review will be instituted based on disclaimed claims.").

*v. Sphere USA*, PGR2022-00030, Paper 31 at 39-40, 54-55 (P.T.A.B. Sept. 19, 2023). Additionally, the Board should deny trial because the petition improperly imports a requirement for hyaluronidase activity into the claims without even identifying how the claims are to be construed, and without soliciting an informed expert opinion grounded in an understanding of claim construction principles. Furthermore, the petition is based on legally and factually flawed arguments. Accordingly, the principles of efficiency, conservation of resources, and fairness would best be served by denying institution. 35 U.S.C. §324(a).

**II. MERCK FAILED TO ESTABLISH PGR ELIGIBILITY BECAUSE IT FAILED TO ASSESS THE '731 PRIORITY APPLICATION AS OF ITS DECEMBER 28, 2012 FILING DATE.**

To show PGR eligibility, Merck bore the burden of proving that at least one claim lacks the benefit of the filing date of a pre-AIA (pre-March 16, 2013) application. *Sandoz v. Biogen*, PGR2022-00054, Paper 16 at 25-28 (P.T.A.B. Feb. 2, 2023) (denying institution where Petitioner failed to “demonstrate that the priority applications’ respective written descriptions were insufficient *in view of the state of the art as of the filing date of each of [the] three pre-AIA applications*”); *Merck v. Wyeth*, PGR2017-00016, Paper 9 at 14 (P.T.A.B. Oct. 20, 2017) (“Petitioner’s failure to address *each relevant date* bolsters our holding that Petitioner fails to show sufficiently that the ’060 patent is post grant review eligible.”). To meet that burden, Merck’s petition needed to show that the ’520

patent or an application to which it claims priority contains or at any time contained a claim that has an effective filing date on or after March 16, 2013. AIA §3(n)(1). Here, Merck needed to prove that the '731 priority Application failed to provide §112 support *as of its December 28, 2012 filing date*. EX1026; *Reiffin*, 214 F.3d at 1346 (“the sufficiency of [a disclosure] under § 112, first paragraph *must be judged as of its filing date*.”); *Ariad v. Eli Lilly*, 598 F.3d 1336, 1355 (Fed. Cir. 2010) (“[A] written description analysis occurs ‘as of the filing date sought.’”); *Chiron v. Genentech*, 363 F.3d 1247, 1254 (Fed. Cir. 2004) (“Whether the earlier applications enable the claims of the '561 patent is determined *as of the filing date of each application*”); *Union Carbide v. Shell*, 308 F.3d 1167, 1185 (Fed. Cir. 2002) (“Enablement is determined as of the filing date ....”).

But rather than assess the '731 application as of its *2012* filing date, Merck's analysis consistently *and only* applied a *2011* date, while fatally ignoring the '731 Application's *December 28, 2012* filing date. Pet., 11-15, 27, 40, 56, 73-78, 82, 88-90, 93-96, 102-103, 107-109. Indeed, Merck's declarants, Hecht and Park, only ever considered a *2011* date in their analyses. EX1003, ¶¶11-14 (Hecht stating “I understand that my analysis and opinions are to be provided ... in the timeframe *before December 29, 2011*”); EX1004, ¶¶10-14 (Park stating “I understand that my analysis and opinions are to be provided ... in the *December 2011* time frame”). Merck therefore failed to meet its burden to judge the sufficiency of the '731

application under §112, because that application “must be judged *as of its filing date*,” which was in *2012, not 2011*.

Merck’s attempt to mix-and-match applications and dates—assessing the ’731 Application in view of the state of the art at the time of a different application—cannot be squared with binding precedents, and is illogical to boot. As such, Merck’s analysis of the pre-AIA ’731 application is legally deficient, and Merck has failed to establish PGR eligibility. EX1026. To the extent Merck argues that Halozyme did not present evidence about differences in the state of the art between 2011 and 2012, that is irrelevant. Halozyme had no obligation to provide evidence on the state of the art. Merck had the burden of analyzing the ’731 application as of its 2012 filing date. Merck failed to meet its burden, and the Board should deny institution.

### **III. MERCK’S POSA DEFINITION OMITTS ANY HYALURONIDASE EXPERIENCE.**

Because the patent relates to modified PH20 polypeptides and the prior art Merck cites (e.g., the ’429 Patent and Chao) relates to hyaluronidases, a POSA or a member of a multi-disciplinary team that includes the POSA would have *at least two years of practical experience with hyaluronidases*. EX2055, ¶¶23-46; EX2004; EX2005. Moreover, *over 20* references cited in Dr. Hecht’s declaration relate to hyaluronidases. EX2055, ¶27. A POSA typically would have a degree such as a B.S., M.S., or a Ph.D., with at least two years of experience and training in cellular

and molecular biology and protein biochemistry. EX2055, ¶¶33, 44. This experience and training could come from a POSA's undergraduate or graduate studies or from employment. EX2055, ¶33. The practical experience with hyaluronidases must come from either the POSA's own experience or through collaborations with a member of a multi-disciplinary team having experience studying and characterizing hyaluronidases. EX2055, ¶¶45-46.

The Federal Circuit has long considered factors such as the “(1) educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of workers active in the field” as a guide in determining the level of ordinary skill in the art. *Envtl. Designs v. Union Oil Co. of Cal.*, 713 F.2d 693, 696–97 (Fed. Cir. 1983); *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the prior art may reflect the appropriate skill level of a POSA). Merck cannot deny that the prior art it uses for alleging obviousness is directed to hyaluronidases: the '429 Patent relates to soluble neutral active hyaluronidases, and Chao discusses the structure of human hyaluronidase-1<sup>3</sup>. EX2055, ¶29; EX1005; EX1006; *Syngenta Crop Protection AG*

---

<sup>3</sup> The other factors also support a POSA definition that requires practical experience with hyaluronidases. EX2055, ¶¶27-42; EX1001, 8, 13-14, 4:15-65,

v. *UPL*, PGR2023-00017, Paper 58 at 21-22 (P.T.A.B. July 26, 2024) (Patent Owner’s addition to the POSA’s skill level was “consistent with the prior art’s demonstration of the level of ordinary skill in the art at the time of the invention.”).

Merck’s POSA definition, which does not require any experience with hyaluronidases, does not account for the requisite level of skill needed to view the prior art and the claimed invention. Pet., 15-16; EX1003, ¶13; *Okajima*, 261 F.3d at 1355 (the level of skill in the art is “a prism or lens” through which to view the prior art and the claimed invention). As explained by Dr. Triggs-Raine, general experience with non-hyaluronidase proteins or enzymes is inadequate because hyaluronidases differ from other proteins and enzymes. EX2055, ¶26. Indeed, hyaluronidases have unique three-dimensional structures, which are intrinsically linked to their substrates and/or functions. *Id.*; EX2018-EX2022. The ’520 patent confirms this understanding. The ’520 patent states that “[o]ne of skill in the art is familiar with *various classes of hyaluronidase inhibitors.*” EX1001, 160:17-20 (emphasis added).

On this point, it is telling that Merck aligned the amino acid sequences of vastly different hyaluronidases, but then jumped to conclusions without

---

109:26-58, 118:37-49, 134:15-23; 188:35-225:9; 130:8-135:26, 171:8-173:5; 188:8-27.

considering the various enzymes' diverse biological activities and substrates, something a POSA having hyaluronidase experience would not ignore. Section VIII.B.2.

Moreover, the '520 patent discusses various problems encountered in the art and contemplated solutions to those problems, which require practical knowledge of hyaluronidases. *Id.*, 109:26-29 (“PH20 hyaluronidase, such as rHuPH20, rapidly loses activity in the presence of preservatives . . . .”), 109:56-67 (“The modified PH20 polypeptides provided herein that exhibit increased stability in the presence of phenolic preservatives exhibit more than 15% enzymatic activity in the presence of at least one phenolic preservative . . . .”); 118:37, 118:47-51; EX2055, ¶¶26, 38. Furthermore, the hyaluronidase assays described in the common disclosure require familiarity with hyaluronidases even if these assays do not require extensive experience to employ. EX2055, ¶39. As such, either the POSA or a member of a multi-disciplinary team that includes the POSA must have practical knowledge of hyaluronidases. EX2055, ¶¶27-42.

#### **IV. MERCK IGNORES THE REQUIREMENT TO IDENTIFY HOW THE CLAIMS ARE TO BE CONSTRUED AND IMPROPERLY IMPORTS A FUNCTIONAL REQUIREMENT INTO THE CLAIMS**

Merck asserts that “[t]he claim terms are either expressly defined in the common disclosure or are used with their common and ordinary meaning” and that “no term requires an express construction . . . .” Pet., 17. Merck does not even

specify which claim terms were expressly defined in the specification or which terms should be given their plain and ordinary meaning. Nor does Merck identify the plain and ordinary meaning for any term. Merck's assertion that no claim requires an express construction is not supported by expert testimony. Indeed, Merck's declarants were never informed about claim construction principles, nor were they presented with the question of whether any claim term should be construed or what the plain and ordinary meaning of any claim term is. EX1003, ¶¶23-32; EX1004.

Merck's petition treats the claims as though they require hyaluronidase activity, but Merck never identifies any claim term(s) that imposes such a functional requirement. Merck's flawed interpretation of the claims infects the entire petition because the petition contains no arguments applying the correct construction and its §112 grounds rely on importing a functional requirement (*viz.*, hyaluronidase activity) into the claims. While "claim terms need only be construed to the extent necessary to resolve the controversy," Merck needed to show that the claims should be construed to require hyaluronidase activity because Merck applies such an interpretation throughout, particularly in its §112 Grounds. *Syngenta*, Paper 58 at 29.

To the extent Merck's claim interpretation relies on Hecht or Park, their testimony does not constitute competent, factual evidence, because neither

declarant evinced any understanding of claim construction principles nor applied them. EX1003, 1004. Merck's claim interpretation is founded *only* on attorney argument. *Invitrogen v. Clontech*, 429 F.3d 1052, 1068 (Fed. Cir. 2005) (“Unsubstantiated attorney argument regarding the meaning of technical evidence is no substitute for competent, substantiated expert testimony.”); *In re Payne*, 606 F.2d 303, 315 (C.C.P.A. 1979).

Having avoided identifying how the claims are to be construed, Merck failed to meet its burden to show that it is more likely than not that at least one construed claim is unpatentable. 37 C.F.R. §§42.204(b)(3)-(4); *Samsung*, Paper 16 at 20-21 (“Where a *petitioner specifically relies on a particular construction of a claim term* ... particularly a construction different from the ordinary meaning, that claim construction is part of the unpatentability analysis, and the *petitioner must provide a sufficient basis to support that construction*.”). Here, Merck specifically relies on a requirement for hyaluronidase activity, but Merck failed to provide any reasoned basis for such an assertion.

The patent defines “modified PH20 polypeptide” as a PH20 polypeptide that contains at least one amino acid modification, such as at least one amino acid replacement as described herein, in its sequence of amino acids compared to a reference unmodified PH20 polypeptide. EX1001, 48:38-43; Section IV.A. Merck

references this definition outside its claim-construction section<sup>4</sup>, but does not otherwise sufficiently construe the term in view of that definition. Pet., 17-18. The Board has held that where “the specification of the challenged patent provides an express construction of an important claim term, Petitioner’s failure to recognize and address the express construction, coupled with Petitioner’s failure to otherwise sufficiently address the meaning of the term, is insufficient to satisfy the requirements of 37 C.F.R. §42.104(b)(3).” *Volkswagen Group of America v. Michigan Motor Techs.*, IPR2020-00229, Paper 13 at 9-10 (P.T.A.B. Jul. 6, 2020).

Although Merck argues that no term requires an express construction, Merck’s §112 attacks are predicated on importing a functional requirement that does not appear in the claims, *viz.* hyaluronidase activity. Merck’s claim interpretation directly contradicts the specification’s express definition of “modified PH20 polypeptide.” EX1001, 48:38-43; Pet., 17-18; *Jack Guttman v. Kpykake Enterprises*, 302 F.3d 1352, 1361 (Fed. Cir. 2002) (“[w]here, as here, the patentee has clearly defined a claim term, that definition usually is dispositive; it is the single best guide to the meaning of a disputed term.”). For this reason, the

---

<sup>4</sup> To the extent Merck acknowledges the express definition of “modified PH20 polypeptide,” it underscores the impropriety of requiring hyaluronidase activity because this definition makes no mention of hyaluronidase activity.

PTAB should deny trial.

**A. “Modified PH20 Polypeptide” is Defined in a Purely Structural Manner**

The terms of the patent claims “are generally given their ordinary and customary meaning.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc). “There are only two exceptions to this general rule” when the patentee (1) “acts as his own lexicographer” or (2) “disavows the full scope of the claim term either in the specification or during prosecution.” *Thorner v. Sony Computer Entm’t Am. LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012). “To act as his own lexicographer, a patentee must ‘clearly set forth a definition of the disputed claim term,’ and must ‘clearly express an intent to define the term.’” *Id.*

The term “modified PH20 polypeptide”—see claim 1—is expressly defined:

*As used herein*, “modified PH20 polypeptide” or “variant PH20 polypeptide” *refers to* a PH20 polypeptide that contains at least one amino acid modification, such as at least one amino acid replacement as described herein, in its sequence of amino acids compared to a reference unmodified PH20 polypeptide.

EX1001, 48:38-43; EX2055, ¶67.

The phrases “as used herein” and “refers to” convey “an intent ... to be definitional.” *ParkerVision v. Vidal*, 88 F.4th 969, 977 (Fed. Cir. 2023); *Kyocera Senco Industrial Tools v. ITC*, 22 F.4th 1369, 1378 (Fed. Cir. 2022). The Federal Circuit’s recent decision in *Alnylam v. Moderna*, No. 23-2357 (Fed. Cir. June 4,

2025) is informative. In *Alnylam*, the Federal Circuit held that a statement is definitional if (1) “the sentence in question appears under the title ‘Definitions’; (2) “the term to be defined...is set off in quotation marks”; (3) the sentence “uses the term ‘refers to’...which generally ‘conveys an intent for that sentence to be definitional’; or (4) “elsewhere in the Definitions section, [the patent] used “non-limiting terms that contrast with the ‘refer to’ language at issue here.” *Id.* at slip op. 9-10.

Applying that same analysis to the facts of the present case leads to the conclusion that the term “modified PH20 polypeptide” is explicitly defined in this first sentence (using the phrases “as used herein” and “refers to”) and the sentences that follow this definition are simply exemplary, non-limiting descriptions of the term. Indeed, “modified PH20 polypeptide” is defined under the “Definitions” section of the patent, set off in quotation marks, and uses “refers to” to convey an intent for that sentence to be definitional. EX1001, 44:55, 48:38-43; POPR, 17. In the sentence right *after* this definition, the ’600 patent states that: “A modified PH20 polypeptide *can have* up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity.”<sup>5</sup> *Id.*, 48:43-

---

<sup>5</sup> Triggs-Raine reviewed the specification and explains that this sentence merely provides the maximum number of modifications that can be made to a PH20

46. By using “non-limiting” terms such as “can have,” the ’600 patent is contrasting the language there with the definitional sentence. Similarly, the paragraph with the express definition of the “modified PH20 polypeptide” contains further exemplary, non-limiting descriptions of the term, including non-limiting language such as “can have” and “can include”:

*“As used herein, “modified PH20 polypeptide” or “variant PH20 polypeptide” refers to a PH20 polypeptide that contains at least one amino acid modification,...A modified PH20 polypeptide can have up to 150 amino acid replacements, ... a modified PH20 polypeptide also can include any one or more other modifications, in addition to at least one amino acid replacement as described herein.*

EX1001, 48:38-53.

Based on this definitional sentence, a POSA would have understood that “modified PH20 polypeptide” is solely defined by its structure, i.e., its sequence of amino acids, and not by function. EX2055, ¶68. Indeed, other disclosures in the specification emphasize that “modified PH20 polypeptide” also refers to polypeptides that *do not* exhibit hyaluronidase activity. *SanDisk v. Memorex*

---

polypeptide while still exhibiting activity. Pet., 26; EX1001, 48:38-53; EX2055, ¶¶77-78. Furthermore, a POSA would have understood that “150 amino acid replacements” would result in a polypeptide that is not “at least 91%” identical to claim 1’s sequences and thus not claimed. EX2006; EX2055, ¶79.

*Prods.*, 415 F.3d 1278, 1285 (Fed. Cir. 2005) (“The court must always read the claims in view of the full specification.”). For example, under the header, “Inactive Mutants,” the ’600 patent specifies that these mutants are “*modified PH20 polypeptides* that contain one or more amino acid replacements in a PH20 polypeptide and that are *inactive, whereby the polypeptides do not exhibit hyaluronidase activity* or exhibit low or diminished hyaluronidase activity.” EX1001, 115:41-46; 251:1-6, 75:58-60, 115:59-62, 116:51-59, 188:21-25, 251:1-256:67, Tables 5 and 10; EX2055, ¶¶75-76.

The plain language of the claims is consistent with this express definition. Claim 1 recites: “A *modified PH20 polypeptide*, comprising one or more amino acid modifications in an unmodified PH20 polypeptide, wherein: the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of *SEQ ID NO: 3, 7 and 32-66* ... the modified PH20 polypeptide comprises an amino acid replacement at a position corresponding to residue 324 ... and the modified PH20 polypeptide has *at least 91% sequence identity* to a polypeptide having the amino acid sequence selected from the group consisting of *SEQ ID NO: 3, 7 and 32-66*.” EX1001, claim 1. Claim 1<sup>6</sup> does not require the “modified PH20 polypeptide” to exhibit hyaluronidase activity and is purely

---

<sup>6</sup> This analysis also applies to claims 2, 6-15, and 17-30.

structural. EX2055, ¶¶63-66, 69-70; EX1001, claim 1. *GlaxoSmithKline v. Banner Pharmacaps*, 744 F.3d 725, 731 (Fed. Cir. 2014) (Structural claims “are not distinguished by a particular performance property” and do “not assert coverage of yet-unidentified ways of achieving a desired result.”). Claim 1’s polypeptides share at least 91% of the *structure* of SEQ ID Nos 3, 7 and 32-66 while limiting any sequence variation to 9%. EX2055, ¶65. Claim 1 also requires another structural feature: one amino acid modification at position 324. EX2055, ¶65. Merck certainly has not identified language that mandates hyaluronidase activity. Thus, claim 1 is defined purely by structure, not function. EX2055, ¶65.

The challenged claims are similar to claims the Board previously construed as purely structural, and upheld under §112 on that basis. *Boehringer*, PGR2022-00021, Paper 9 at 6, 19 (P.T.A.B. July 15, 2022) (claims to a vector encoding a protein having “at least 90% sequence homology” with SEQ ID NOs. 4, 6, or 8 was “not [a] case where the claims use functional language to define a composition”); *Ex parte Friedberg et al.*, No. 2004-2314, Decision on Appeal (B.P.A.I. Nov. 17, 2004) (claims to an “isolated and purified polypeptide comprising at least 10 contiguous amino acids of [various SEQ ID Nos]” were adequately supported by the disclosure of the “complete structure of the claimed fragments of SEQ ID NO:2 or SEQ ID NO:4.”).

The dependent claims further support construing “modified PH20

polypeptide” as not requiring hyaluronidase activity. For example, dependent claims 17-19 specify further modifications, including glycosylation, which Merck has admitted “can abolish [hyaluronidase] enzymatic activity” if mutated. Pet., 12; EX2055, ¶¶71-74. The patent states glycosylation “is required for PH20 hyaluronidase activity” and “at least N-linked glycosylation sites corresponding to amino acid residues N200, N333, and N358 are required for secretion and/or activity of the enzyme.” EX1001, 70:67-71:4; EX2055, ¶72. Under the doctrine of claim differentiation, claim 1 encompasses unglycosylated PH20 polypeptides that, as such, lack hyaluronidase activity. EX2055, ¶¶73-74; *Am. Med. Sys. v. Biolitec*, 618 F.3d 1354, 1360 (Fed. Cir. 2010).

While the specification states a “modified PH20 polypeptide can have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity,” this disclosure is not part of the definition of “modified PH20 polypeptide,” and it does not support construing the term to require hyaluronidase activity. Indeed, Triggs-Raine reviewed the specification and explains that a POSA would have concluded that the patent does not support construing the claims to require functional activity. EX2055, ¶82. This above disclosure merely provides the maximum number of modifications that can be made to a PH20 polypeptide while still exhibiting activity. Pet., 26; EX1001, 48:38-53; EX2055, ¶¶77-78. Furthermore, a POSA would have understood that

“150 amino acid replacements” would result in a polypeptide that is not “at least 91%” identical to claim 1’s sequences and thus not claimed. EX2006; EX2055, ¶79.

Given the express definition of “modified PH20 polypeptide,” the plain language of the claims, and the specification and prosecution history (which are consistent with the express definition), a POSA would have understood that “modified PH20 polypeptide” means “a PH20 polypeptide that contains at least one amino acid modification compared to a reference unmodified PH20 polypeptide,” and the claims do not require hyaluronidase activity. EX2055, ¶¶80-82.

**B. The Board Should Deny Trial Under 37 C.F.R. §42.204(b)(3) Because Merck Does Not Identify How the Claims Should Be Construed Or Provide Sufficient Evidence Supporting Its Claim Interpretation.**

Instead of construing any claim term, Merck merely offers an incontrovertible statement of law: “[t]he terms used in the claims are either expressly defined in the specification of the common disclosure or are used with their common and ordinary meaning.” Pet., 17. However, under 37 C.F.R. §42.204(b)(3), Merck carries an “affirmative burden” to identify how the claims are to be construed. *Orthopediatrics v. K2M*, IPR2018-01548, Paper 9 at 10 (P.T.A.B. Mar. 1, 2019) (“our rules place an affirmative burden on [P]etitioners to ‘set forth: ... [h]ow the challenged claim is to be construed.’”). Petitioners must

also explain “[h]ow the construed claim is unpatentable” under §42.204(b)(4). *Id.*

By failing to identify—and provide sufficient support for—how the challenged claim is to be construed (e.g., identify which terms are given their plain and ordinary meaning and provide that meaning, or identify and apply an express definition), Merck failed to comply with §42.204(b)(3). Pet., 17; *Samsung*, Paper 16 at 20-21; *Volkswagen*, Paper 13 at 9-10.

Neither Merck nor its declarants expressly construes any claim term. Park never states he even reviewed the patent or its claims. And his declaration reflects no understanding of the concept of claim construction. EX1004. Likewise, Hecht does not mention claim construction principles or how to apply them, revealing his lack of understanding of claim construction. EX1003, ¶¶23-32. Moreover, his declaration does not even purport to engage in claim construction under *Phillips*. *Id.*

Nonetheless, Hecht states, “[a] skilled artisan would have understood the claims to necessarily *cover* modified PH20 polypeptides that are active mutants, *and would not view them as including inactive mutants.*”<sup>7</sup> EX1003, ¶134; EX2055,

---

<sup>7</sup> By stating that the claims only *cover* active mutants, Hecht wrongly assumes what the claims *cover* in lieu of performing claim *construction*. *In re Entresto*, 125 F.4th 1090, 1098 (Fed. Cir. 2025) (determining what a claim covers is not claim

¶63. Without any appreciation for claim-construction principles, Hecht essentially repeats the Petition’s arguments improperly importing a requirement for hyaluronidase activity. Pet., 25-26; EX1003, ¶¶126-135; EX2055, ¶63; *Xerox*, Paper 12 at 4-5 (Vidal, Dir.) (giving “little weight” to the expert testimony that “merely offer[s] conclusory assertions without underlying factual support and repeated, verbatim, [Xerox’s] conclusory arguments.”); *Deeper v. Vexilar*, IPR2018-01310, Paper 7 at 26-27 (P.T.A.B. Jan. 24, 2019) (“This conclusory analysis set forth in the Petition . . . , by itself, renders Petitioner’s showing insufficient. But even if we were to go beyond the Petition and also consider the cited [expert] testimony . . . , Petitioner’s showing would still be insufficient because that cited testimony is itself conclusory”).

Although Hecht cites the express definition of “modified PH20 polypeptide,” he completely ignores that the definition does not require hyaluronidase activity. EX1003, ¶129; EX1001, 48:38-46. Thus, Merck failed to offer evidence as to how the claims would be construed by a POSA since Merck’s

---

construction); *ParkerVision*, 88 F.4th 977 (the specification, when read as a whole, and the lexicography did not *restrict* the claim term “storage element” to an element of an energy transfer system, only that it “*encompasses* storage elements that are part of energy transfer systems.”).

declarants evince no understanding of claim construction principles and neither declarant performed an analysis under *Phillips. Head Sport v. Vermont Safety Developments*, IPR2024-01099, Paper 15 at 39 (P.T.A.B. Jan. 15, 2025) (Petitioner failed to provide evidence of how a term “would be understood by a [POSA].”).

Merck’s failure to construe the claims, particularly in light of their improper importation of a limitation (*See* Section IV.C), undermines the entire petition because claim construction is a predicate to assessing all unpatentability arguments. 37 C.F.R. §42.204(b)(3). Merck’s §112 arguments are all premised on Merck’s improper “functional requirement” in an attempt to meld the facts to the case law Merck cites. Pet., 17; *Samsung*, Paper 16 at 20 (“[w]here a petitioner specifically relies on a particular construction of a claim term in order to demonstrate unpatentability, ... that claim construction is part of the unpatentability analysis, and the petitioner must provide a sufficient basis to support that construction”); *Head Sport*, Paper 15 at 34. Merck’s position that “no term requires an express construction” is based solely on attorney argument, not competent expert testimony. Pet., 17; *Invitrogen*, 429 F.3d at 1068. Accordingly, Merck fails to meet its burden under 37 C.F.R. §42.204(b)(3), and institution should be denied.

**C. Merck Improperly Imports a Functional Limitation into the Claims.**

Despite failing to identify how the claims are to be construed, Merck

incorrectly treats the claims as requiring hyaluronidase activity, violating claim construction principles. Pet., 22-26; *Phillips*, 415 F.3d at 1313-1315.

*First*, Merck argues the claims are limited to only active mutants. Pet., 22. The Federal Circuit has noted that claim terms should not be interpreted “in a way that excludes embodiments disclosed in the specification.” *Oatey v. IPS*, 514 F.3d 1271, 1276 (Fed. Cir. 2008). Merck does just that in stating, “the specification describes two mutually exclusive categories of ‘*modified PH20 polypeptides*’ (i.e., ‘active mutants’ vs. ‘inactive mutants’) *but the claims are limited to one of them: ‘active mutants.’*” Pet., 22; EX1003, ¶126; EX2055, ¶¶83-84. Merck did not—and could not—identify any claim language limiting the claims to just active mutants. EX1003, ¶98; Pet., 22-25; EX2055, ¶¶85-86. And, the specification indisputably uses the term “modified PH20 polypeptide” to refer to both active and inactive mutants. EX1001, 115:40-123:22, 251:1-6; EX2055, ¶75.

Merck<sup>8</sup> further states that “active mutants” are “therapeutically useful

---

<sup>8</sup> Merck misapplies *TIP Systems* (holding “the claims need not be construed to encompass all disclosed embodiments *when the claim language is clearly limited to one or more embodiments*”). Pet., 22; *TIP Sys. v. Phillips & Brooks/Gladwin*, 529 F.3d 1364, 1375 (Fed. Cir. 2008). Here, the claim language is not “clearly limited” to “active mutants.”

because they possess hyaluronidase activity,” but alleges “inactive mutants” allegedly have “implausible” utility despite the specification identifying their utility “as antigens in contraception vaccines.” Pet., 24. Merck’s attempt to discredit the utility of “inactive mutants” to justify importing a hyaluronidase-activity limitation into the claims is improper: claims must be read “in light of the specification,” not in spite of the specification. *Phillips*, 415 F.3d at 1315 (“Claims must always be read in light of the specification.”). Although claim terms are interpreted in the context of the entire patent, it is improper to import limitations from the specification into the claims. *Head Sport*, Paper 15 at 27 (citing *Phillips*, 415 F.3d at 1323).

Merck also relies on the specification’s disclosure that modifications *can be* in any PH20 polypeptide “so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity.” Pet., 26; EX1001, 48:38-53; 47:61-65, 76:7-10, 77:2-9. Again, the specification merely states that modifications *can be made to* create active “modified PH20 polypeptides;” it does not state that all claimed “modified PH20 polypeptides” must exhibit hyaluronidase activity. The identified statements—divorced from the express definition of “modified PH20 polypeptide” and uses of the term elsewhere—do not indicate that Patent Owner “clearly express[ed] an intent to redefine” “modified PH20 polypeptide” to require enzymatic activity. EX1001, 115:40-123:22, 251:1-6; EX2055, ¶87; *Bradium*

*Techs. v. Iancu*, 923 F.3d 1032, 1044 (Fed. Cir. 2019).

*Second*, Merck wrongly argues that the claims are limited to “active mutants” because they require each “modified PH20 polypeptide” to have one of seven replacements at position 324 that yielded an “active mutant.” Pet., 25; EX1003, ¶¶126-128; EX2055, ¶¶86, 89. Merck ignores that dependent claims 17-18 further require glycosylation<sup>9</sup>, which the patent states is critical for hyaluronidase activity. Pet., 12; EX2055, ¶86; EX1001, 70:67-71:4. Merck’s claim interpretation disregards the doctrine of claim differentiation. *Seachange Int’l v. C-Cor*, 413 F.3d 1361, 1368–69 (Fed. Cir. 2005); *United Services Automobile v. PNC Bank*, IPR2021-01248, Paper 27 at 18, 23 (P.T.A.B. Jan. 3, 2023). Merck’s claim interpretation contradicts the express definition of “modified PH20 polypeptide,” is inconsistent with the plain language of the claims, and contradicts the specification—each violations of black letter claim construction law.

Because Merck improperly imports into the claims a requirement for hyaluronidase activity and relies on this interpretation for all grounds, institution should be denied. *Head Sport*, Paper 15 at 50 (denying institution because Petitioner relied on an incorrect claim construction); *Samsung*, Paper 16 at 16–23

---

<sup>9</sup> Hecht states, “PH20 enzymes must be glycosylated to exhibit their catalytic activity.” EX1003, ¶197; EX2055, ¶72.

(holding that because Petitioner’s obviousness showing was based on an incorrect claim construction, Petitioner did not demonstrate a reasonable likelihood that a claim limitation was disclosed by, or would have been obvious over, the cited reference).

**V. CLAIMS 1-2, 6-15, AND 17-30 ARE ENTITLED TO AT LEAST THE ’731 APPLICATION’S DECEMBER 28, 2012 FILING DATE.**

As discussed in Sections VI-VII, Merck does not provide sufficient evidence or argument to sustain its written-description and enablement challenges. *Reiffin*, 214 F.3d at 1345 (“the sufficiency [of a disclosure] under §112, first paragraph *must be judged as of its filing date.*”). As discussed in Section II, Merck wrongly assesses the sufficiency of the ’731 application as of *2011*, rather than the ’731 application’s December 28, *2012* filing date. Pet., 40, 56, 73-78; EX1003, ¶¶11-14; EX1004, ¶¶10-14 (Hecht and Park applied the December *2011* timeframe). And Merck never assesses the sufficiency of *any* application in the priority chain as of that application’s filing date.<sup>10</sup>

---

<sup>10</sup> Merck fails to show that Halozyne is not entitled to the November 1, 2012 date of Application 61/796,208, and Merck does not substantively address Halozyne’s provisional applications, which Hecht and Park never considered. EX1051-1052; EX1003, 122-123; EX1004, App’x A. The Board need not assess priority to the provisionals, because the ’731 Application’s 2012 filing date is

For both §112 grounds, Merck relies on the “common disclosure” between the patent and the ’731 Application, which Merck admits has a substantively identical specification to the ’520 patent. Pet., 6, 23, 27, 32-86. For the same reasons as discussed in the Grounds, Merck fails to show that Halozyme is not entitled to at least the December 28, 2012 filing date of the ’731 Application.

**VI. GROUND 1: MERCK FAILS TO SHOW THAT IT IS MORE LIKELY THAN NOT THAT THE CLAIMS LACK WRITTEN DESCRIPTION.**

Merck’s written description analysis inappropriately evaluates what the specification describes instead of assessing a properly construed claim, and so violates recent, binding Federal Circuit law. *In re Entresto*, 125 F.4th at 1097-1100. Specifically, Merck’s written-description arguments are predicated on the claims supposedly requiring hyaluronidase activity. But, the “scope of what is claimed (and must be adequately described) is, in turn, determined through claim construction.” *In re Entresto*, 125 F.4th at 1098; *Phillips*, 415 F.3d at 1312. Here, Merck (i) fails to offer any claim construction and (ii) fails to apply a correct claim construction, each failure, independently, warranting denying Merck’s written-description challenge.

---

sufficient to defeat PGR-eligibility (Section II).

**A. Merck’s Cited Written-Description Law Concerns Functionally Defined Claims, Not Structural Claims.**

On January 10, 2025, the Federal Circuit issued its decision in *In re Entresto*, where the Federal Circuit expressly stated that a patent need only describe and enable what the claim *requires* as ascertained via claim construction, and *not* what the claim simply *covers*. *In re Entresto*, 125 F.4th at 1097-1100 (finding that, although the claims covered certain subject matter, they did not require it, and so the specification did not need to describe and enable the covered but not required subject matter). As discussed above in Section IV.A, when properly construed, the claims do not require hyaluronidase activity. Yet Merck’s written description ground (and enablement ground discussed below) wrongly focus entirely on whether the ’520 patent describes and enables a feature that is *not* actually required by the claims, i.e. hyaluronidase activity.

For example, Merck’s three allegedly “especially probative” cases (*AbbVie*, *Idenix*, and *Boehringer I*) are inapposite because they are directed to claims reciting *functionally defined* genera, which are not germane to the challenged patent’s purely structural modified PH20 polypeptide claims. Pet., 28-32. Because Merck failed to identify any authority supporting its written-description challenge of *structural*, not functional, claims, Merck’s arguments fall short.

Indeed, in *AbbVie v. Janssen*, the Federal Circuit found that claims directed to an antibody “that *binds to human IL-12 and dissociates from human IL-12 with*

*a k<sub>off</sub> rate constant of  $1 \times 10^{-2} \text{ s}^{-1}$  or less*” lacked written description support. 759 F.3d 1285, 1292 (Fed. Cir. 2014). The Court held, “[w]hen a patent claims a *genus using functional language* to define a desired result, ‘the specification must demonstrate that the applicant has made a generic invention that *achieves the claimed result* ... by showing ... species sufficient to support a claim to the *functionally-defined* genus.’” *Id.* at 1299. Likewise, in *Idenix*, claims to a “*method for the treatment* [of HCV]” lacked written description because the specification “fail[ed] to provide sufficient blaze marks to direct a POSA to the specific subset of 2’-methyl-up nucleosides that are *effective in treating HCV.*” *Idenix v. Gilead*, 941 F.3d 1149, 1164 (Fed. Cir. 2019).

Merck also cites *Boehringer v. Kansas State*, PGR2020-00076, Paper 42 at 6 (P.T.A.B. Jan. 31, 2022) (“*Boehringer I*”). There, the Board found credible Petitioner’s expert’s testimony that “the ’351 Patent does not disclose which of the thousands of different claimed homologous sequences, if any, the inventor possessed, much less had discovered *to be antigenic.*” *Boehringer I*, Paper 42 at 35. In other words, the Board held that the claims required functional activity (*see* block quote below).

In a subsequent decision involving the same parties and a related patent, the Board reiterated that the claims in *Boehringer I* “used functional language to

define a composition.”<sup>11</sup> *Boehringer v. Kansas State*, PGR2022-00021, Paper 9 at 19 (P.T.A.B. July 15, 2022) (“*Boehringer II*”); *Boehringer II*, Paper 11 at 5-6 (P.T.A.B. Feb. 24, 2023).

In contrast to *Boehringer I*, the Board in *Boehringer II* found that claims reciting “at least 90% sequence homology” to specific recited sequences were structural and adequately supported by the specification, stating:

[I]n contrast to the claims set forth in [*Boehringer I*], *this is not the case where the claims use functional language to define a composition.* PGR2020-00076. Specifically, the challenged claims are not directed to a subset of species with certain antigenic properties. *The recited sequences share at least 90% of the structure of disclosed sequences while limiting the amount of variation to 10% sequence homology or sequence identity.* Thus, unlike the claims [in *Boehringer I*], the products claimed in the ’274 patent recite *structural limitations*—there is *no requirement* that the protein be capable of inducing immunological response, for example. *Id.*

PGR2022-00021, Paper 13 at 20 (P.T.A.B. Mar. 22, 2023).

Notably, upon Director Review of *Boehringer II*, Director Vidal agreed that the claims in *Boehringer II* did not use functional language, stating “The Board

---

<sup>11</sup> The ’274 Patent in *Boehringer II* is a divisional of the ’351 patent in *Boehringer I*, both claiming priority to the same provisional. *Boehringer II*, Paper 9 at 5-6.

was correct to focus on whether the claims themselves were enabled and *to find inapposite Petitioner’s arguments as to whether functional language — appearing only in the specification — was enabled.*” *Id.*, Paper 11 at 5. Like the claims in *Boehringer II*, the challenged claims here are not functional and recite at least 95% sequence identity.

It is surprising that Merck alleges that *Boehringer I* “provides another direct analogy” but never acknowledges the existence of, and similarity to, *Boehringer II*. Pet., 31-32. This is particularly surprising because Merck was named a real-party-in-interest (RPI) in both *Boehringer* cases. PGR2022-00021, Paper 4 at 1; PGR2020-00076, Paper 6 at 1.

In sum, all of the cases Merck cites involve functional claims, with the holdings all turning on that specific fact. Meanwhile, Merck conveniently ignores cases finding written-description support of purely structural claims. *GlaxoSmithKline*, 744 F.3d at 731; *Boehringer II*, Paper 9 at 19; *Ex parte Friedberg* at 4-6. It is no wonder Merck improperly imports a functional requirement into the claims to support its arguments that the claims lack written description. *In re Entresto*, 125 F.4th at 1098 (an improper construction of the claims, conflating claim *coverage* with claim *construction*, “led [the district court] astray in evaluating written description”); *ParkerVision*, 88 F.4th at 977. Because no law supports Merck’s written-description arguments, Ground 1 fails.

Additionally, Merck fails to establish that the claims lack written description support under the correct legal standard. Section VI.A-B. Indeed, the Federal Circuit has held that “[s]ufficient description of a genus [] requires the disclosure of *either* a representative number of species falling within the scope of the genus *or structural features common to the members of the genus so that one of skill in the art can ‘visualize or recognize’ the members of the genus.*” *Ariad*, 598 F.3d at 1350. Similarly, the PTAB has found that a disclosure of structural features common to the genus is sufficient to establish written-description support for structural claims. For example, claims reciting an “isolated polynucleotide ... at least 95% identical to the polynucleotide sequence of SEQ ID NO:2” were adequately supported by the specification because “*the complete structure of the polynucleotide of SEQ ID NO: 2 has been described, and the genus [is] limited to [] polynucleotide[s] comprising a naturally occurring polynucleotide sequence at least 95% identical to the polynucleotide sequence of SEQ ID NO: 2.*” *Ex parte Bandman*, No. 2004-2319, Decision on Appeal at 4-5 (B.P.A.I. Jan. 6, 2005).

Likewise, in *Ex parte Friedberg*, the Board held that claims to an “isolated and purified polypeptide comprising at least 10 contiguous amino acids of SEQ ID [NOs 2 and 4]” were adequately supported because “*the complete structure of SEQ ID [Nos 2 and 4] has been described, and the polypeptides of the claimed genus share at least 10 contiguous amino acids of the structure of SEQ ID [Nos 2 and*

4].” *Ex parte Friedberg* at 6. The Board further held that “*the structural features that are common to the genus* make up at least 10 contiguous amino acids of the *structure* set forth in SEQ ID [Nos 2 and 4].” *Id.* Disclosing such structure is sufficient; the written-description requirement does not require a “nucleotide-by-nucleotide recitation of the entire genus of claimed genetic material.” *Ariad*, 598 F.3d at 1352; *Falko-Gunter v. Inglis*, 448 F.3d 1357, 1368 (Fed. Cir. 2006).

**B. Merck Does Not Grapple With the Common Structural Features Shared by the Claimed Polypeptides.**

Merck argues that the “common disclosure ... does not identify to a skilled artisan *any* structural features shared by the many, diverse ‘*active mutant[s]*.’” Pet., 54. Merck is wrong. Contrary to Merck’s insistence upon a disclosure of a structure-function relationship, the written-description requirement is satisfied here by disclosing structural features common to the members of the genus such that POSAs can “visualize or recognize” the members of the genus. Pet., 52-54; EX2055, ¶¶20, 99-100; *Ariad*, 598 F.3d at 1350. By interpreting the claims to require hyaluronidase activity, Merck fails to assess whether there is adequate written-description for the claims.

Merck cannot credibly deny that the recited structural features allow POSAs to visualize or recognize the identity of all members of the genus, because the members share “at least 91%” of the structure of disclosed amino acid sequences (SEQ ID Nos: 3, 7 and 32-66) while limiting any amino acid sequence variation to

9%. EX1001, claim 1. EX2055, ¶¶90-92. Indeed, Hecht and Park use these structural features to determine the size of the genus. EX1003, ¶¶120, 122; EX1004, ¶¶180-184, App'x F; Pet., 18-21; EX2055, ¶93.

Additionally, all claimed polypeptides have an “amino acid replacement [selected from “A, D, H, M, N, R and S”] at ... residue 324”—another structural feature. EX1001, claim 1; EX2055, ¶92. Thus, Merck is wrong in alleging that the common disclosure “makes no effort to identify (and never contends there is) a common structure shared by enzymatically active, multiply modified PH20 polypeptides within each claimed genus.” Pet., 2. Such structures are disclosed and claimed. EX1001, claim 1; EX2055, ¶92.

Merck also cannot deny that the specification's incorporated sequence listing adequately describes the sequences (i.e., structure) of SEQ ID Nos: 3, 7 and 32-66<sup>12</sup>. EX2055, ¶94. EX1001, 4:4-12; EX2006.

A POSA in 2012 would have been able to visualize or recognize the identity of all members of the claimed genus of modified PH20 polypeptides manually or by using a computer and sequence-comparison software like CLUSTAL-Omega

---

<sup>12</sup> SEQ ID Nos: 3 and 32-66 are a series of single-residue C-terminal truncations, while SEQ ID No: 7 contains additional residues. EX1001, 12:62-67, 30:45-51. EX2055, ¶95.

and BLAST, given the disclosed sequences. EX1001, 58:57-61:7; EX1039, 125; EX2055, ¶¶96-98. A POSA would have understood that using a computer was not required but would expedite the process. EX2055, ¶96. Even before the patent's priority date, the Board previously found adequate description for claims reciting 90% sequence identity because POSAs "may well be able to visualize or recognize the identity of members of that genus" using "a computer and sequence-comparison software." *Ex parte Porro*, No. 2008-0184, Decision on Appeal at 7-8 (B.P.A.I. Mar. 11, 2008); *Ex parte Joo-Eun Bae*, No. 2009-013469, Decision on Appeal at 5-7 (B.P.A.I. Apr. 5, 2010) ("With the aid of a computer, it is possible to list the sequences of all of the fragments and variants of SEQ ID NO: 13 that fall within the scope of the claimed genus."). Given the ample disclosure of structural features common to all members of the claimed genus, Merck's written-description challenge fails. Indeed, reviewing similar facts, the Board has denied institution when the Petitioner bases its written-description challenge on "certain functional characteristics disclosed in the Specification that are *not recited in the challenged claims.*" *Boehringer II*, Paper 13 at 21. In importing a functional limitation into the claims, this is precisely Merck's gambit. Accordingly, Merck's written-description ground should be rejected.

**C. Merck Ignores Disclosures of Modified PH20 Polypeptides Containing Multiple Substitutions.**

Merck argues that the common disclosure "does not describe a

representative number of multiply modified enzymatically *active* PH20 polypeptides,” and Merck criticizes the working examples. Pet., 55, 58. Not only is this the wrong analysis premised on a false requirement for hyaluronidase activity (Section IV), but Merck ignores the specification’s disclosures of multiply modified PH20 polypeptides. Pet., 55-59. For example, the specification discloses:

- “any of such modified PH20 polypeptides contain a single amino acid modification, such as a replacement, and *combinations of modifications.*” EX1001, 18:43-49, *id.* 48:46-50, 75:61-65; EX2055, ¶¶110-111.
- “[e]xemplary modifications include *at least one amino acid replacement* selected from among replacement with ... R at a position corresponding to *position 324 ... and/or* with Q at a position corresponding to position 447, with reference to amino acid positions set forth in SEQ ID NO:3.”; *id.*, 14:24-17:64;
- “For example, the modified PH20 polypeptides provided herein contain an amino acid replacement (substitution) at *one or more amino acid positions* corresponding to positions ... 324 ... with reference to amino acid positions set forth in SEQ ID NO:3.” EX1001, 97:64-98:10, 85:60-87:8; EX2055, ¶112.

Thus, POSAs would have recognized that the specification describes multiply

modified PH20 polypeptides. EX2055, ¶112.

Merck wrongly requires *working examples* of multiply modified polypeptides. Pet., 55-59. But written description is “not about whether the patentee has proven to the skilled reader that the invention works ....” and it “does not demand either examples or an actual reduction to practice.” *Alcon v. Barr*, 745 F.3d 1180, 1191 (Fed. Cir. 2014); *Ariad*, 598 F.3d at 1352.

Additionally, Merck concedes that the specification “reports results from testing a portion of a randomly generated library of ~6,743 single-replacement PH20<sub>1-447</sub> polypeptides.” Pet., 41. And, of these, “over 600 tested mutants exhibit activity.” EX1001, 228:25-30, 194:51-55; EX2055, ¶¶101-103. Merck fails to establish that disclosures of multiply modified PH20 polypeptides and ~6,800 working examples are not representative of the structurally claimed polypeptides.

Contrary to Merck’s assertions regarding the “diversity” of claimed polypeptides, the claims recite at least 91% sequence identity, which a POSA would have understood reflects an incredibly uniform and homogeneous group of polypeptides. EX2055, ¶104. Notably, Park alleges that bee venom hyaluronidase and human PH20 were “highly homologous” despite only “sharing about 30% sequence identity.” EX1004, ¶¶40, 163. A POSA would have understood that if 30% sequence identity constitutes “high” homology, then the claimed polypeptides, reciting  $\geq 95\%$ , are extremely uniform. EX2055, ¶104.

In attempting to establish the examples are “non-representative,” Merck offers a “simple illustration” Pet., 58. But neither declarant testified as to the accuracy of Merck’s illustration; it constitutes unsupported attorney argument. 37 C.F.R. §42.65. Moreover, Hecht merely repeats, *verbatim*, the petition’s conclusory assertion that the examples are non-representative (*compare* Petition, 58-59, *and* EX1003, ¶143, last sentence), and he does not offer any additional evidence to support the stated conclusion. His testimony should be accorded little to no weight, and this unsupported attorney argument should be disregarded. *Xerox*, Paper 12.

Written description does not require a recitation of every species in the genus. *Ariad*, 598 F.3d at 1336; *Cordis v. Medtronic*, 339 F.3d 1352, 1365 (Fed. Cir. 2003) (“an applicant is not required to describe in the specification every conceivable and possible future embodiment of his invention;” “a specification may ... contain a written description of a broadly claimed invention without describing all species that [the] claim encompasses.”); *RiceTec v. BASF SE*, PGR2021-00113, Paper 35 at 15 (P.T.A.B. Mar. 8, 2023) (“a specification may ... contain a written description of a broadly claimed invention without describing *all species* that the claim encompasses.”).

The Petition makes no effort to explain why disclosures of single-modified PH20 polypeptides are not representative of multiply modified PH20 polypeptides

when the claims do not require hyaluronidase activity. Merck focuses myopically on the alleged absence of “any multiply-modified PH20 polypeptides that are ‘active mutants,’” but the claims do not require “active mutants.” Pet., 48-61; EX2055, ¶¶113-114. It is established Federal Circuit law that “[w]ritten description asks whether that which is claimed is adequately described.” *See In re Entresto*, 125 F.4th at 1097-1100. Here, Merck inappropriately evaluates whether the specification describes and enables what the claim simply *covers* but does not require, and so violates recent, binding Federal Circuit law. *See id.* Indeed, Merck focuses myopically on the alleged absence of “any multiply-modified PH20 polypeptides that are ‘active mutants,’” but the claims do not require “active mutants.” Pet., 48-59; EX2001, ¶¶113-114.

Thus, Merck fails to establish that the disclosed polypeptides are not representative of the claimed genus.

**D. The Claims Do Not Capture Multiply Modified PH20 Polypeptides Excluded from the Specification.**

Merck alleges that the claims capture polypeptides “the common disclosure explicitly says to not make,” and “affirmatively exclude[d]” subject matter. Pet., 60-61. Merck is referring to the following six combinations of replacements:

- P13A/L464W, N47A/N131A, N47A/N219A, N131A/N219A, and N333A/N358A, which the specification states should not be made if the polypeptide contains *only* two amino acid replacements and

- N47A/N131A/N219A, if the polypeptide contains *only* three amino acid replacements. Pet., 60; EX1001, 77:56-59.

Again, Merck is wrong regarding claim scope, because none of the six combinations is encompassed by the claims. EX2055, ¶¶105-109. The disclosed combinations all require replacements at positions that do not include the claimed modification at position 324. EX1001, 77:47-59, claim 1; EX2055, ¶107.

Accordingly, the claims never captured these six combinations of replacements.

**E. “Modified PH20 Polypeptide” in the Remaining Claims is Also Structural.**

The term “modified PH20 polypeptide” in Claims 2, 6-15, and 17-30 does not require hyaluronidase activity. These claims, too, are adequately supported by the specification for at least the same reasons identified for claim 1. EX2055, ¶¶113-114.

\* \* \*

Ultimately, “the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.” *Harmonic v. Avid*, 815 F.3d 1356, 1363 (Fed. Cir. 2016). Merck has not met its burden, and Ground 1 fails.

**VII. GROUND 2: MERCK FAILED TO SHOW THAT IT IS MORE LIKELY THAN NOT THAT THE CLAIMS LACK ENABLEMENT.**

**A. Merck’s Cited Enablement Law Concerns Functionally Defined, Not Structural, Claims.**

Merck repackages its written-description arguments to argue lack of enablement. Merck again improperly imports a functional requirement (hyaluronidase activity) in an effort to align its arguments with the cited cases (*Amgen*, *Idenix*, *Wyeth*, and *Baxalta*) and in violation of recent Federal Circuit law. *See In re Entresto*, 125 F.4th at 1098 (the “scope of what is claimed [ ] is, in turn, determined through claim construction”). Indeed, all cited cases involved claims having functional, not structural, limitations even though the claims at issue here do not require hyaluronidase activity. Pet., 67-68. Because Merck relied on an improper claim interpretation for its enablement ground, Merck relies solely on inapposite law in support of its analysis.

*Amgen*’s claims to antibodies that “bind to” PCSK9 and “block PCSK9 from binding to [receptors]” recited functional, not structural, language and therefore lacked enablement. *Amgen v. Sanofi*, 598 U.S. 594, 614 (2023) (“Amgen seeks to monopolize an entire class of things defined by their *function*.”). *Idenix* also involved functionally defined claims (method of treating HCV infection), and the patent lacked enablement. *Idenix*, 941 F.3d at 1162.

Likewise, *Wyeth* and *Baxalta* involved functional claims and are similarly

inapposite. Pet., 67-68; *Wyeth v. Abbott*, 720 F.3d 1380 (Fed. Cir. 2013) (method of treating restenosis); *Baxalta v. Genentech*, 81 F.4th 1362 (Fed. Cir. 2023) (antibodies that bind Factors IX or IXa and increase procoagulant activity).

Accordingly, Merck’s cited cases are distinguishable because they do not concern structural claims.

**B. Merck Failed to Show Undue Experimentation Would be Required.**

Merck argues that using the common disclosure and knowledge in the art, POSAs “would have to perform undue experimentation to identify ... PH20 polypeptides having multiple amino acid replacements and/or truncations [that] are ‘*active mutant[s]*.’” Pet., 68; EX2055, ¶¶20, 115. Like its written-description arguments, Merck’s enablement arguments are based on the false premise that the claims require “active mutants.” Pet., 69-78; *supra*. But, Merck fails to show that undue experimentation would have been required to practice the *claimed* invention. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

**1. Merck Failed To Establish that Making Modified PH20 Polypeptides Required Undue Experimentation.**

The nature of the invention—modified PH20 polypeptides—weighs in favor of enablement, because making such polypeptides was well within the skill of a POSA in December 2012 given the guidance in the specification and the general knowledge in the art. EX2055, ¶¶116-119. Merck does not even allege that the

techniques for making the claimed polypeptides would have required undue experimentation. POSAs would have understood that given the specification's guidance and the state of the prior art, making the claimed polypeptides requires only routine molecular biology and protein biochemistry techniques. EX2055, ¶¶118-119.

Likewise, the guidance in the specification, the prior art, and the relative skill of a POSA each weigh in favor of enablement. EX2055, ¶¶118-120. Indeed, the patent discloses that the claimed polypeptides can be “obtained by methods *well known in the art for protein purification and recombinant protein expression.*” EX1001, 135:28-149:54, *id.*, 135:40-137:32, 137:33-42, 137:42-140:63, 140:64-144:58. EX2055, ¶¶118-119. The patent also incorporates the Sequence Listing providing sequences for SEQ ID Nos: 3, 7 and 32-66. *Id.*, 4:8-12; EX2055, ¶120; EX2006<sup>13</sup>. Park and Hecht both fail to mention relevant disclosures in the specification, discussed below, or provide substantive discussion of whether such disclosures would have enabled POSAs to make the claimed polypeptides. For example, the specification describes how to make PH20 polypeptides comprising the claimed sequences using techniques that were well within the level of skill of a POSA. EX2055, ¶121; EX1001, 75:20-36; EX2007; EX2008.

---

<sup>13</sup> Neither Park nor Hecht provide the sequence listing as an exhibit.

The quantity of experimentation required also weighs in favor of enablement, and Merck fails to explain why it would have required anything more than repetition of routine, commonly used molecular biology and protein biochemistry techniques that a POSA would have been fully capable of performing in light of the specification's guidance. *Cephalon v. Watson*, 707 F.3d 1330, 1338-1339 (Fed. Cir. 2013) (“extensive experimentation does not necessarily render the experiments unduly extensive where the experiments involve repetition of *known or commonly used techniques*.”). EX2055, ¶¶128-130. Triggs-Raine confirms that making the claimed polypeptides in light of the specification's guidance would have involved only routine, not undue, experimentation and known, commonly used molecular biology and protein biochemistry techniques. EX2055, ¶128. Indeed, Hecht agrees that the methodology was conventional. EX1003, ¶¶198-203; EX2055, ¶¶124-126. Moreover, a POSA would have understood that practicing the claims does not require performing iterative rounds of randomized mutations to discover modified PH20 polypeptides that “might possess hyaluronidase activity” because, *inter alia*, the claims do not require hyaluronidase activity. EX2055, ¶129.

Merck alleges that making *and testing* only one molecule of each mutant with multiple substitutions would require “exceed[ing] the mass of the Earth.” But Merck fails to establish that the structural modified PH20 polypeptide claims

impose any requirement for *testing*. Pet., 27. Merck also ignores that the disclosed and claimed requirement that the modified PH20 polypeptides have at least 91% sequence identity to SEQ ID Nos: 3, 7 and 32-66 and a modification at position 324 is a common quality running throughout the claimed genus. *Amgen*, 598 U.S. at 611 (disclosing a “general quality ... running through” the genus reliably enables the claimed invention.)

Moreover, even if testing were required, Merck fails to establish that such tests would have required anything more than routine experimentation and repetition of known or commonly used techniques given the specification’s guidance. Pet., 72; *Wands*, 858 F.2d at 737 (“Enablement is not precluded by the necessity for some experimentation such as routine screening”); *Cephalon*, 707 F.3d at 1338-1339; *Amgen*, 598 U.S. at 611 (“[A] specification [is not] necessarily inadequate just because it leaves the skilled artist to engage in some measure of adaptation or testing”); *Baxalta*, 81 F.4th at 1367. Therefore, the quantity of experimentation supports enablement. *Wands*, 858 F.2d at 737.

Merck alleges the specification “provides no meaningful guidance in producing ‘*active mutant[s]*,’”<sup>14</sup>—again relying on an improper claim

---

<sup>14</sup> Merck wrongly implies the specification discloses only polypeptides having >40% hyaluronidase activity (“active mutants”) and those having <20% activity or

interpretation. Pet., 73; Section IV.C. Nonetheless, the specification discloses thousands of examples of modified PH20 polypeptides, weighing in favor of enablement. Supra. As Merck concedes, the specification reports results from a “library of ~6,743 single-replacement PH20<sub>1-447</sub> polypeptides.” Pet., 41. Because the claims are not limited to “active mutants,” Merck failed to show that these examples do not provide practical guidance for making the claimed polypeptides. *Boehringer II*, Paper 13 at 25-26 (“Petitioner’s enablement challenge focuses on certain *functional characteristics* disclosed in the Specification that are not recited in the challenged claims, and therefore, lacks sufficient merit in the context of the challenged claims”).

Moreover, Example 1 provides step-wise guidance for predictably making recombinant human PH20, Example 2 teaches making a library of PH20 mutants, and Example 6 teaches large-scale preparations. EX1001, 188:35-194:5, 194:6-225:11, 277:46-279:67. In view of the working examples’ guidance, making the claimed polypeptides would not have been unpredictable. EX2055, ¶¶121-123. Thus, the working examples and predictability weigh in favor of enablement.

---

no activity at all (“inactive mutants”). Pet., 22-23; EX2055, ¶87. The specification also discloses 192 modified PH20 polypeptides having 20-40% activity. EX1001, Table 9; EX2055, ¶87.



equipped with the specification's guidance. *Id.*; EX2055, ¶131.

**2. Merck Fails To Demonstrate that Using Modified PH20 Polypeptides Required Undue Experimentation.**

Merck also fails to satisfy its burden of demonstrating that using the claimed modified PH20 polypeptides would have required undue experimentation. *First*, it is undisputed that the specification expressly discloses that “active mutant” PH20 polypeptides are useful because they possess hyaluronidase activity and can be used, e.g., “for treating a hyaluronan-associated disease or condition” or to “increas[e] delivery of a therapeutic agent to a subject.” EX1001, 4:21-50, 39:5-15, 25-28, 174:38-39, 175:39-187:37 132:50-63, 171:7-173:21, 225:11-278:33, Examples 3-5, 281:16-287:56, Examples 8-11, 290:47-293:16, Examples 14-15; EX2055, ¶¶132-136.

*Second*, Merck bases its enablement challenge on the false assumption that the claims are limited to “active mutants.” Pet., 69-84. In doing so, Merck ignores Director Vidal's decision in *Boehringer II*—where Merck was a real party-in-interest—stating that “the Board was correct to focus on whether the claims themselves were enabled and *to find inapposite Petitioner's arguments as to whether functional language*—appearing only in the specification—was *enabled*.” *Boehringer II*, Paper 11 at 5-6.

*Third*, the specification discloses that the claimed polypeptides are useful as “antigens in contraception vaccines,” irrespective of whether they exhibit

hyaluronidase activity. EX1001, 75:58-60, 194:54-195:6, *id.* 72:48-73:51; EX1011, 814; EX2055, ¶¶140-141; *Ex parte Friedberg* at 7 (purely structural claims to polypeptides identified by sequence were enabled simply because “*there is some use for the polypeptides ...*”). Here, the specification reports that “[m]odified PH20 polypeptides provided herein *can be used as vaccines in contraceptive applications.*” EX1001, 188:6-27; EX2055, ¶¶39, 140. And it teaches that “PH20 is present in the male reproductive tract, and is expressed in both the testis and epididymis and is present in sperm,” and was known to “[p]lay[] a role in fertilization by facilitating entry of the sperm through the cumulus layer surrounding the unfertilized egg.” EX1001, 188:11-13; EX2055, ¶¶39, 140. The specification further explains that PH20 is able to bind to hyaluronic acid on the zona pellucida during early phases of fertilization and “initiates intracellular signaling that aids in the acrosome reaction.” EX1001, 188:14-18; EX2055, ¶140.

The specification then cites Primakoff 1988 (EX2010) and Tung 1997 (EX1023) as teaching that “[i]mmunization with PH20 has been shown to be an effective contraceptive in male guinea pigs” and “an effective contraceptive in female guinea pigs due to the generation of anti-PH20 antibodies that prevent sperm and egg binding.” EX1001, 188:18-23; EX2055, ¶¶137-138, 142. As explained below, Merck fails to undermine the data demonstrating that PH20 could have been used as contraceptives. Section VII.C; EX2055, ¶¶142-151; EX1006,

6911, 6916. Indeed, in 2012, there was a “strong rationale” with recent data indicating that the development of anti-sperm contraceptive vaccines, like PH20, was an “exciting proposition” and a “viable alternative to other modalities of contraception.” EX2009, 5; EX2055, ¶146. Accordingly, the specification disclosed a valid, i.e., credible, utility for all claimed polypeptides.

Thus, Petitioner failed to show that making and using the claimed polypeptides would have required undue experimentation as of 2012. Merck fails to satisfy its burden of demonstrating that the claims lack enablement.

**C. Merck Did Not Refute the Data Showing that PH20 Polypeptides Are Useful as Contraceptives in Guinea Pigs.**

Merck argues that the specification’s disclosure that inactive PH20 polypeptides can be used as “antigens in contraception vaccines” is “not scientifically credible,” but Merck does not disprove the significant findings in two studies in guinea pigs (Primakoff 1988 and Tung 1997) that are incorporated by reference into the specification. Pet., 81-84; EX1023; EX2010; EX2055, ¶¶143-151; *Alcon*, 745 F.3d at 1190 (a patentee is not required to provide actual working examples; we have rejected enablement challenges based on the theory that there can be no guarantee that prophetic examples actually work, as “[t]he burden is on one challenging validity to show ... that the prophetic examples together with other parts of the specification are not enabling.”); *Rasmusson v. SmithKline*, 413 F.3d 1318, 1323 (Fed. Cir. 2005); M.P.E.P. §2164.01(c). Merck fails to discredit

data from peer-reviewed studies cited in the specification demonstrating that PH20 polypeptides were known to be specifically useful as contraceptives in *guinea pigs*. EX2055, ¶149; EX2011.

*First*, Merck alleges that the specification does not portray “active mutants” as having contraceptive utility, but Merck is wrong. The specification expressly states that “modified PH20 polypeptides *provided herein can be used as vaccines in contraceptive applications.*” EX1001, 188:8-10; EX2055, ¶¶88, 140. In this regard, the specification draws no distinction between inactive or active mutants, reflecting that all modified PH20 polypeptides “provided herein” can be used as contraceptives. EX2055, ¶¶88, 140.

*Second*, both Primakoff 1988 and Tung 1997 reported that PH20 polypeptides were successful as contraceptives. Primakoff 1988 reported “100% *effective contraception*” in guinea pigs immunized with PH20, and the “contraceptive effect was long-lasting and reversible.” EX2010, Abstract; EX2055, ¶143. Primakoff 1988 was published in *Nature*, a prestigious peer-reviewed journal. EX2010; EX2055, ¶143; EX2012.

Notably, rather than address Primakoff 1988, Merck cites Primakoff 1997. But Primakoff 1997 *confirmed* the findings in Primakoff 1988, reporting “*reproducible, completely effective contraceptive action.*” EX1022, 1142, Abstract; EX2055, ¶143.

Similarly, Tung 1997 reported:

*Most males that became infertile after PH-20 immunization (and all that received a total dose  $\geq 5 \mu\text{g}$ ) showed either a complete loss of sperm ... or the presence of only abnormal sperm ....*

EX1023, 1138; EX2055, ¶143. Hecht and Park fail to substantively address Primakoff 1988 or Tung 1997. EX2055, ¶142.

*Third*, Merck's cited art does not undermine the specification. EX2055, ¶¶144-151. For example, Hardy 2004 (EX1019) acknowledges the "strong immunocontraceptive effect in guinea pigs." EX1019, 333; EX2055, ¶147. Likewise, Pomeroy 2002 (EX1020) acknowledged that "[i]mmunization of ... guinea-pigs with the [ ] rPH-20 has been shown to elicit infertility." EX1020, 175; EX2055, ¶147. Baba 2002 (EX1021) disclosed only that "PH-20 is not essential for fertilization, *at least in the mouse* ...." EX1021, Abstract; EX2055, ¶147. Both Pomeroy 2002 and Baba 2002 only studied whether PH20 was essential for fertilization *in mice*. EX1020; EX1021; EX2055, ¶¶147-148. And Merck's citation to post-filing data (EX1024, EX1061) in humans does not discredit Primakoff 1988 or Tung 1997, and nor is it informative of a POSA's understanding in 2012. Pet., 82; EX2055, ¶¶145, 147. Moreover, Rosengren 2015 cites Primakoff 1997 and acknowledged that guinea pigs "experienced infertility following PH20 immunization." EX1061, 1154; EX2055, ¶147. None of these cited references refute or contradict the reported success in using PH20 as a contraceptive in both

male and female guinea pigs in Primakoff 1988, Primakoff 1997, or Tung 1997.

Even the Chao reference Merck cites (EX1006) recognized that PH20 played a role in “binding of [ ]sperm to the zona pellucida (a glycoprotein membrane) of oocyte *during fertilization.*” EX1006, 6916; EX2055, ¶148. Merck ignores this teaching in Chao which is consistent with Primakoff and Tung.

Triggs-Raine explains: in light of the guidance from the specification and the general knowledge in the art, a POSA would have appreciated that the claimed PH20 polypeptides could be effective for contraception in guinea pigs. EX2055, ¶¶140-151. And, separately, a POSA would have understood that human PH20 has a high degree of sequence identity to guinea pig PH-20, suggesting “they may have a conserved function and immunogenicity.” EX2013, Abstract, 10075; EX2055, ¶150. And, a POSA would have understood that if PH20 were to be used as contraception in humans, it would “clearly be advantageous to use a [modified PH20] polypeptide for immunization that is devoid of enzymatic activity.” EX1011, 814; EX2055, ¶140. Given the high degree of similarity between guinea pig PH20 and human PH20, a POSA would have appreciated the contraceptive utility of the claimed modified PH20 polypeptides. EX2013, Abstract, 10075; EX2055, ¶140. Though Merck questions any “*contraceptive effect[ ] in humans,*” Merck has not disproven that modified PH20 polypeptides have a contraceptive effect, and, in any event, the claims do not require such an effect in humans. Pet.,

83; EX1003, ¶113; *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995). Once again, Merck applies the wrong legal standard.

**D. The Remaining Claims Are Also Enabled.**

The term “modified PH20 polypeptide” of claims 2, 6-15, and 17-30 likewise does not require functional activity; these claims are also enabled for at least the same reasons identified above for claim 1. EX2055, ¶156.

\* \* \*

Merck has previously argued to the Patent Office that claims containing structural language similar to the claims here were enabled. In U.S. Patent No. 7,872,107, Merck claimed:

1. A variant of an IL-12p40 protein, the variant being *at least 90% identical to SEQ ID NO:2* and comprising an *amino acid alteration at one or more positions corresponding to residues 258-266*, wherein the amino acid alteration comprises an amino acid substitution selected from the group consisting of Lys260Asn, Lys260Gln, and Lys260Gly.”

EX2055, ¶152.

Merck argued that these purely structural claims were enabled even though the claimed genus required only *90% sequence identity* to a polypeptide 306 amino acids in length. EX2015, 516-524; EX2055, ¶¶153-155. Merck’s prior arguments undermine its Petition.

\* \* \*

Merck failed to meet its burden regarding enablement.

**VIII. GROUND 3: MERCK FAILED TO SHOW THAT IT IS MORE LIKELY THAN NOT THAT THE CLAIMS WOULD HAVE BEEN OBVIOUS.**

**A. Merck’s Art Does Not Teach All Claim Elements.**

Merck fails to identify where the specific elements of the claims are found within the references combined for Ground 3: the ’429 Patent and Chao. EX2055, ¶¶21, 157-165. *Lenovo v. LiTL*, IPR2021-00800, Paper 7 at 18-19 (P.T.A.B. Nov. 2, 2021) (Petitioner must “specify where each element of the claim is found in the prior art [] relied upon” and to both “identify[] specific portions of the evidence that support the challenge” and explain “the relevance of [that] evidence to the challenge raised.” 37 C.F.R. §§42.104(b)(4)–(5); 37 C.F.R. §42.22(a)(2).

Merck cannot deny that a modified PH20 polypeptide with an amino acid modification at position 324 is not mentioned in the ’429 Patent or Chao, much less the specific A, D, H, M, N, R and S replacements claimed for position 324. The elements of the claims are absent from the asserted prior art.<sup>16</sup> Unsurprisingly,

---

<sup>16</sup> To support its obviousness arguments, Merck also cites EX1010-EX1014, EX1017, EX1031-EX1032, EX1035, EX1037, EX1038, EX1043, EX1049, EX1050, EX1053-EX1058, EX1064, EX1066-EX1067, and EX1069-EX1070, but fails to establish *in the Petition* that a POSA would have considered all of these other

neither Merck nor its declarants provides a claim chart identifying where each claim limitation is found in the art, because they cannot do so. EX2055, ¶¶164-165; *PAR Pharmaceutical v. TWI Pharmaceuticals*, 773 F.3d 1186, 1196 (Fed. Cir. 2014) (a proper analysis under §103 requires “determining that claimed elements are present in the prior art.”).

Not only does the prior art not teach E324D, E324N, and E324R substitutions in PH20, Merck has not identified any other reason why POSAs would have made this modification. EX2055, ¶¶166-168. For example, Merck has not asserted nor shown that common sense might supply this limitation. *Arendi v. Apple*, 832 F.3d 1355, 1361-1362 (Fed. Cir. 2018) (common sense can fill a missing limitation when the “limitation in question was unusually simple and the technology particularly straightforward” and “cannot be used as a wholesale substitute for reasoned analysis and evidentiary support, especially when dealing with a limitation missing from the prior art references specified.”).

Even if Merck had argued that common sense supplied this missing

---

references. Pet., 86-114. To the extent Merck relies only on Hecht and Park’s testimony that a POSA would consider these references, Merck is attempting to circumvent the rules on word limits and incorporation-by-reference. 37 C.F.R. §§42.6(a)(3), 42.24(a)(1)(ii).

limitation, Merck’s petition still fails to provide a reasoned analysis with evidentiary support to show that the E324D, E324N, and E324R modifications were “unusually simple” or “particularly straightforward.” Nor has Merck provided a reasoned explanation supported by evidence that POSAs would have had a reason to make the claimed modifications at position 324 in the first place. EX2055, ¶165. Indeed, Park’s analysis focuses on position 324 at the request of Merck’s counsel, and Hecht does not provide any reason to pick position 324 beyond referring to Park’s analysis. EX2055, ¶168; EX1003, ¶215; EX1004, ¶¶32, 103 (Park conceding he was “asked by counsel to report [his] conclusions with respect to position 324”). Further detracting from any potential argument that the claimed modification was straightforward without using the ’520 patent as a roadmap, Merck alleges that POSAs would have had to engage in approximately *30 steps* to arrive at the E324D, E324N, and E324R modifications and *an additional 50 steps* to expect that the claimed substitution would yield an active PH20 protein. Section VIII.B-C. Had Merck alleged that “common sense” bridged this missing limitation from the cited art, Merck still failed to explain away the caveats to such an argument established in *Arendi* and provide a reasoned analysis with evidentiary support.<sup>17</sup>

---

<sup>17</sup> Merck has also failed to establish that “ordinary creativity” served as a gap-

Merck also fails to demonstrate that common knowledge supplied this missing limitation. As discussed below, Merck fails to provide a reasoned explanation supported by evidence that POSAs would have had a reason to combine the '429 Patent and Chao to arrive at the claimed invention with a reasonable expectation of success. *In re Google*, 56 F.4th 1363, 1368 (Fed. Cir. 2023) (“while common knowledge can be invoked even potentially to supply a limitation missing from the prior art, it must still be supported by evidence and a reasoned explanation.”).

**B. Merck Failed to Establish a Reason to Combine the '429 Patent and Chao to Arrive at the Claimed Invention.**

**1. Merck Fails to Show that a POSA Would Have Been Motivated to Make an Amino Acid Substitution in Non-Essential Regions of PH20 and Identify Position 324.**

Even in combination, the '429 Patent and Chao fail to provide a reason why POSAs would have been motivated to make single amino acid substitutions in non-essential regions of PH20, or make the claimed amino acid modification at position 324. EX2055, ¶¶169-174.

---

filler for the modification at position 324. *DSS v. Apple*, 885 F.3d 1367, 1374-1375 (Fed. Cir. 2018) (“the Board’s invocation of ‘ordinary creativity’ is no different from the reference to ‘common sense’” and requires the same “searching” inquiry for a reasoned basis for resorting to ordinary creativity to supply a missing limitation).

Merck fails to establish that the '429 Patent “motivates a skilled artisan to make single amino acid substitutions in non-essential regions of PH20.” Pet., 87-89. The '429 Patent merely states that “[s]uitable conservative substitutions of amino acids are known to those of skill in this art and *can be* made generally without altering the biological activity ...” and “in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity ....” EX1005, 16:14-22; EX2055, ¶171. This disclosure—that substitutions *can be* made—would not have provided a POSA a *reason* to make such substitutions, let alone, the claimed amino acid modification. EX1005, 16:14-22; EX2055, ¶171. As the Federal Circuit has long held, “obviousness concerns whether a skilled artisan *not only could have made*” any particular modification, “*but would have been motivated to make the combinations or modifications of prior art to arrive at the claimed invention.*” *Belden v. Berk-Tek*, 805 F.3d 1064, 1073 (Fed. Cir. 2015); *AT&T Services v. Innovative Sonic*, IPR2024-01143, Paper 15 at 37-38 (P.T.A.B. Feb. 11, 2025) (Petitioner had not shown a reasonable likelihood that the proposed combination teaches the claim because Petitioner “at best, merely posits that a skilled artisan *could have* modified” the prior art without explaining why).

The Petition provides no *reason* why a POSA would have been motivated to make an amino acid substitution(s) in non-essential regions of PH20, let alone

identify position 324 as one such position, particularly given that the '429 Patent does *not* identify any non-essential residues. Section VIII.A-B. Merck, Hecht, and Park do not explain why a POSA would have been motivated to expend resources to make an amino acid substitution in non-essential regions of PH20 when Merck's cited art suggests that doing so would be pointless ("without altering biological activity"). EX2055, ¶171.

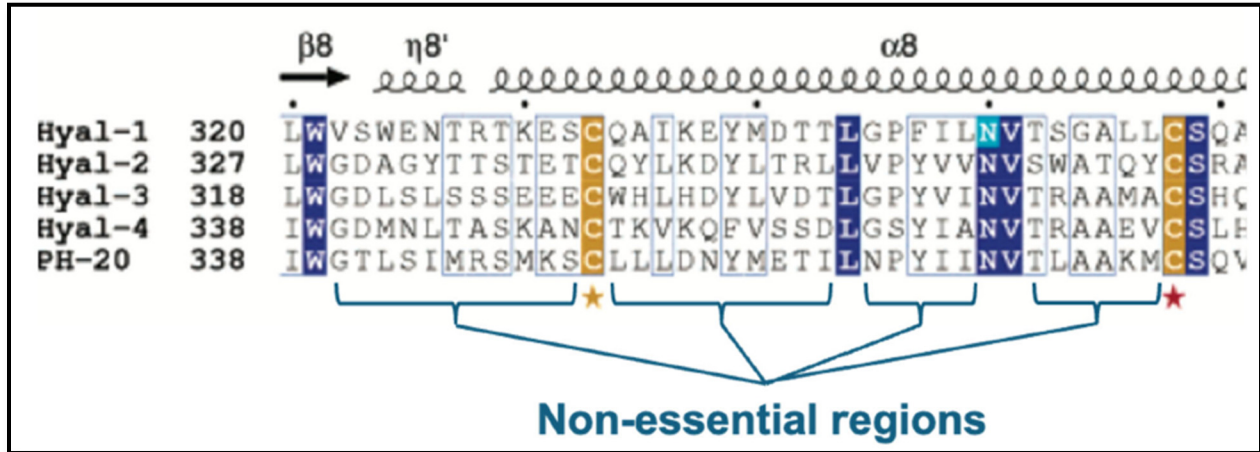
Merck's reliance on Chao fares no better. Merck attempts to draw a connection between the '429 Patent's alleged suggestion to make modifications in "non-essential" regions and Chao's alleged identification of non-essential residues in its alignment of five human hyaluronidases. Pet., 93-94. However, Chao only identifies *invariant conserved residues* in his alignment of hyaluronidases, not "non-essential" residues or regions. EX1006, FIG. 3, 6916; EX2055, ¶¶173-174. Contrary to the Petition, Hecht, and Park, *Chao never suggested that invariant conserved residues were non-essential residues*. Instead, Chao reported that non-conserved residues may be *essential* residues responsible for different catalytic properties of hyaluronidases and Chao identified "the loop connecting  $\beta 5$  and  $\alpha 5$ " as an example of one such non-conserved region. EX1006, 6915-6916; EX2055, ¶188. As depicted below, this loop, boxed in red, contains several non-conserved residues (not colored in blue, turquoise, or yellow).



EX2055, ¶188; EX1006, FIG. 3. Chao reported that variations in these non-conserved residues “may be responsible for the *different catalytic properties* of the human hyaluronidases.” EX1006, 6916; EX2055, ¶¶182, 189-193. Chao also notes that sequence variations “may contribute to the apparent different substrate specificity” of the various hyaluronidases. EX1006, 6916; EX2055, ¶182. Merck’s own cited reference, Brandon 1999 (EX1014), explained that “loop regions” like the one disclosed above in Chao Figure 3, “frequently participate in forming binding sites and enzyme active sites” and are essential regions for “substrate specificity and catalytic function.” EX1014, 21, 55; EX1017; EX2055, ¶¶191-193. Thus, Chao suggests that non-conserved residues may actually be essential to the activity of certain hyaluronidases.

Other prior art references support Chao’s conclusion that non-conserved residues impact the activity and function of proteins. EX2016; EX1014, 21, 55; EX2055, ¶190. In fact, Pils 2005 reported that “functional sites can vary in subfamilies and homologous protein sequences can perform different functions using a *different set of functional residues*.” EX2016, 2; EX2055, ¶190. Only Park

(and Hecht in reliance on Park), who has *no experience with hyaluronidases*, makes the leap in assuming that non-conserved residues are “non-essential” and does so by pointing to his own ad-hoc alignment and Chao Figure 3 without providing any support for his conclusory opinion that these residues are actually *non-essential* in PH20<sup>18</sup>. Pet., 94; EX1004, ¶32 (“*I believe the positions I identified in Appendix D-2 [non-conserved positions in Park’s alignment], including position 324, align with what I consider to be the ‘non-essential regions’ referred to by the ‘429 Patent.*”); EX2055, ¶186. In fact, Park annotates Chao’s Figure 3 depicted below without citing to any additional support from Chao identifying these regions as “non-essential:”



Pet., 94; EX1004, ¶32; EX2055, ¶¶185-186. POSAs would not have considered

<sup>18</sup> EX1014, EX1016, and EX1017 do *not* establish that “non-conserved” residues are “non-essential.” Pet., 13-14; EX2055, ¶191.

non-conserved regions to be “non-essential” in PH20 given that each hyaluronidase differs functionally and in their tissue distribution profiles, catalytic efficiencies, and pH profiles. EX1006, 6911, 6914; EX2055, ¶¶179-183. In falsely equating non-conserved residues as “non-essential,” Merck fails to establish that POSAs would have considered position 324 as a region to modify in view of the ’429 Patent and Chao. EX2055, ¶¶188-193.

Merck further alleges that Chao provides three “new insights into the shared characteristics of human hyaluronidase enzymes,” but none of these supposed insights provide any reason why a POSA would have identified position 324 to modify. Pet., 90-93; EX2055, ¶¶194-199. *First*, Chao’s identification of shared catalytic active site structures between non-human and human hyaluronidases (previously reported in Stern) and, *second*, Chao’s predicted secondary structures and conserved residues shared between human hyaluronidases have no bearing as to why POSAs would have modified position 324. Pet., 90-92; EX2055, ¶¶194-199, 245-249. *Third*, Merck overstates Chao’s disclosure regarding the presence of “a novel, EGF-like domain” in PH20. Pet., 92-93. Chao only “expected” that all human hyaluronidases would contain an “EGF-like” domain after identifying this domain in human Hyal-1 but without resolving the structure of PH20. EX1006, 6916-6917; EX1004, ¶36 (Park admitting “In December of 2011 (and even today), the structure of human PH20 was not solved”); EX2055, ¶¶194-199. Even so, the

fact that Chao identified a HyalEGF-like domain at positions 337-409 of PH20 still bears no relation to claimed position 324, which lies outside this domain. *Id.*, 91; EX2055, ¶¶196, 199. Merck fails to establish that a POSA would have had a reason to modify position 324 based on Chao in combination with the '429 Patent.

Merck alleges that a person “[g]uided by her familiarity with rational protein design and the teachings of the '429 Patent and Chao, the artisan would have readily identified single amino acid substitutions in non-essential regions of PH20<sub>1-447</sub> that would have been tolerated (i.e., a PH20<sub>1-447</sub> with that single substitution would retain its enzymatic activity).” Pet., 86-87. But, such an argument is simply a restatement that such mutations *can be* made, and Merck never provides a *reason why* a POSA would have been motivated to combine the two references (or any of the dozen or so references Merck also cites) to make the claimed amino acid substitution in PH20.

For example, Merck never argues that making a modification in non-essential regions of PH20 would have improved or increased hyaluronidase enzymatic activity. And Merck has alleged that inactive PH20 polypeptides are not useful. Pet., 80-84. Thus, Merck failed to offer a reason why a POSA would have been motivated to modify PH20 at a non-essential region that would merely “retain” comparable activity and not alter existing enzymatic activity. Pet., 109; *Virtek v. Assembly*, 97 F.4th 882, 886-87 (Fed. Cir. 2024) (prior art must provide a

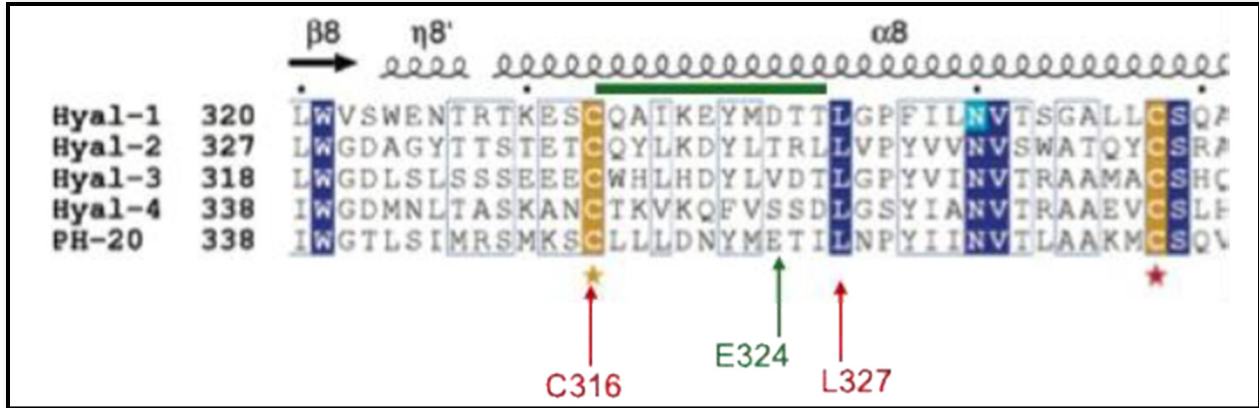
“reason why a skilled artisan” would make the claimed invention).

Merck alleges that a POSA would implement the '429 Patent's suggestion to produce modified PH20 polypeptides with single amino acid substitutions in *non-essential* regions by first identifying the non-essential regions of PH20. Pet., 93-94. In doing so, Merck alleges that a POSA would use a multiple sequence alignment of proteins homologous to PH20 to identify the essential and non-essential residues in PH20<sup>19</sup>. Pet., 93-94. Merck relies on two separate alignments, one alignment of five homologous sequences found in Chao, and another created by Park for this proceeding using 88 homologous sequences. Pet., 94; EX2055, ¶¶175, 184.

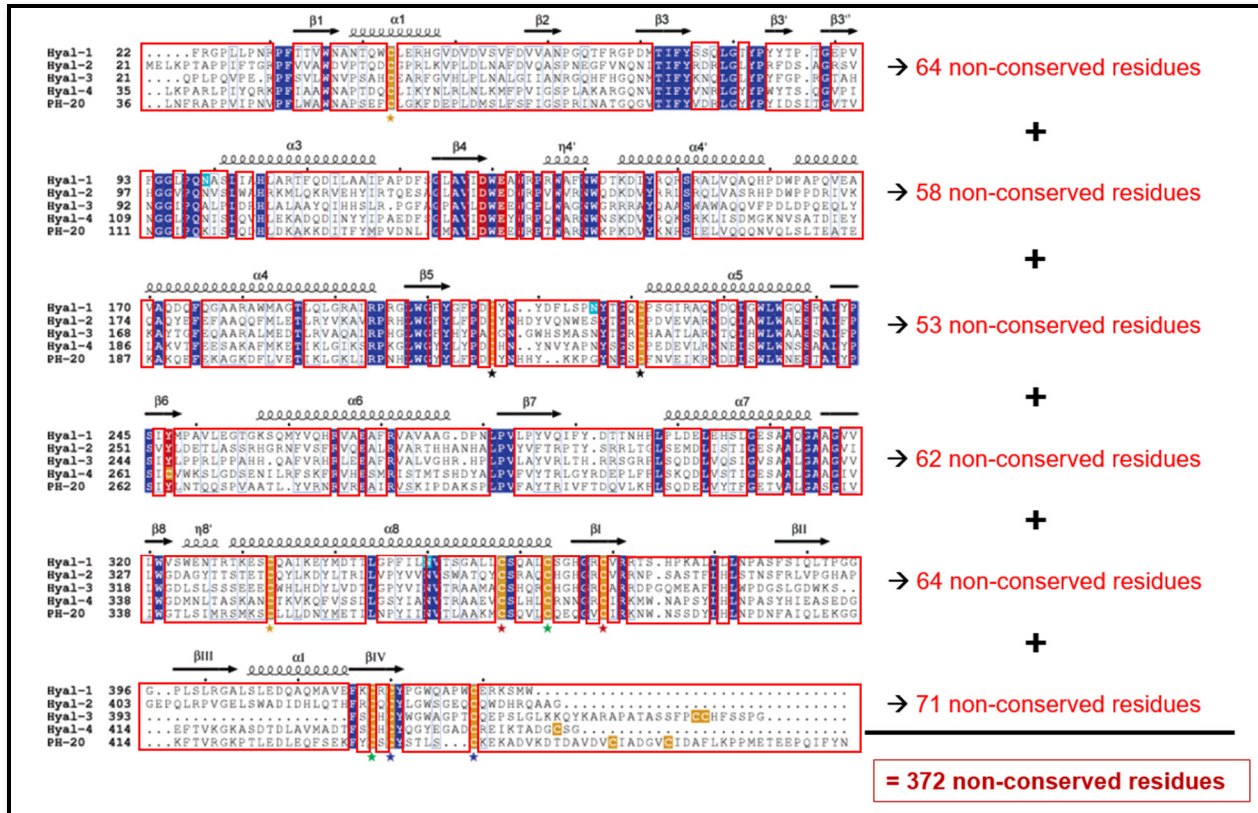
Merck alleges that the claimed position 324 is “within a non-essential region of PH20<sub>1-447</sub>” flanked by the bounding essential residues highlighted in yellow and blue at positions 316 and 327, respectively. Pet., 95. To illustrate the point, Merck annotates and crops Chao's Figure 3 below to visualize position 324 relative to its bounding essential residues at positions 316 and 327:

---

<sup>19</sup> Merck alleges that “non-essential regions in PH20 [are] the sequences between essential residues and are positions at which variations occur at a frequency above ~5%,” but neither Park nor Hecht provides underlying evidence to support this conclusion. Pet., 93; EX1004, ¶¶20, 30-32; EX1003, ¶215; EX2055, ¶167.



Pet., 95; EX1003, ¶217; EX2055, ¶200. Merck, however, fails to grapple with the fact that there are nearly 90 bounding essential residues in Chao's Figure 3 (highlighted in yellow, blue, and red), and 372 non-conserved residues that fall within these 90 bounding residues. EX2055, ¶201. In the annotated Figure 3 below, there are a total of 372 non-conserved residues boxed in red.



EX2055, ¶201; EX1006, FIG. 3 (annotated). Merck offers no reason to make the claimed modifications at position 324 out of the 371 other non-conserved residues disclosed in Chao’s Figure 3. EX2055, ¶202. Similar to Chao, Park’s alignment<sup>20</sup> of 88 sequences, which was not in the art, identifies “379 positions in PH20<sub>1-447</sub>” that he considers “non-essential.” EX1004, ¶¶31-32, Appendix D-1; EX2055, ¶213. Merck does not even attempt to explain why POSAs would have selected position 324 out of the other 378 options in Park’s alignment. EX2055, ¶¶202-203.

<sup>20</sup> Merck has not established that Park’s alignment of 88 sequences—prepared solely for this proceeding—was known in the art in 2011. EX1004, ¶¶26-29.

**2. Merck Further Fails to Explain Why a POSA Would Have Been Motivated to Make the E324D, E324N, or E324R Modifications.**

Merck alleges that POSAs would have been motivated to replace glutamic acid “E” at position 324 with aspartic acid “D”, asparagine “N”, or arginine “R”. Merck is wrong. To start, Merck uses hindsight to lead Park to the claimed modification at position 324. In fact, Park concedes he was “asked by counsel to report [his] conclusions with respect to position 324.” EX1004, ¶103; EX2055, ¶168. Park never provides a reason why POSAs would have focused on position 324 among the 300 or so non-conserved residues. EX1004, ¶32. Instead, Park simply states that he believes that “position 324, align[s] with what I consider to be the ‘non-essential regions’ referred to by the ’429 Patent.” EX1004, ¶32; EX2055, ¶186. Likewise, Hecht relies on Park and does not provide any reason to pick 324. Instead, Hecht broadly alleges that POSAs “would have performed in 2011” the analysis that Park performed. EX1003, ¶215; EX2055, ¶167. But Park’s analysis focuses on position 324 only because counsel directed him to that position. Neither of Merck’s declarants provide a concrete reason to identify position 324 apart from Merck’s counsel instructing Park to analyze position 324 and Hecht simply relying on Park’s attorney-directed analysis. Triggs-Raine confirms that, even in combination, the ’429 Patent and Chao do not provide any reason to select position 324 as an amino acid to modify. EX2055, ¶¶161-203.

Merck argues that POSAs would have had to perform nearly *thirty* different steps—beyond the disclosures in the '429 Patent and Chao—to make the E324D, E324N, or E324R modifications, but Merck does not provide a sufficient reason why a POSA would have performed *any* of these steps based on the combination of the '429 Patent and Chao<sup>21</sup>. Pet., 95-99; EX1003, ¶¶83, 195, 217-222; EX1004, ¶¶20-159, Appendix C, Appendix D-1; EX2055, ¶¶212-214; *Adapt v. Teva*, 25 F.4th 1354, 1365 (Fed. Cir. 2022) (obviousness requires “identify[ing] a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.”); *TQ Delta v. Cisco*, 942 F.3d 1352, 1359 (Fed. Cir. 2019) (“a conclusory assertion with no explanation is inadequate to support a finding that there would have been a motivation to combine.”); *AT&T*, Paper 15 at 27 (“declaration evidence unpersuasive because it is conclusory, and it does not set forth a suggestion or motivation to modify” the art.).

These approximately *thirty* steps include, *inter alia*, 15 discrete steps for performing sequence searches, extracting sequence information, using high-level

---

<sup>21</sup> Merck has also failed to provide a reason POSAs would have made E324A, E324H, E324M, or E324S modifications. Pet., 95-99; EX1004, ¶¶113-153; EX2055, ¶¶204-211.

computer programming language to determine the accession history of each sequence, removing duplicate sequences, *four steps* for generating a multiple sequence alignment, and *eleven steps* for identifying “non-essential” residues, identifying frequencies of amino acids that occur in homologous PH20 sequences, and determining the variability of amino acids at position 324, just to arrive at the alleged conclusion that it was obvious to substitute glutamic acid at position 324 of PH20<sup>22</sup>. Pet., 95-99; EX2055, ¶213. No combination of the ’429 Patent and Chao discloses these steps, and Merck has not established that these steps would have been merely a matter of exercising “ordinary creativity” or common sense. EX2055, ¶214; *KSR v. Teleflex*, 550 U.S. 398, 421 (2007).

Under 37 C.F.R. §42.65(b)(2), Merck must explain how the test was performed and the data was generated. Here, Park does not explain how he prepared “Perl scripts” and how the data was generated using his bespoke scripts. Park merely states that he “wrote” and “ran” several “perl scripts,” but failed to disclose what Perl code he used in his scripts, how he determined that these scripts would work as intended, or how he ran the scripts. EX1004, ¶¶157-158; EX2055, ¶¶215-216; *Qualcomm v. UNM*, IPR2021-00375, Paper 14 at 26-27 (P.T.A.B. July

---

<sup>22</sup> Halozyme does not concede that a POSA would have had to perform all of these steps to practice the full scope of the claims in light of the specification.

19, 2021) (the declarant did not provide the factual basis for the formulas used in his analyses and such testimony was entitled to little to no weight under 37 C.F.R. §42.65(b)(2)); *AT&T*, Paper 15 at 28 (under 37 C.F.R. §42.65(a), “expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight.”). Merck fails to satisfy its burden here.

Merck argues that POSAs allegedly would have had a reason to substitute glutamic acid (E) with aspartic acid (D), asparagine (N), and arginine (R) at the claimed position 324 because aspartic acid (D) was the most prevalent amino acid found at position 324 and asparagine (N) and arginine (R) appeared in some of the 88 different hyaluronidases. *Pet.*, 95-98. However, Merck fails to establish that POSAs would have drawn any conclusions regarding what residues to substitute in PH20 based on an alignment containing mostly non-PH20 sequences. Indeed, of the 88 sequences aligned by Park, *only 18* are PH20 sequences, while the other 70 comprise a mix of different hyaluronidase sequences, including, *inter alia*, Hyaluronidase-1-6 sequences. EX1056; EX2055, ¶¶176, 204.

Merck does not establish that POSAs would have drawn conclusions about which amino acid substitutions would be tolerated at positions within PH20 based on an alignment of sequences that include other hyaluronidases, particularly given that it was known that hyaluronidases have different substrate specificities and exhibit varying levels of activity. EX2055, ¶¶177-178, 187. For example, it was

known before 2012 that HYAL3 does not exhibit any activity while HYAL2 is only weakly active, and in many cases, not active at all. EX2055, ¶178; EX2018, 33495, 33507; EX2019, 653, 658; EX2020, 286. HYAL4 was also known to catalyze different substrates. EX2055, ¶178; EX1008, 825; EX2022, 6-7. EX1001, 72:45-48, 167:25-30. HYAL2 was known to be a receptor for a retrovirus in sheep, while HYAL4 was identified specifically as a chondroitinase, which means it catalyzes the breakdown of chondroitin sulfate proteoglycans. EX2055, ¶178; EX2021, 296; EX1008, 825; EX2022, 6-7. Even Chao recognized that sequence “variations may be responsible for the *different catalytic properties* of the human hyaluronidases.” EX1006, 6916; EX2055, ¶¶188-189.

Therefore, the fact that aspartic acid (D) was the most prevalent amino acid found at position 324 and asparagine (N) and arginine (R) appeared in some of Park’s 88 different hyaluronidases is of no moment because Merck has not shown why a POSA would have selected the most frequent amino acids at a position from among a set of hyaluronidases having different substrates and activities. EX2055, ¶¶176-181, 204-206. In other words, Merck has not established that a POSA would have substituted E for D, N, or R at position 324 of PH20 using data from other hyaluronidases besides PH20 in view of the known differences among hyaluronidases. *Id.*

To determine whether aspartic acid, asparagine, or arginine were prevalent

amino acids found at position 324 *among PH20 sequences*, Triggs-Raine prepared an alignment of only the 18 PH20 sequences of the 88 sequences Park aligned.

EX2055, ¶¶204-206. As shown in the alignment below, three of the 18 PH20 sequences have the wild-type glutamic acid “E” indicated in grey<sup>23</sup>, *none* have a aspartic acid (D) and four total have an asparagine (N) or arginine (R) at the claimed position 324 (labeled position 359 because of the signal sequence).

EX2055, ¶¶205-206; EX1004, ¶104 (Park agreeing that position 324 is equivalent to position 359 with the signal sequence). Accordingly, contrary to Merck’s assertions, a POSA would have not have found aspartic acid, asparagine, or arginine to be suggested as an obvious single amino acid substitution at position 324 of PH20 in view of an alignment of the PH20 sequences known before 2011.

EX2055, ¶¶204-2010.

---

<sup>23</sup> In the alignment, amino acids in red differ from the wildtype human PH20 sequence (NP\_003108.2, first row). EX2055, ¶205. If the sequence contains the same amino acid as the human wildtype PH20, the position is colored grey with a “+.” *Id.*



at position 324. Pet., 98. Again, Merck provides no reason why a POSA would have chosen D, N, or R when there were other more hydrophilic amino acids. EX1014, 245; EX2055, ¶217.

Rather than provide a reason why a POSA would have replaced glutamic acid with aspartic acid, asparagine, or arginine at *position 324*, Merck directs Park to report his “conclusions with respect to position 324” (an analysis on which Hecht then relies). EX1004, ¶103; EX1003, ¶215.

**C. Merck Failed to Establish a Reasonable Expectation of Success.**

Merck argues that a POSA would have reasonably expected the E324D, E324N, or E324R substitutions in PH20<sub>1-447</sub> “would yield an enzyme with substantially the same activity<sup>24</sup> as unmodified PH20<sub>1-447</sub>.” Pet., 100-109. As support, Merck alleges that a POSA would have undertaken over *fifty* additional steps to expect and prove that the claimed substitution would yield an active PH20 protein, but again fails to provide evidence demonstrating that a POSA would have been motivated to perform each of these steps. Pet., 100-109; EX1004, ¶¶33-36, 39-40, 44-103, 105-110, 113-153, 162-165, 167, 177-178; EX2055, ¶¶219-224.

---

<sup>24</sup> Although the claims do not *require* hyaluronidase activity, Merck is bound by its obviousness theory. *Corephotonics v. Apple*, 84 F.4th 990, 1002 (Fed. Cir. 2023).

Moreover, Park fails to explain how he performed a number of different steps as required by 37 C.F.R. §42.65(b). *First*, Park states that he “periodically used a custom script that I wrote which runs within the PyMol environment” and that this script “shows all of the neighboring amino acids encompassed in a shell,” but he fails to explain how he prepared these scripts to visualize the chemical moieties surrounding an amino acid at a given position as required by 37 C.F.R. §42.65(b)(2). EX1004, ¶¶60, 177, 179, 183, App’x E, F; EX2055, ¶225. *Second*, Park utilizes a methodology to score each substitution, but provides no explanation as to how he developed this scoring system or how this methodology is regarded in the relevant art required under 37 C.F.R. §42.65(b)(4). EX1004, ¶87. Park further explains that as he analyzed each substitution, he “would revisit the scores for each position multiple times to make sure that the way [he] assigned scores was consistent.” EX1004, ¶102. Again, Park fails to explain if this methodology was accepted in the relevant art. Park also provides in Appendix C of his declaration his “observations” after performing each substitution, but fails to explain how *each* of his data points, including residue %, fSASA, hydrophobicity, secondary structure, and interaction are used to score each substitution using his methodology. EX1004, ¶¶104-112, 121, 129, 137, 142, 147, 153, App’x C. *Third*, Park provides the multiple sequence alignment he performed (EX1058), but fails to explain how the data shown in EX1058 is being used pursuant to 37 C.F.R. §42.65(b)(3).

Furthermore, Merck fails to establish that the '429 Patent combined with Chao provides the requisite reasonable expectation of success that a E324D, E324N, or E324R substitution in PH20 would not only be tolerated, but would result in a protein that exhibits at least comparable hyaluronidase activity to unmodified PH20<sub>1-447</sub>, particularly when Merck merely offers the “general approach” that “[s]uitable conservative substitutions of amino acids” can be “made generally without altering the biological activity, for example enzymatic activity, of the resulting molecule.” Pet., 88; EX1003, ¶236; EX1005, 16:14-22; *Medichem v. Rolabo*, 437 F.3d 1157, 1165-66 (Fed. Cir. 2006) (prior art fails to provide reasonable expectation of success where “the prior art gave only *general guidance* as to the particular form of the claimed invention or how to achieve it.”). Here, the '429 Patent provides only *general guidance* that amino acid substitutions in non-essential regions of a polypeptide “do not *substantially* alter biological activity,” and POSAs would not have reasonably expected a E324D, E324N, or E324R substitution to yield a protein that exhibits at least comparable hyaluronidase activity to unmodified PH20<sub>1-447</sub> based on this general guidance. EX1005, 9:47-50; EX2055, ¶¶226-228.

Moreover, “to have a reasonable expectation of success, one must be motivated to do more than merely to *vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result*,” where the prior

art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.” *In re Stepan*, 868 F.3d 1342, 1347 (Fed. Cir. 2017). Merck fails to explain how the ’429 Patent provides a reasonable expectation of success when the ’429 Patent and Chao give no direction as to which of the many non-conserved residues of PH20 is likely to be successful. *Id.*; EX2055, ¶227.

Furthermore, Merck has not established that any alleged reasonable expectation of success was “founded in the prior art,” including the ’429 Patent and Chao. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991) (“the reasonable expectation of success must be founded in the prior art, not in the applicant’s disclosure.”).

Because Merck failed to provide the requisite reason to combine the ’429 Patent and Chao to arrive at the claimed invention with a reasonable expectation of success, Merck failed to meet its burden of showing that it is more likely than not that the claims would have been obvious. *Eli Lilly. v. Teva*, 8 F.4th 1331, 1348-49 (Fed. Cir. 2021) (it is, “at all times, [Petitioner]’s burden to show that the claims would have been obvious, including that a skilled artisan would have had a reasonable expectation of success in achieving the claimed invention.”).

**D. Merck Relies on Hindsight.**

Merck’s arguments rely on hindsight; indeed, Park’s only stated reason for

focusing on position 324 is because he was “asked by counsel to report [his] conclusions with respect to position 324.” EX1004, ¶103; EX2055, ¶¶200-203. Hecht then relied on Park’s hindsight-based analysis and offers no other reason to select position 324. EX1003, ¶¶215-217. Moreover, Merck never provides any reason to distinguish position 324 from the other ~370 non-conserved residues. Only hindsight—provided by counsel—led Park and Hecht to position 324. *In re Stepan*, 868 F.3d at 1346 n.1 (when “selecting from large lists of elements in a single reference, there must be a motivation to make the combination and a reasonable expectation [of success], otherwise a skilled artisan would not arrive at the claimed combination.”).

Additionally, only hindsight led Merck to scour the art for an argument to substitute D, N, or R at position 324, particularly since D, N, or R are *not* the most prevalent amino acids at position 324 in PH20 polypeptides. EX2055, ¶207.

Merck’s hindsight analysis is even more pronounced now that Merck has filed *ten other* PGRs challenging Halozyme’s patents claiming other modifications. EX2055, ¶¶229-232. In each, Hecht and Park use the exact same art and reasoning to argue obviousness of modifying positions 307, 309, 312, 313, 317, and 320.

<b>PGR</b>	<b>Patent</b>	<b>Position Modified</b>
PGR2025-00003	11,952,600	320
PGR2025-00004	12,018,298	313
PGR2025-00006	12,152,262	317
PGR2025-00009	12,123,035	312
PGR2025-00024	12,060,590	307

<b>PGR</b>	<b>Patent</b>	<b>Position Modified</b>
PGR2025-00030	12,054,758	317
PGR2025-00033	12,049,652	320
PGR2025-00039	12,104,185	320
PGR2025-00042	12,037,618	309
PGR2025-00046	12,091,692	313
PGR2025-00053	12,195,773	320

EX2023, 91-107; EX2024, 85-111; EX2025, 92-108; EX2026, 86-113; EX2027, 84-113; EX2028, 84-113; EX2029-EX2034; EX2036; EX2037, 85-109; EX2038, EX2039, 89-110; EX2055, ¶¶133-136; EX2056-EX2057; EX2060, 90-110; EX2061; EX2065; EX2064, 89-109.<sup>25</sup>

Given Merck’s overt hindsight, Merck failed to meet its burden to demonstrate obviousness.

**IX. THE BOARD SHOULD GIVE HECHT’S AND PARK’S TESTIMONY LITTLE TO NO WEIGHT.**

Nothing in Hecht’s and Park’s CVs or discussion of “Qualifications” indicates that either declarant has any experience with hyaluronidases, let alone, PH20, and there is no evidence that they consulted with anyone who had it before rendering their opinions. EX1003, App’x B; EX1004, App’x B; EX2055, ¶26. Notably, Dr. Hecht’s published works in his CV indicate that he has minimal

---

<sup>25</sup> In Merck’s latest filed Petition, PGR2025-00050, Merck does not allege obviousness of the challenged claims. EX2062-EX2063.

experience even with enzymes in general. EX1003, 232-237; EX2055, ¶26. In fact, only ~four of Dr. Hecht's published works relate to enzymes, none of which exist in nature because they were designed *de novo*. *Id.*; EX1003, 236-237. This dearth of hyaluronidase experience is relevant because he relies on Dr. Park's 88-sequence alignment, which contains 70 non-PH20 hyaluronidases and only 18 PH20 sequences. EX2055, ¶26; EX1004, ¶27; EX1056. But, as explained by Dr. Triggs-Raine, a POSA with the requisite hyaluronidase experience (or a POSA working with a team member having hyaluronidase experience) would have been aware of the differences between PH20 and other hyaluronidase proteins, including, for example, their structures, substrates (or lack thereof), biological origins, functions, and/or optimal pH. EX2055, ¶26. Thus, a POSA would not have aligned these 88 different hyaluronidases in seeking to modify PH20 as Drs. Hecht and Park propose.

The absence of any hyaluronidase experience or any significant enzyme experience is also relevant because Dr. Hecht dismisses PH20's well-known contraceptive utility, even though record evidence demonstrates that a POSA would have known of the data demonstrating that PH20 was an effective contraceptive in guinea pigs. EX2055, ¶26; Section IX; EX1003, ¶109; EX1023, Abstract; EX2010, 1, Abstract.

In short, Hecht and Park's combined lack of hyaluronidase experience

undermines the reliability of their testimony regarding, e.g., how POSAs would have interpreted the claims, reasons to modify the art, conclusions drawn from aligning hyaluronidase sequences, and contraceptive use of PH20 polypeptides. EX2055, ¶¶26, 139, 146. Their opinions should be given little to no weight.

“[A]n expert must at a minimum possess ordinary skill in the art.” *Osseo v. Planmeca*, 116 F.4th 1335, 1340 (Fed. Cir. 2024); *Kyocera v. ITC*, 22 F.4th 1369, 1376–77 (Fed. Cir. 2022); *Avail v. Teladoc*, IPR2022-00444, Paper 10 at 24-28 (P.T.A.B. July 21, 2022) (“it would be inappropriate for us to consider any testimony by [the inexperienced expert] on any issue that is analyzed through the lens of [a POSA]”). A person of ordinary skill *in this art*, or a member of that POSA’s multidisciplinary team, would have practical experience with hyaluronidases. In contrast to Hecht and Park, Triggs-Raine is a leading expert in hyaluronidases, and her testimony should be given more weight than theirs. EX2055, ¶¶9-19; EX2002, 8-9.

## **X. CONCLUSION**

The Petition fails to show that the ’520 patent is PGR-eligible and fails to show that it is more likely than not that any of the challenged claims are unpatentable. Therefore, the Board should deny institution.

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 11, 2025

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 Preliminary Response complies with the type-volume limitation of 18,700 words, comprising 18,640 words, excluding the parts exempted by 37 C.F.R. § 42.24(a)(1).

2. This Patent Owner Preliminary Response complies with the general format requirements of 37 C.F.R. § 42.6(a) and has been prepared using Microsoft® Word 2016 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 11, 2025

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

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

I certify that the above-captioned **PATENT OWNER PRELIMINARY RESPONSE UNDER 37 C.F.R. § 42.207(a)** and associated Exhibits 2007-2013, 2015-2016, 2055 and 2064-2065 were served in their entireties on June 11, 2025, upon the following parties via electronic mail:

Jeffrey P. Kushan (Lead Counsel)  
Leif Peterson (Back-up Counsel)  
SIDLEY AUSTIN LLP  
[jkushan@sidley.com](mailto:jkushan@sidley.com)  
[leif.peterson@sidley.com](mailto:leif.peterson@sidley.com)  
[HalozymePGRs@sidley.com](mailto:HalozymePGRs@sidley.com)

Mark Stewart (Back-up Counsel)  
MERCK SHARP & DOHME LLC  
[mark.stewart@merck.com](mailto:mark.stewart@merck.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 11, 2025

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