**UNITED STATES PATENT AND TRADEMARK OFFICE**

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**BEFORE THE PATENT TRIAL AND APPEAL BOARD**

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Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyme Inc.,
Patent Owner.

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Case No. PGR2025-00042
U.S. Patent No. 12,037,618

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# Declaration of Jeffrey P. Kushan

I, Jeffrey P. Kushan, make the following Declaration pursuant to 28 U.S.C. § 1746:

1. I am a partner at the law firm of Sidley Austin LLP.

2. I provide this declaration in connection with the above-identified post grant review proceeding before the United States Patent and Trademark Office and initiated by Merck Sharp & Dohme LLC ("Merck") against Halozyme Inc. under 35 U.S.C. § 321. Unless otherwise stated, the facts stated in this Declaration are based on my personal knowledge.

3. For each of the exhibits addressed below, an exhibit label and page numbers have been added, but no other alterations have been made. Where the exhibit is a PDF generated from a webpage displayed in a web browser, the PDF may contain information in the header and footer (*e.g.*, the URL, the title of the page being displayed, or similar items), which was generated automatically by the web browser displaying the page.

4. Exhibit 1120 is a true and correct copy of a publication by Zhiming Huo, et al., titled "Systemic and Mucosal Immune Responses to Sublingual or Intramuscular Human Papilloma Virus Antigens in Healthy Female Volunteers" ("Huo"). This paper was published as a chapter in "PLoS ONE," Vol. 7, on pages 1-8. A true and correct copy of this paper was obtained from the following URL: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0033736. As the

Huo paper itself does not include the supplemental material, I have appended the supplemental material to the end of Exhibit 1120 as pages 9-42. Pages 9-42 of Exhibit 1120 are a true and correct copy of the PDF file available for download from the following URL: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0033736#s5.

5. Exhibit 1122 is a true and correct copy of a publication by Marie A. Printz, et al., titled "Risk Factors, Hyaluronidase Expression, and Clinical Immunogenicity of Recombinant Human Hyaluronidase PH20, an Enzyme Enabling Subcutaneous Drug Administration" ("Printz"). This paper was published as a chapter in "AAPS," Vol. 24, on pages 1-15. A true and correct copy of this paper was obtained from the following URL: https://link.springer.com/article/10.1208/s12248-022-00757-3. As the Printz paper itself does not include the supplemental material, I have appended the supplemental material to the end of Exhibit 1122 as pages 16-19. Pages 16-19 of Exhibit 1122 are a true and correct copy of the PDF file available for download from the following URL: https://link.springer.com/article/10.1208/s12248-022-00757-3#Sec26.

6. Exhibit 1135 is a PDF of an Excel Workbook titled "Dr. Naismith Analysis Spreadsheet" ("Naismith Spreadsheet"). The Naismith Spreadsheet was produced by staff at my law firm working under my supervision in collaboration

with Dr. James Naismith. The Naismith Spreadsheet contains eleven (11) separate sheets that each compile information from several exhibits in this, and related, PGR proceeding(s). Each sheet was created as described below:

a. The first sheet ("Basic Counts") on pages 1-22 of EX1135 compiles $PH20_{1-447}$ mutagenesis data reported in Tables 9 and 10 in EX1026. Inconsistencies in and between Tables 9 and 10 were denoted as errors. Columns W (SASA (Å)) and X (fSASA) were copied from EX2176 (Park 2070).

b. The second sheet ("Protein Space – All") on pages 23-46 of EX1135 compiles $PH20_{1-447}$ mutagenesis data reported in Table 9 of the EX1026. Columns A and B contain position and amino acid values for $PH20_{1-447}$. Columns C to V contain activity values reported for mutants having an amino acid substitution specified in row 1. Columns C-V were classified by Dr. Naismith based on physicochemical characteristics of the amino acid (*e.g.*, large vs. small hydrophobes). Columns AE and AF contain SASA (Å) and fSASA data values copied from EX2176 (Park 2070). Column AG contains Local QMEAN values obtained from the b-factor field of the "model_01.pdb.cif" file provided by Halozyme's counsel. Column Z contains the number of tested active mutants with activities >40%

(col. Z) from the first sheet of EX1135. Columns AL and AM repeat the position and wild-type residues in columns A and B. Columns AN-AR report counts of amino acids in each row for the sets of columns reflecting different physicochemical characteristics (i.e., columns C-V). Rows in columns AL-AM shaded red are those did not survive interrogation with all of the physicochemical categories of the 20 amino acids per Dr. Naismith's explanation in ¶ 309 of EX1133.

c. The third sheet ("EX1004 – SASA Data") on pages 47-50 of EX1135 compiles solvent accessible surface area (SASA) data from EX1004, Appendix D, Part 5 (Declaration of Dr. Sheldon Park) and EX2175 at 0062-0065 (Park 2069).

d. Rows 1 to 8 of the fourth sheet ("Counts") on page 51 of EX1135 list numbers of positions classified into various categories by Dr. Petsko in ¶ 274 of EX2070; corrected numbers of classifications in the first sheet of EX1135; and as identified by Dr. Naismith in ¶¶ 305, 315-316, with 414 being the calculation of 447 – 21 – 12. Values reported in the cells starting at row 25 were obtained from column AF of the second sheet of EX1135. Values reported in the cells starting at row 39 were obtained from column AG of the second sheet of EX1135.

Values reported in the cells starting at row 43 were obtained from column Z of the second sheet of EX1135. Values reported in the cells starting at row 49 were obtained from column X of the second sheet of EX1135. Values reported in the cells starting at row 55 were obtained from columns X and AL-AM of the second sheet of EX1135.

e. The fifth sheet ("Activity Distribution") on page 52 of EX1135 contains the number of $PH20_{1-447}$ mutants having activity values within identified ranges of activity (*e.g.,* 0.50-0.55, 1.0-1.05, etc.) reported in Table 9 of EX1026. The number of $PH20_{1-447}$ mutants having activity within the specified ranges was plotted as a histogram. A line was superimposed identifying the 100% activity value.

f. The sixth sheet ("US-457 Plots") on pages 53-55 of EX1135 contains activity data reported for C-terminally truncated PH20 variants in U.S. Patent Application Publication No. 2010/0143457 (EX2165) and U.S. Patent No. 7,767,429 (EX1005). Absolute activity data of PH20 variants reported in EX2165 are reported in column F, while column D normalized each activity value to the activity reported for $PH20_{1-447}$ ("SPAM1-QIFY"). Column E contains activity values normalized to the activity of $PH20_{1-447}$.

g. Columns C and D of the seventh sheet ("US-457 Comparison") on page 56 of EX1135 contain activity data for C-terminally truncated PH20 variants in U.S. Patent Application Publication No. 2010/0143457 (EX2165). Activity data was normalized in columns E and F to the activity reported for $PH20_{1-447}$. Column G contains the description of the reported activity data in columns C and D, as explained in ¶ 188 of EX2068. Column H contains the classification of the activity data in columns C and D from EX2165, as per Dr. Naismith's explanation in ¶ 217 of EX1133.

h. Columns A and B of the eighth sheet ("MSA Alternatives Data") on pages 57-62 of EX1135 contain the position numbers in PH20 and wildtype amino acid, respectively. Column C contains alternate amino acids at each position identified in column F of EX2176, pp. 4-50 and EX1004, Appendix D, Part 1. Column E reports which amino acids were assessed from the list in column C, based on information in column H of EX2176, pp. 4-50. Columns D and F report the number of alternate amino acids listed in columns C and E, respectively. Column G reports the percentage of amino acids assessed (column F) out of the total number reported in column D. The coloring of amino acids in columns C, E and G is explained in the Note field on that

sheet. Positions listed in column A contain the same shading as column G, with red shading indicating positions identified as "essential" in EX1004, Appendix D, Part 3.

i. The ninth sheet ("MSA Data Condensed Aligned") on page 63 of EX1135 contains a reformatted version of columns A and B of the eighth sheet in EX1135 ("MSA Alternatives Data").

j. The tenth sheet ("PH20 Positional Domains-Motifs") on page 64 of EX1135 contains the precursor and mature numbering, as well as wildtype amino acids in $PH20_{1\text{-}447}$. Positions 3-339 (mature sequence) are shaded in blue and identify the "common core hyaluronidase domain" as described in EX1026. Wildtype residues L336-D416 were shaded to indicate the Hyal-EGF domain, as described by Dr. Naismith in ¶ 191 of EX1133, and K170-N200 were shaded purple to denote the peptide 2 binding domain as described in EX1026. Residues shaded in red are truncation sites reported in EX1011 (Arming), as described by Dr. Naismith in ¶¶ 191-192 of EX1133.

k. Column A of the eleventh sheet ("Petsko Rank v. Essential Res.") on pages 65-71 of EX1135 contain position numbers of PH20 and shading as described in ¶ 274 of EX2070. Column B of that sheet contains the wildtype amino acid sequence of PH20. Rows in column

C have markings and are shaded based on EX1004, Appendix D, Part 3. Rows in column D have markings and are shaded based on positions listed in EX1026 ('731 App.), 80:19-35.

7. Exhibit 1144 is a true and correct copy of a publication by Adrián Ochoa-Leyva, et al., titled "Protein Design through Systematic Catalytic Loop Exchange in the $(\beta/\alpha)_8$ Fold" ("Ochoa-Leyva"). This paper was published as a chapter in "Journal of Molecular Biology," Vol. 387, on pages 949-964. A true and correct copy of this paper was obtained from the following URL: https://www.sciencedirect.com/science/article/abs/pii/S0022283609001764?via%3Dihub. As the Ochoa-Leyva paper itself does not include the supplemental material, I have appended the supplemental material to the end of Exhibit 1144 as pages 965-980. Pages 965-980 of Exhibit 1144 are a true and correct copy of the zip file available for download from the following URL: https://www.sciencedirect.com/science/article/pii/S0022283609001764?via%3Dihub#app1.

8. Exhibit 1145 is a true and correct copy of a publication by Ruth Huey, et al., titled "AutoDock Vina Tutorial 2011" ("Huey"). This paper was published by The Scripps Research Institute Molecular Graphics Laboratory. A true and correct copy of this paper was obtained from the following URL: https://www.bch.cuhk.edu.hk/croucher11/tutorials/day1_autodock_tutorial.pdf.

The Huey paper was filed as it appears at the publicly available location specified above.

9. Exhibit 1146 is a true and correct copy of a publication by Gábor Pál, et al., titled "Comprehensive and Quantitative Mapping of Energy Landscapes for Protein-Protein Interactions by Rapid Combinatorial Scanning" ("Pál"). This paper was published as a chapter in "Journal of Biological Chemistry," Vol. 281, on pages 22378-22385. A true and correct copy of this paper was obtained from the following URL: https://www.jbc.org/article/S0021-9258(19)47756-9/fulltext. The Pál paper is accompanied by electronic supplementary materials, also available at https://www.jbc.org/article/S0021-9258(19)47756-9/fulltext. As the electronic supplementary materials are published as native files, I have included those native files for Exhibit 1146 with the materials being served in the submission of the Merck's Petitioner Reply in the PGR2025-00042 proceeding.

10. Exhibit 1151 is a true and correct copy of a publication by Douglas M. Fowler, et al., titled "High-resolution mapping of protein sequence function relationships" ("Fowler"). This paper was published as a chapter in "Nature Methods," Vol. 7, on pages 741-748. A true and correct copy of this paper was obtained from the following URL: https://www.nature.com/articles/nmeth.1492. As the Fowler paper itself does not include the supplemental material, I have appended the supplemental material to the end of Exhibit 1151 as pages 749-765.

Pages 749-765 of Exhibit 1151 are a true and correct copy of the PDF file available for download from the following URL: https://www.nature.com/articles/nmeth.1492#Sec22.

11. EX1154 is a document mapping citations in Merck's Petitioner Reply to U.S. Patent No. 12,037,618 ("the '618 Patent") to corresponding text in U.S. Patent Application No. 13/694,731 ("the '731 Application"). This mapping was prepared by staff at my law firm working under my supervision, and is true and accurate to the best of my knowledge.

12. Exhibit 1155 is a true and correct copy of a publication by Giulia Calloni, et al., titled "Investigating the Effects of Mutations on Protein Aggregation in the Cell" ("Calloni"). This paper was published as a chapter in "The Journal of Biological Chemistry," Vol. 280, on pages 10607-10613. A true and correct copy of this paper was obtained from the following URL: https://www.jbc.org/article/S0021-9258(19)30466-1/fulltext. As the Calloni paper itself does not include the supplemental material, I have appended the supplemental material to the end of Exhibit 1155 as pages 10614-10617. Pages 10614-10617 of Exhibit 1155 are a true and correct copy of the PDF file available for download from the following URL: https://www.jbc.org/article/S0021-9258(19)30466-1/fulltext.

13. Exhibit 1157 is a true and correct copy of a publication by Fabrizio Chiti, et al., titled "Rationalization of the effects of mutations on peptide and protein aggregation rates" ("Chiti 2003"). This paper was published as a chapter in "Nature," Vol. 424, on pages 805-808. A true and correct copy of this paper was obtained from the following URL: https://www.nature.com/articles/nature01891. As the Chiti 2003 paper itself does not include the supplemental material, I have appended the supplemental material to the end of Exhibit 1157 as pages 809-811. Pages 809-811 of Exhibit 1157 are a true and correct copy of the PDF file available for download from the following URL: https://www.nature.com/articles/nature01891#Sec3.

14. Exhibit 1173 is a true and correct copy of a publication by Mark S. Anderson, et al., titled "Projection of an Immunological Self Shadow Within the Thymus by the Aire Protein" ("Anderson"). This paper was published as a chapter in "Science," Vol. 298, on pages 1395-1401. A true and correct copy of this paper was obtained from the following URL: https://www.science.org/doi/10.1126/science.1075958. As the Anderson paper itself does not include the supplemental material, I have appended the supplemental material to the end of Exhibit 1173 as pages 1402-1434. Pages 1402-1434 of Exhibit 1173 are a true and correct copy of the PDF file available for

download from the following URL:

https://www.science.org/doi/10.1126/science.1075958#supplementary-materials.

15. Exhibit 1175 is a true and correct copy of a publication by Lyubov Popova, et al., titled "Immunodominance of Antigenic Site B over Site A of Hemagglutinin of Recent H3N2 Influenza Viruses" ("Popova"). This paper was published as a chapter in "PLoS ONE," Vol. 7, on pages 1-11. A true and correct copy of this paper was obtained from the following URL: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0041895. As the Popova paper itself does not include the supplemental material, I have appended the supplemental material to the end of Exhibit 1175 as pages 12-14. Pages 12-14 of Exhibit 1175 are a true and correct copy of the PDF file available for download from the following URL:

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0041895#s5.

16. Exhibit 1190 is a true and correct copy of a publication by Ryan P. Nolan, et al., titled "The safety of recombinant human hyaluronidase PH20 in nonclinical models: An overview of toxicology, pharmacology, and impact of anti-PH20 antibodies" ("Nolan"). This paper was published as a chapter in "Journal of Controlled Release," Vol. 374, on pages 369-383. A true and correct copy of this paper was obtained from the following URL:

https://www.sciencedirect.com/science/article/abs/pii/S0168365924005200?via%3

Dihub. As the Nolan paper itself does not include the supplemental material, I have appended the supplemental material to the end of Exhibit 1190 as pages 384-402. Pages 384-402 of Exhibit 1190 are a true and correct copy of the PDF file available for download from the following URL: https://www.sciencedirect.com/science/article/pii/S0168365924005200?via%3Dihub#s0180.

17. Exhibit 1193 ("CDC Press Release: 'Highly Pathogenic Avian Influenza A (H5N1) Virus Infection Reported in a Person in the U.S.'") is a true and correct copy of the web page available from the following URL: https://www.cdc.gov/media/releases/2024/p0401-avian-flu.html.

I, Jeffrey P. Kushan, do hereby declare and state, that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, under Section 1001 of Title 18 of the United States Code.

Dated: May 11, 2026

Respectfully Submitted,

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