UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyme Inc.,
Patent Owner.

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

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 inter partes 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 1010 is a true and correct copy of a publication by Ling Zhang, et al., titled "Hyaluronidase Activity of Human Hyal1 Requires Active Site Acidic and Tyrosine Residues" ("Zhang"). This paper was published as a chapter in "The Journal of Biological Chemistry," Vol. 284, on pages 9433-9442. A true and correct copy of this paper was obtained from the following URL: https://www.sciencedirect.com/science/article/pii/S0021925820323425. As the

Zhang paper itself does not include Supplemental Figure 1 or Supplemental Table 1, I have appended the supplementary material at the end of Exhibit 1010, as pages 9443-9445. Pages 9443-9445 of Exhibit 1010 are a true and correct copy of the PDF file available for download from the following URL: https://www.sciencedirect.com/science/article/pii/S0021925820323425#sec1.

5. EX1015 is a document mapping citations in Merck's Petition to U.S. Patent No. 11,066,656 ("the '656 Patent") to corresponding text in U.S. Patent Application No. 13/694,731 ("the '731 Application") and U.S. Patent Publication No. 2013/0302275 ("US-275"). 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.

6. Exhibit 1016 is a true and correct copy of a publication by Boris Steipe titled "Consensus-Based Engineering of Protein Stability: From Intrabodies to Thermostable Enzymes" ("Steipe"). This paper was published as a chapter in "Methods in Enzymology," Vol. 388, on pages 176-186. As the Steipe paper itself does not include the year in which it was published, I have appended the publication information at the end of Exhibit 1016, as pages 187-192. Pages 187-192 of Exhibit 1016 are a true and correct copy of the web page available from the following URL: https://www.sciencedirect.com/science/article/abs/pii/S0076687904880169

7. Exhibit 1024 is a true and correct copy of a publication by Sanna Rosengren, et al., titled "Recombinant Human PH20: Baseline Analysis of the Reactive Antibody Prevalence in the General Population Using Healthy Subjects" ("Rosengren 2018"). This paper was published as a chapter in "BioDrugs," Vol. 32, on pages 83-89. A true and correct copy of this paper was obtained from the following URL: https://link.springer.com/article/10.1007/s40259-018-0260-y. As the Rosengren 2018 paper itself does not include Supplemental Table 1, I have appended the supplementary material at the end of Exhibit 1024, as pages 90-91. Pages 90-91 of Exhibit 1024 are a true and correct copy of the PDF file available for download from the following URL: https://link.springer.com/article/10.1007/s40259-018-0260-y#Sec17.

8. Exhibit 1040 is a true and correct copy of a publication by Yanan He, et al., titled "NMR Structures of Two Designed Proteins with High Sequence Identity but Different Fold and Function" ("He"). This paper was published as a chapter in "PNAS," Vol. 105, on pages 14412-14417. A true and correct copy of this paper was obtained from the following URL: https://www.pnas.org/doi/10.1073/pnas.0805857105. As the He paper itself does not include the supporting figures and tables, I have appended the supporting information at the end of Exhibit 1040, as pages 14418-14421. Pages 1441814421 of Exhibit 1040 are a true and correct copy of the PDF file available for download

from the following URL:

https://www.pnas.org/doi/10.1073/pnas.0805857105#supplementary-materials.

9. Exhibit 1041 is a true and correct copy of a publication by Patrick A. Alexander, et al., titled "A Minimal Sequence Code for Switching Protein Structure and Function" ("Alexander"). This paper was published as a chapter in "PNAS," Vol. 106, on pages 21149-21154. A true and correct copy of this paper was obtained from the following URL:

https://www.pnas.org/doi/10.1073/pnas.0906408106. As the Alexander paper itself does not include the supporting text, figures, and tables, I have appended the supporting information at the end of Exhibit 1041, as pages 21155-21160. Pages 21155-21160 of Exhibit 1041 are a true and correct copy of the PDF file available for download from the following URL:

https://www.pnas.org/doi/10.1073/pnas.0906408106#supplementary-materials.

10. Exhibit 1042 is a true and correct copy of a publication by Biao Ruan, et al., titled "Design and Characterization of a Protein Fold Switching Network" ("Ruan"). This paper was published as a chapter in "Nature Communications," Vol. 14, on pages 1-14. A true and correct copy of this paper was obtained from the following URL: https://www.nature.com/articles/s41467-023-36065-3. As the Ruan paper itself does not include the supplemental figures, tables and descriptions, I have appended the supplementary information at the end of Exhibit

1042, as pages 15-30. Pages 15-30 of Exhibit 1042 are a true and correct copy of the PDF file available for download from the following URL: https://www.nature.com/articles/s41467-023-36065-3#Sec29.

11. Exhibit 1045 is a true and correct copy of a redline that I had created for U.S. Patent Application No. 13/694,731 and U.S. Patent No. 11,066,656 using Litera Compare for Microsoft Word. To create this redline, the text of U.S. Patent Application No. 13/694,731 (as published in U.S. Patent Application Publication 2013-0302275) was copied and compared to the text of U.S. Patent No. 11,066,656, both obtained from the USPTO's Patent Center website. The text of both documents was pasted into separate Word documents. Any text that appeared before the "Background/Summary" heading and the claim language was deleted. The Word document with the text from U.S. Patent Application No. 13/694,731 was designated as the original file and the Word document with the text from U.S. Patent No. 11,066,656 was designated as the modified file. I saved the redline as a PDF and included it here as Exhibit 1045. The redline shows certain differences as a result of formatting changes. In my review of the redline (with one exception[1]), I

[1] The '656 Patent alters the list of mutations that should be avoided in enzymatically active PH20 proteins by removing positions 282, 298, and

have not identified any substantive differences between U.S. Patent Application No. 13/694,731 and U.S. Patent No. 11,066,656, and I believe them to be substantively identical.

a. The text file that I copied for the '731 Application is available from the following URL: https://ppubs.uspto.gov/pubwebapp/authorize.html?redirect=patents/html/20130302275?source=US-PGPUB.

b. The text file that I copied for the '656 Patent is available from the following URL: https://ppubs.uspto.gov/pubwebapp/authorize.html?redirect=patents/html/11066656?source=USPAT.

12. Exhibit 1061 is a true and correct copy of a publication by Rosengren, et al., titled "Clinical Immunogenicity of rHuPH20, a Hyaluronidase Enabling Subcutaneous Drug Administration" ("Rosengren 2015"). This paper was published as a chapter in "AAPS Journal," Vol. 17, on pages 1144-1156. A true and correct copy of this paper was obtained from the following URL: https://link.springer.com/article/10.1208/s12248-015-9782-0. As the Rosengren

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431 from the list in the '731 Application. *See* EX1045, 75; *also* EX1001, 77:36-48; EX1026, 91:30-92:1.

2015 paper itself does not include the supplemental clinical trial descriptions, I have appended the supplementary material at the end of Exhibit 1061, as pages 1157-1160. Pages 1157-1160 of Exhibit 1061 are a true and correct copy of the DOCX file available for download from the following URL: https://link.springer.com/article/10.1208/s12248-015-9782-0#Sec17.

13. Exhibit 1066 is a true and correct copy of a set of web pages available from the Internet Archive at the URLs listed below:

a. Pages 1-2 of Exhibit 1066 ("SWISS-MODEL") are a true and correct copy of the web page available from the following URL: https://web.archive.org/web/20110519141121/http://swissmodel.expasy.org/?pid=smh01&uid=&token=

b. Pages 3-4 of Exhibit 1066 ("Introduction to SWISS-MODEL Workspace") are a true and correct copy of the web page available from the following URL: https://web.archive.org/web/20110519140410/http://swissmodel.expasy.org/?pid=smd11&uid=&token=

c. Pages 5-12 of Exhibit 1066 ("Help – Introduction to SWISS-MODEL Workspace") are a true and correct copy of the web page available from the following URL:

https://web.archive.org/web/20110519144707/http://swissmodel.expasy.org/?pid=smd02&uid=&token=

d. Pages 13-24 of Exhibit 1066 ("Tutorial – Introduction") are a true and correct copy of the web page available from the following URL: https://web.archive.org/web/20110519144916/http://swissmodel.expasy.org/?pid=smd03&uid=&token=

e. Pages 25-26 of Exhibit 1066 ("SwissModel Automatic Modelling Mode") are a true and correct copy of the web page available from the following URL: https://web.archive.org/web/20110519141354/http://swissmodel.expasy.org/workspace/index.php?func=modelling_simple1

f. Pages 27-28 of Exhibit 1066 ("Protein Structure & Model Assessment Tools") are a true and correct copy of the web page available from the following URL: https://web.archive.org/web/20110519144444/http://swissmodel.expasy.org/workspace/index.php?func=tools_structureassessment1&userid=USERID&token=TOKEN

g. Pages 29-38 of Exhibit 1066 ("Template Library – Introduction to SWISS-MODEL Workspace") are a true and correct copy of the web page available from the following URL:

https://web.archive.org/web/20110925072951/http://swissmodel.expasy.org/workspace/index.php?func=special_help&=#QMEAN6

h. Pages 39-42 of Exhibit 1066 ("QMEAN Server – Quick Help") are a true and correct copy of the web page available from the following URL: https://web.archive.org/web/20110924165101/http://swissmodel.expasy.org/qmean/cgi/index.cgi?page=help

i. Pages 43-44 of Exhibit 1066 ("Visualisation") are a true and correct copy of the web page available from the following URL: https://web.archive.org/web/20110519144341/http://swissmodel.expasy.org/repository/?pid=smd08

14. 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 1-13 of EX1135 compiles $PH20_{1\text{-}447}$ mutagenesis data reported in Tables 9 and 10 in EX1026.

Inconsistencies in and between Tables 9 and 10 were denoted as errors.

b. The second sheet ("Protein Space – All") on pages 14-24 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.*, polar uncharged vs. hydrophobic residues). Column Z contains Local QMEAN values obtained from the b-factor field of the "model_01.pdb.cif" file provided by Halozyme's counsel. Columns AE and AF repeat the position and wild-type residues in columns A and B. Columns AG-AK 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 AE-AF shaded red are those that did not evaluate at least one amino acid in each of the five physicochemical classes explained in Dr. Naismith's declaration (EX1003) at ¶ 166. Column AL contains the number of

tested active mutants with activities >40% from the first sheet of EX1135.

c. The third sheet ("Activity Distribution") on page 25 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.

d. The fourth sheet ("Table 11 Data") on pages 26-31 of EX1135 contains $PH20_{1-447}$ mutagenesis activity data reported in Table 11 in EX1026.

e. The fifth sheet ("Table 12 Data") on pages 32-37 of EX1135 contains $PH20_{1-447}$ mutagenesis relative activity data reported in Table 12 in EX1026.

f. The sixth sheet ("Table 12 Selected Data") on page 38 contains $PH20_{1-447}$ mutagenesis relative activity data for mutants tested at the 37°C/4°C conditions reported in Table 12 in EX1026.

g. The seventh sheet ("PC Control Data") on pages 39 contains unmodified $PH20_{1-447}$ positive control mutagenesis relative activity

data reported in Table 12 in EX1026. The accompanying plots were generated from the data in columns B-G, rows 3-19.

h. The eighth sheet ("US-457 Plots") on pages 40-42 of EX1135 contains activity data reported for C-terminally truncated PH20 variants in U.S. Patent Application Publication No. 2010/0143457 (EX1105) and U.S. Patent No. 7,767,429 (EX1005). Absolute activity data of PH20 variants reported in EX1105 are reported in column F, while column D normalized each activity value to the activity reported for $PH20_{1\text{-}447}$ ("SPAM1-QIFY"). Column E contains activity values normalized to the activity of $PH20_{1\text{-}447}$.

i. Columns C and D of the nineth sheet ("US-457 Classification") on page 43 of EX1135 contain activity data for C-terminally truncated PH20 variants in U.S. Patent Application Publication No. 2010/0143457 (EX1105). Activity data was normalized in columns E and F to the activity reported for $PH20_{1\text{-}447}$. Column G contains the classification of the activity data in columns C and D from EX1105, as discussed in ¶ 144 of EX1003.

j. The tenth sheet ("PH20 Positional Domains-Motifs") on page 44 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 ¶ 131 of EX1003, 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).

k. Columns A-R of the eleventh sheet ("Essential Res.") on page 45 of EX1135 contain alternating columns of position numbers of PH20 and wildtype ("WT") residue. Rows in columns A-R are shaded based on positions listed in EX1026 ('731 App.), 80:19-35.

15. 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. Supplemental material for Exhibit 1144 is contained in Exhibit 1215, which is 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.

16. 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 with Petitioner's Updated Exhibit List, served on February 10, 2025.

17. 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. Supplemental material for Exhibit 1151 is contained in Exhibit 1216, which is a

true and correct copy of the PDF file available for download from the following URL: https://www.nature.com/articles/nmeth.1492#Sec22.

18. 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. Supplemental material for Exhibit 1155 is contained in Exhibit 1217, which is 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.

19. 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. Supplemental material for Exhibit 1157 is contained in Exhibit 1218, which is a true and correct copy of the PDF file available for download from the following URL: https://www.nature.com/articles/nature01891#Sec3.

20. Exhibit 1208 is a true and correct copy of a redline that I had created for U.S. Patent Application No. 13/694,731 (EX1026) and U.S. Patent Application Publication 2013-0302275 (EX1004) using Litera Compare for Microsoft Word. To create this redline, the PDF of U.S. Patent Application No. 13/694,731 was made machine-readable using the Optical Character Recognition tool in Adobe Acrobat. The text of the PDF of U.S. Patent Application No. 13/694,731 was then copied and compared to the text of U.S. Patent Application Publication 2013-0302275. Both documents were obtained from the USPTO's Patent Center website. The text of both documents was pasted into separate Word documents. Any text that appeared before the "Background/Summary" heading and the claim language was deleted. The Word document with the text from U.S. Patent Application No. 13/694,731 was designated as the original file and the Word document with the text from U.S. Patent Application Publication 2013-0302275 was designated as the modified file. I saved the redline as a PDF and included it here as Exhibit 1208. Although the redline shows certain differences as a result of formatting changes, in my review of the redline I have not identified any substantive differences between U.S. Patent Application No. 13/694,731 and U.S. Patent Application Publication 2013-0302275, and I believe them to be substantively identical.

a. The PDF file that I copied for the ’731 Application is available for download from the following URL: https://patentcenter.uspto.gov/applications/13694731/ifw/docs?application=

b. The text file that I copied for US-275 is available from the following URL: https://ppubs.uspto.gov/pubwebapp/authorize.html?redirect=patents/html/20130302275?source=US-PGPUB

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: March 23, 2026

Respectfully Submitted,

/Jeffrey P. Kushan/

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