UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TAKEDA VACCINES, INC.
Petitioner,

v.

VALNEVA AUSTRIA GMBH,
Patent Owner

Case IPR2023-00354
U.S. Patent No. 11,219,681

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 11,219,681

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A. ZIKV was a recognized global health threat, creating an urgent need to develop vaccines. 6

B. Aspects of ZIKV structure and maturation were known. 7

C. NAb titers were used to assess the likelihood of protection. 8

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B. Ground 1 Art: Zika Pipeline, Srivastava, the H/PF/2013 Sequence, Baronti, and Thomas render claims 1−11, 15, and 21−25 obvious. 16

1. Claim 1 recites obvious vaccines. 17

a. POSAs would have had a reason to make an inactivated ZIKV vaccine using known flavivirus vaccine technology. 17

b. Srivastava discloses a safe, effective, and economical inactivated JEV vaccine. 20

c. POSAs would have had a reason to use Baronti's H/PF/2013 ZIKV strain. 21

d. Baronti and the H/PF/2013 Sequence disclose a ZIKV strain having an RNA genome that is ≥80% identical to SEQ ID NO: 72.....23

e. POSAs would have made a ZIKV vaccine capable of stimulating a MN_{50} of >15 in ≥70% of vaccinated subjects. 24

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TABLE OF AUTHORITIES

Cases

AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.,
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Advanced Bionics v. MED-EL Elektromedizinische,
IPR2019-01469, Paper 6 (P.T.A.B. Feb. 13, 2020) 63

Amgen Inc. v. Sanofi, Aventisub LLC,
872 F.3d 1367 (Fed. Cir. 2017) 41

Amgen Inc.v. Sanofi, Aventisub LLC,
987 F.3d 1080 (Fed. Cir. 2021) 55, 57, 59

Amneal Pharm. LLC v. Supernus Pharm., Inc.,
IPR2013-00368, Paper 8 (P.T.A.B. Dec. 17, 2013).....36

Apple v. Fintiv,
IPR2020-00019, Paper 11 (P.T.A.B. Mar. 20, 2020).....63

Ecolochem, Inc. v. S. Cali. Edison Co.,
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Enzo Biochem, Inc. v. Calgene, Inc.,
188 F.3d 1362 (Fed. Cir. 1999) 57

Fresenius Kabi USA LLC v. Chugai Seiyaku Kabushiki Kaisha,
IPR2021-01336, Paper 27 (P.T.A.B. Feb. 23, 2022) 59

Galderma Labs. L.P. v. Tolmar, Inc.,
737 F.3d 731 (Fed. Cir. 2013) 37

General Plastic v. Canon Kabushiki Kaisha,
IPR2016-01357, Paper 19 (P.T.A.B. Sept. 6, 2017) 63

Idenix Pharm. LLC v. Gilead Sciences Inc.,
941 F.3d 1149 (Fed. Cir. 2019) ..... passim

In re Baxter Travenol Lab'y,
952 F.2d 388 (Fed. Cir. 1991) 38

In re Grasselli,
713 F.2d 731 (Fed. Cir. 1983) 38

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

Juno Therapeutics, Inc. v. Kite Pharma,
10 F.4th 1330 (Fed. Cir. 2021) 3, 41

Kennametal, Inc. v. Ingersoll Cutting Tool Co.,
780 F.3d 1376 (Fed. Cir. 2015) 62

Leapfrog Enterprises, Inc. v. Fisher-Price, Inc.,
485 F.3d 1157 (Fed. Cir. 2007) 36

Lockwood v. Am. Airlines, Inc.,
107 F.3d 1565 (Fed. Cir. 1997) 15, 16

Monsanto Tech. LLC v. DuPont De Nemours & Co.,
878 F.3d 1336 (Fed. Cir. 2018) 37

Regents of Univ. of Cali. v. Broad Inst.,
903 F.3d 1286 (Fed. Cir. 2018) 38

Titanium Metals Corp. of Am. v. Banner,
778 F.2d 775 (Fed. Cir. 1985) 60

Wyeth & Cordis Corp. v. Abbott Lab'ys,
720 F.3d 1380 (Fed. Cir. 2013) 55, 57, 59

PETITIONER'S EXHIBIT LIST

Exhibit #	***Description***
1001	Barbero Calzado, J., et al., U.S. Patent No. 11,219,681, "Zika Virus Vaccine" (filed March 10, 2020; issued Jan. 11, 2022)
1002	Declaration of Dan H. Barouch, M.D., Ph.D.
1003	*Curriculum Vitae* of Dan H. Barouch, M.D., Ph.D.
1004	File History of U.S. Patent No. 11,219,681
1005	Yoshii, K., et al., "A Conserved Region in the prM Protein Is a Critical Determinant in the Assembly of Flavivirus Particles," *J. General Virology*, 93: 27−38 (2012)
1006	Larocca, R.A., et al., "Vaccine Protection Against Zika Virus from Brazil," *Nature*, 536: 474−478 (2016)
1007	Halloway, T., "WRAIR Technology Helps Create Japanese Encephalitis Vaccine," *available at*: https://web.archive.org/web/20150920175227/http://www.army.mil/article/19643/WRAIR_Technology_helps_create_Japanese_Encephalitis_Vaccine/ (last accessed November 9, 2022)
1008	Barbero Calzado, J., et al., International Patent Appl. Publ. No. WO 2017/109225 A1, "Zika Virus Vaccine" (filed Dec. 23, 2016; published June 29, 2017)
1009	BLAST alignment of SEQ ID NO: 47 to SEQ ID NO: 73
1010	*Intentionally Left Blank*
1011	*Intentionally Left Blank*
1012	*Intentionally Left Blank*
1013	*Intentionally Left Blank*
1014	European Patent Appl. No. 15202585.4 (filed Dec. 23, 2015)
1015	European Patent Appl. No. 16161068.8 (filed Mar. 18, 2016)
1016	European Patent Appl. No. 16176025.1 (filed June 23, 2016)
1017	European Patent Appl. No. 16176049.1 (filed June 23, 2016)
1018	European Patent Appl. No. 16182845.4 (filed Aug. 4, 2016)

Exhibit #	***Description***
1019	GenBank: KJ776791.1, "Zika Virus Strain H/PF/2013 Polyprotein Gene, complete CDs," *available at*: https://www.ncbi.nlm.nih.gov/nuccore/KJ776791.1 (last modified June 13, 2014) (last accessed November 9, 2022)
1020	BLAST alignment of KJ776791.1 to SEQ ID NO: 72
1021	Watanaveeradej, V., et al., "Safety and Immunogenicity of a Rederived, Live-Attenuated Dengue Virus Vaccine in Healthy Adults Living in Thailand: A Randomized Trial," *Am. J. Trop. Med. Hyg.*, 91(1): 119−128 (2014)
1022	Orenstein, W.A., et al., "Global Vaccination Recommendations and Thimerosal," *Pediatrics*, 131(1): 149−151 (2012)
1023	Eckels, K.H., et al., "Japanese Encephalitis Virus Live-Attenuated Vaccine, Chinese Strain SA14-14-2; Adaptation to Primary Canine Kidney Cell Cultures and Preparation of a Vaccine for Human Use," *Vaccine*, 6(6): 513−518 (1988)
1024	Martinez, L.J., et al., "Safety and Immunogenicity of a Dengue Virus Serotype-1 Purified-Inactivated Vaccine: Results of a Phase 1 Clinical Trial," *Am. J. Trop. Med. Hyg.*, 93(3): 454−460 (2015)
1025	WHO Director-General Summarizes the Outcome of the Emergency Committee Regarding Clusters of Microcephaly and Guillain-Barré Syndrome, World Health Organization, (Feb. 1, 2016), *available at*: https://web.archive.org/web/20160204040311/http://www.who.int/mediacentre/news/statements/2016/emergency-committee-zika-microcephaly/en/ (last accessed November 9, 2022)
1026	*Intentionally Left Blank*
1027	Li, X-F, et al., "Complete Genome Sequence of a Chikungunya Virus Isolated in Guangdong, China," J. Virology, 86(16): 8904−8905.
1028	Putnak, R., et al. "Development of a Purified, Inactivated, Dengue-2 Virus Vaccine Prototype in Vero Cells: Immunogenicity and Protection in Mice and Rhesus Monkeys," *J. Infectious Diseases*, 174: 1176−1184 (1996)

Exhibit #	***Description***
1029	Musso, D., et al., "Potential Sexual Transmission of Zika Virus," *Emerging Infectious Diseases*, 21(2): 359−361
1030	Cox, B.D., et al., "Predicting Zika Virus Structural Biology: Challenged and Opportunities for Intervention," *Antiviral Chemistry & Chemotherapy*, 24(3−4): 118−126 (2015)
1031	Duffy, M.R., "Zika Virus Outbreak on Yap Island, Federated States of Micronesia," *New England J. of Med.*, 360(24): 2536−2543
1032	Cao-Lormeau, V. and Musso, D., "Emerging Arboviruses in the Pacific," *The Lancet*, 384: 1571−1572 (2014)
1033	Zika Virus Microcephaly and Guillain-Barré Syndrome, Situation Report, World Health Organization, *available at*: https://web.archive.org/web/20160320210243/http://apps.who.int/iris/bitstream/10665/204633/1/zikasitrep_17Mar2016_eng.pdf?ua=1 (Mar. 17, 2016) (last accessed November 9, 2022)
1034	Maurice, J., "WHO Reveals its Shopping List for Weapons Against Zika," *The Lancet* 387: 733 (2016)
1035	Besnard, M., et al., "Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014," 19(13): pii=20751 (2014)
1036	Monath, T.P., "Inactivated Yellow Fever 17D Vaccine: Development and Nonclinical Safety, Immunogenicity and Protective Activity," *Vaccine*, 28: 3827−3840 (2010)
1037	Rasmussen, S.A., "Vaccines and Pregnancy: Past, Present, and Future," *Seminars in Fetal & Neonatal Med.*, 19: 161−169 (2014)
1038	Plotkin, S.A. and Plotkin, S.L., "The Development of Vaccines: How the Past Led to the Future," *Nature Reviews Microbiology* 9: 889−893 (2011)
1039	Heinz, F.X. and Stiasny, K., "Flaviviruses and Flavivirus Vaccines," *Vaccine* 30: 4301−4306 (2012)
1040	Shan, C., "Zika Virus: Diagnosis, Therapeutics, and Vaccine," *ACS Infectious Diseases*, 2: 170−172 (2016)

Exhibit #	***Description***
1041	Ishikawa, T., et al., "A Review of Successful Flavivirus Vaccines and the Problems with Those Flaviviruses for Which Vaccines are Not Yet Available," *Vaccine*, 32: 1326−1337 (2014)
1042	Burton, D.R., "Antibodies, Viruses and Vaccines," *Nature Review Immunology* 2: 706−713 (2002)
1043	Roehrig, J.T., et al., "Guidelines for Plaque-Reduction Neutralization Testing of Human Antibodies to Dengue Viruses," *Viral Immunology*, 21(2): 123−132 (2008)
1044	Laurie, K.L., et al., "International Laboratory Comparison of Influenza Microneutralization Assays for A(H1N1)pdm09, A(H3N2), and A(H5N1) Influenza Viruses by CONSISE," *Clinical & Vaccine Immunology*, 22(8): 957−964 (2015)
1045	Klasse, P.J., "Neutralization of Virus Infectivity by Antibodies: Old Problems in New Perspectives," *Advances in Biology* 2014(157895): 24 pages (2014)
1046	Bauer, K., "A Phase II, Randomized, Safety and Immunogenicity Trial of a Re-Derived, Live-Attenuated Dengue Virus Vaccine in Healthy Children and Adults Living in Puerto Rico," *Am. J. Trop. Med. Hyg.*, 93(3): 441−453 (2015)
1047	Hombach, J., et al., "Report on a WHO consultation on immunological endpoints for evaluation of new Japanese encephalitis vaccines, WHO, Geneva, 2–3 September, 2004," *Vaccine*, 23: 5205−5211
1048	Lindenbach, B.D. and Rice, C.M., "Molecular Biology of Flaviviruses," *Advances in Virus Research* 59: 23−61 (2003)
1049	Tauber, E., et al., "Safety and immunogenicity of a Vero-cell-derived, inactivated Japanese encephalitis vaccine: a non-inferiority, phase III, randomised controlled trial," *The Lancet*, 370: 1847−1853 (2007)
1050	Brinton, M.A. and Basu, M., "Functions of the 3' and 5' Genome RNA Regions of Members of the Genus Flavivirus," *Virus Research* 206: 108−119 (2015)

Exhibit #	***Description***
1051	Okada, K., et al., "Safety and Immunogenicity of a Freeze-Dried, Cell Culture-Derived Japanese Encephalitis Vaccine (Inactivated) (JEBIK®V) in Children," *Vaccine*,
1052	Cohen, J., "The Race for a Zika Vaccine Is On," *Science* 351(6273): 543−544 (2016)
1053	GenBank: AY632535.2, "Zika Virus Strain MR-766, Complete Genome," *available at*: https://www.ncbi.nlm.nih.gov/nuccore/AY632535 (last modified Nov. 23, 2010) (last accessed November 9, 2022)
1054	GenBank: KU501215.1, "Zika Virus Strain PRVABC59, Complete Genome," *available at*: https://www.ncbi.nlm.nih.gov/nuccore/KU501215.1 (last modified Feb. 1, 2016) (last accessed November 9, 2022)
1055	GenBank: KU497555.1, "Zika Virus Isolate Brazil-ZKV2015, Complete Genome," *available at*: https://www.ncbi.nlm.nih.gov/nuccore/KU497555.1 (last modified Feb. 18, 2016) (last accessed November 9, 2022)
1056	Zhang, X., et al., "Genetic and Biochemical Characterizations of Zika Virus NS2A Protein," *Emerging Microbes & Infections*, 8(1): 585−602 (2019)
1057	Sample GenBank Record *available at*: https://www.ncbi.nlm.nih.gov/genbank/samplerecord/#ModificationDateB (last accessed November 9, 2022)
1058	Musso, D., "Zika Virus Transmission from French Polynesia to Brazil," *Emerging Infectious Diseases* 21(10): 1887 (2015)
1059	Schuller, E., et al., "Comparison of a Single, High-Dose Vaccination Regimen to the Standard Regimen for the Investigational Japanese Encephalitis Vaccine, IC51: A Randomized, Observer-Blind, Controlled Phase 3 Study," *Vaccine*, 27: 2188−2193 (2009)
1060	Schuller, E., et al., "Long-term Immunogenicity of the New Vero Cell-Derived, Inactivated Japanese Encephalitis Virus Vaccine IC51 Six and 12 Month Results of a Multicenter Follow-Up Phase 3 Study," *Vaccine*, 26: 4382−4386 (2008)

Exhibit #	***Description***
1061	Assessment Report for IXIARO, European Medicines Agency, (2009), *available at*: https://www.ema.europa.eu/en/documents/assessment-report/ixiaro-epar-public-assessment-report_en.pdf (last accessed November 9, 2022)
1062	Abbink, P., "Protective Efficacy of Multiple Vaccine Platforms Against Zika Virus Challenge in Rhesus Monkeys," *Science*, 353(6304) 1129−1132 (2016)
1063	Schlegl, R., et al., "Influence of Elemental Impurities in Aluminum Hydroxide Adjuvant on the Stability of Inactivated Japanese Encephalitis Vaccine, IXIARO®," *Vaccine*, 33: 5989−5996 (2015)
1064	Vaccines, Blood & Biologics: IXIARO® - Summary Basis for Regulatory Action, (March 30, 2009), *available at*: https://web.archive.org/web/20090619154725/https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm142580.htm (last accessed November 9, 2022)
1065	Duggan, S.T. and Plosker, G.L., "Japanese Encephalitis Vaccine (Inactivated, Adsorbed) [IXIARO®]," *Drugs* 69(1): 115−122 (2009)
1066	Schellack, C., et al., "IC31, A Novel Adjuvant Signaling via TLR9, Induces Potent Cellular and Humoral Immune Responses," *Vaccine*, 24: 5461−5472 (2006)
1067	Annunziato, F., et al., "The 3 Major Types of Innate and Adaptive Cell-Mediated Effector Immunity," *J. Allergy & Clinical Immunology*, 135(3): 626−635 (2014)
1068	Smith, D.W. and Mackenzie, J., "Zika Virus and Guillain-Barré Syndrome: Another Viral Cause to Add to the List," *The Lancet*, 387: 1486−1488 (2016)
1069	Benson, D.A., et al., "GenBank," *Nucleic Acids Research*, 41: D36−D42 (2012)
1070	Samarasekera, U. and Triunfol, M., "Concern Over Zika Virus Grips the World," *The Lancet* 387:521-524 (2016)
1071	BLAST alignment of translation of KJ776791.1 ORF to SEQ ID NO: 73

Exhibit #	***Description***
1072	Fox, M., "Could We Have A Zika Vaccine Soon?" NBCNews.com (Jan. 30, 2016), *available at*: https://web.archive.org/web/20160130130441/https://www.nbcnews.com/storyline/zika-virus-outbreak/could-we-have-zika-vaccine-soon-n507186 (last accessed November 9, 2022)
1073	Fauci, A.S. and D.M. Morens, "Zika Virus in the Americas – Yet Another Arbovirus Threat," *The New England Journal of Medicine*, 374(7): 601−604 (2016)
1074	Dyer, O., "Zika Vaccine Could Be In Production By Year's End, Says Maker," BMJ 352:i630 (2016)
1075	BLAST alignment of PRVABC59 to SEQ ID NO: 72
1076	BLAST alignment of translation of PRVABC59 ORF to SEQ ID NO: 40
1077	Kumar, S., et al., "Metal Ion Leachates and the Physio-Chemical Stability of Biotherapeutic Drug Products," *Current Pharmaceutical Design*, 20: 1173−1181 (2014)
1078	Declaration of Scott Bailey, Ph.D.
1079	*Curriculum Vitae* of Scott Bailey, Ph.D.
1080	Luca, V.C., et al., "*Crystal Structure of the Japanese Encephalitis Virus Envelope Protein*," *J. Virology*, 86(4): 2337−2346 (2012)
1081	Klema, V.J., et al., "Dengue Virus Nonstructural Protein 5 (NS5) Assembles into a Dimer with a Unique Methyltransferase and Polymerase Interface," *PLOS Pathogens*, 12(2): e1005451 (2016)
1082	Mukhopadhyay, S., et al., "A Structural Perspective of the *Flavivirus* Life Cycle," *Nature Review Microbiology*, 3: 13−22 (2005)
1083	Möhlen, M., et al., International Patent Appl. Publ. No. WO 2013/083726 A1, "Aluminum Compounds for Use in Therapeutics and Vaccines" (filed Dec. 6, 2012; published June 13, 2013)
1084	GenBank entry for KJ776791.2 *available at*: https://www.ncbi.nlm.nih.gov/nuccore/KJ776791.2 (last modified Aug. 31, 2016) (last accessed November 9, 2022)

Exhibit #	***Description***
1085	Ledgerwood, J.E., "A West Nile Virus DNA Vaccine Utilizing a Modified Promoter Induces Neutralizing Antibody in Younger and Older Healthy Adults in a Phase I Clinical Trial," *J. Infectious Diseases*, 203: 1396−1404 (2011)
1086	International Preliminary Report on Patentability, International Appl. No. PCT/EP2016/082664, dated June 26, 2018
1087	Delrue, I., et al., "Inactivated Virus Vaccines from Chemistry to Prophylaxis: Merits, Risks and Challenges," *Expert Review of Vaccines*, 11(6): 695−719 (2012)
1088	Stephenson, K.E., et al., "Safety and Immunogenicity of a Zika Purified Inactivated Virus Vaccine Given Via Standard, Accelerated, or Shortened Schedules: A Single-Centre, Double-Blind, Sequential-Group, Randomised, Placebo-Controlled, Phase 1 Trial," *Lancet Infectious Disease*, 20: 1061−1070 (2020)
1089	Collette, N.M., et al., "Single Amino Acid Mutations Affect Zika Virus Replication In Vitro and Virulence In Vivo," *Viruses*, 12(11): 1295 (2020)
1090	*Intentionally Left Blank*
1091	DiNunno, N.M., et al., "Identification of a Pocket Factor That Is Critical to Zika Virus Assembly," *Nature Communications*, 11: 4953 (2020)
1092	Barnard, T.R., et al., "Molecular Determinants of Flavivirus Virion Assembly," *Trends in Biochemical Sciences*, 46(5): 378−390 (2021)
1093	Tan, T.Y., et al., "Capsid Protein Structure in Zika Virus Reveals the Flavivirus Assembly Process," *Nature Communications*, 11: 895 (2020)
1094	Ma, X., et al., "Identification and Characterization of Key Residues in Zika Virus Envelope Protein for Virus Assembly and Entry," *Emerging Microbes & Infections*, 11(1): 1604−1620 (2022)
1095	Pierson, T.C. and Diamond, M.S., "Degrees of Maturity: The Complex Structure of Biology of Flaviviruses," *Current Opinion in Virology*, 2: 168−175 (2012)

Exhibit #	***Description***
1096	Barzon, L., et al., "Zika Virus: From Pathogenesis to Disease Control," *FEMS Microbiology Letters*, 363(18): 1−17 (2016)
1097	Declaration of Ingrid Hsieh-Yee, Ph.D.
1098	BLAST alignment of KJ776791.2 to SEQ ID NO: 72
1099	Poland, G.A., et al., "Zika Vaccine Development: Current Status," *Mayo Clinic Proceedings*, 94(12): 2572−2586 (2019)
1100	Aubry, F., et al., "Flavivirus Reverse Genetic Systems, Construction Techniques and Applications: A Historical Perspective," *Antiviral Research*, 114: 67−85 (2015)
1101	Shan, C., et al., "An Infectious cDNA Clone of Zika Virus to Study Viral Virulence, Mosquito Transmission, and Antiviral Inhibitors," *Cell Host & Microbe*, 19: 891−900 (2016)
1102	Singh, U. and Wurtele, E.S., "orfipy: A Fast and Flexible Tool for Extracting ORFs," *Bioinformatics*, 37(18): 3019−3020 (2021)
1103	Bennett, J., "How Many Particles Are in the Observable Universe?", *Popular Mechanics*, July 11, 2017, *available at*: https://www.popularmechanics.com/space/a27259/how-many-particles-are-in-the-entire-universe/ (last visited December 14, 2022)
1104	File History of U.S. Patent Application No. 16/063,007
1105	BLAST alignment of SEQ ID NO: 2 and SEQ ID NO: 72
1106	BLAST alignment of SEQ ID NO: 3 and SEQ ID NO: 72
1107	BLAST alignment of SEQ ID NO: 4 and SEQ ID NO: 72
1108	BLAST alignment of SEQ ID NO: 5 and SEQ ID NO: 72
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1115	BLAST alignment of SEQ ID NO: 12 and SEQ ID NO: 72
1116	BLAST alignment of SEQ ID NO: 13 and SEQ ID NO: 72
1117	BLAST alignment of SEQ ID NO: 11 and SEQ ID NO: 12
1118	Nema, S. and Brendel, R.J., "Excipients and Their Role in Approved Injectable Products: Current Usage and Future Directions," *PDA J. Pharmaceutical Science & Technology*, 65(3): 287−332 (2011)
1119	Chen, R. and Vasilakis, N., "Dengue – Quo tu et quo vaids?," *Viruses*, 3: 1562−1608 (2011)
1120	Manikandan, S., "Measures of Central Tendency: The Mean," *J. Pharmacology & Pharmacotherapeutics*, 2(2): 140−142 (2011)
1121	COLLEGE PHYSICS 790 (Franklin Miller, Jr. ed., 4th ed. 1977)
1122	Bayat, A., "Bioinformatics," *BMJ*, 324: 1018−1022 (2002)
1123	Ekmekci, B., et al., "An Introduction to Programming for Bioscientists: A Python-Based Primer," *PLoS Computational Biology*, 12(6): e1004867 (2016)
1124	Sauter, N.K., et al., "New Python-Based Methods for Data Processing," *Acta Crystallographica Section D*, D69: 1274−1282 (2013)
1125	Venners, B., "The Making of Python A Conversation with Guido van Rossum, Part I," *available at*: https://www.artima.com/articles/the-making-of-python
1126	Adams, P.D., et al., "PHENIX: A Comprehensive Python-Based System for Macromolecular Structure Solution," *Acta Crystallographica Section D*, D66: 213−221 (2010)
1127	Hayes, R.P., et al., "Structural Basis for Promiscuous PAM Recognition in Type I-E Cascade from *E. coli*," *Nature*, 530(7591): 499−503 (2016)
1128	BLAST: Basic Local Alignment Search Tool, *available at*: https://blast.ncbi.nlm.nih.gov/Blast.cgi

Exhibit #	***Description***
1129	Mount, D.W., "Using the Basic Local Alignment Search Tool (BLAST)," *Cold Spring Harbor Protocols* (2007), *available at*: http://cshprotocols.cshlp.org/content/2007/7/pdb.top17.full
1130	Chen, H., et al., "Cut Site Selection by the Two Nuclease Domains of the Cas9 RNA-guided Endonuclease," *J. Biological Chemistry*, 289(19): 13284−13294 (2014)
1131	INTRODUCTORY STATISTICS (Prem S. Mann ed., 7th ed. 2010)
1132	Summation Notation, *available at*: http://www.columbia.edu/itc/sipa/math/summation.html)
1133	Harvey, A. and Howell, E., "How Many Stars Are in the Universe?," *available at*: https://www.space.com/26078-how-many-stars-are-there.html
1134	Lopez, M.J. and Mohiuddin, S.S., "Biochemistry, Essential Amino Acids," *NCBI Bookshelf* (2022), *available at*: https://www.ncbi.nlm.nih.gov/books/NBK557845/?report=printable
1135	Shchelochkov, O.A., "Open Reading Frame," *National Human Genome Research Institute* (2002), *available at*: https://www.genome.gov/genetics-glossary/Open-Reading-Frame
1136	Genomics Education Programme, "Read," NHS Health Education England, *available at*: https://www.genomicseducation.hee.nhs.uk/glossary/read/
1137	Kurnaz, M.L., et al., "A Statistical Analysis of the Robustness of Alternate Genetic Coding Tables," *Int. J. Mol. Sci.*, 9: 679−697 (2008)
1138	Enfissi, A., et al., "Zika Virus Genome from the Americas," *The Lancet*, 387: 227−228 (2016)
1139	PubMed metadata record for *Baronti*, *available at*: https://pubmed.ncbi.nlm.nih.gov/24903869/, accessed and obtained on November 10, 2022

Exhibit #	***Description***
1140	Wayback Machine response page indicating that the old URL of "Current Zika product pipeline" at https://web.archive.org/web/20160309222523/http://www.who.int/entity/csr/research-and-development/zika-rd-pipeline.pdf?ua=1 was not archived by the Internet Archive. The Wayback Machine response page was accessed and obtained on December 15, 2022
1141	Table of contents of vol. 2, no. 3 (2014) of *Genome Announcements* that contains *Baronti*, archived on June 29, 2014 by the Internet Archive, *available at*: https://web.archive.org/web/20140629173328/http://genomea.asm.org/content/2/3.toc, accessed and obtained on November 11, 2022
1142	Citations to *Baronti*, obtained from Google Scholar
1143	Copy of *Zika Pipeline* archived on March 11, 2016 by the Internet Archive, *available at*: https://web.archive.org/web/20160311113550/http://www.who.int/csr/research-and-development/zika-rd-pipeline.pdf, accessed and obtained on November 10, 2022
1144	"WHO and Experts Prioritize Vaccines, Diagnostics and Innovative Vector Control Tools for Zika R&D," a March 9, 2016 WHO Note for media, archived on March 9, 2016 by the Internet Archive, *available at*: https://web.archive.org/web/20160309222523/http://www.who.int/mediacentre/news/notes/2016/research-development-zika/en/, accessed and obtained on December 5, 2022
1145	*Sifferlin-TIME* archived on January 22, 2016 by the Internet Archive, *available at*: https://web.archive.org/web/20160122154151/http://time.com/4188973/zika-virus-vaccine-nih/, accessed and obtained on December 5, 2022
1146	Copy of *Srivastava* obtained from the University of Wisconsin-Madison Steenbock Library
1147	Bibliographic and MARC record for *Vaccine* that contains *Srivastava*, *available at*: https://search.library.wisc.edu/catalog/999552122802121, from the online catalog of the University of Wisconsin-Madison Library System, accessed and obtained on November 11, 2022

Exhibit #	***Description***
1148	PubMed metadata record for *Srivastava*, *available at*: https://pubmed.ncbi.nlm.nih.gov/11483284/, accessed and obtained on November 10, 2022
1149	*Vaccine* website archived by the Internet Archive on October 3, 2002, *available at*: https://web.archive.org/web/20021003015903/http://www.elsevier.com:80/locate/vaccine, from the Internet Archive, accessed and obtained on November 26, 2022
1150	Citations to *Srivastava* obtained from Google Scholar
1151	Copy of *Thomas* obtained from the National Library of Medicine
1152	Bibliographic and MARC record of *The American Journal of Tropical Medicine and Hygiene* that contains *Thomas*, *available at*: https://catalog.nlm.nih.gov/permalink/01NLM_INST/1o1phhn/alma991179293406676, from the online catalog of the National Library of Medicine, accessed and obtained on November 15, 2022
1153	PubMed metadata record for *Thomas*, *available at*: https://pubmed.ncbi.nlm.nih.gov/23208878/, accessed and obtained on November 10, 2022
1154	Citations to *Thomas*, obtained from Google Scholar
1155	*Intentionally Left Blank*
1156	*Intentionally Left Blank*
1157	*Intentionally Left Blank*
1158	*Intentionally Left Blank*
1159	*Intentionally Left Blank*
1160	Baronti, C., Piorkowski, G., Charrel, R. N., Boubis, L., Leparc-Goffart, I., & de Lamballerie, X., (2014, June 5), "Complete Coding Sequence of Zika Virus from a French Polynesia Outbreak in 2013," *Genome Announcements*, vol. 2, no. 3, p. e00500-14
1161	World Health Organization, *Current Zika Product Pipeline*, (3 March 2016), *available at*: https://www.who.int/publications/m/item/current-zika-product-pipeline

Exhibit #	***Description***
1162	Sifferlin, A., "U.S. Launches 'Full-Court Press' for a Zika Vaccine," *TIME* (Jan. 21, 2016, 3:24 PM), *available at*: https://time.com/4188973/zika-virus-vaccine-nih/
1163	Srivastava, A. K., Putnak, J. R., Lee, S. H., Hong, S. P., Moon, S. B., Barvir, D. A., ... & Eckels, K. H., (14 August 2001, available online 30 July 2001), "A Purified Inactivated Japanese Encephalitis Virus Vaccine Made in Vero cells," *Vaccine*, vol. 19, no. 3, pp. 4557-4565
1164	Thomas, S. J., Eckels, K. H., Carletti, I., De La Barrera, R., Dessy, F., Fernandez, S., ... & Innis, B. L., (2013), "A Phase II, Randomized, Safety and Immunogenicity Study of a Re-derived, Live-attenuated Dengue Virus Vaccine in Healthy Adults," *American Journal of Tropical Medicine and Hygiene*, vol. 88, no. 1, pp. 73-88
1165	*Intentionally Left Blank*
1166	Declaration of Mr. Nathaniel E. Frank-White of the Internet Archive
1167	*Curriculum Vitae* of Ingrid Hsieh-Yee, Ph.D.
1168	"Understanding MARC Bibliographic: Machine-Readable Cataloging," Library of Congress, Parts VII to X
1169	"Stop Codon," excerpt from G. Davies et al., *Molecular Therapies for Cystic Fibrosis*, in *Kendig's Disorders of the Respiratory Tract in Children* (9th ed., 2019), *available at*: https://www.sciencedirect.com/topics/neuroscience/stop-codon#:~:text=Premature%20stop%20codons%20are%20those,as%20truncated)%20protein%20is%20formed
1170	Shiver, J. et al., "Scientific Notation and Order of Magnitude," VisionLearning, *available at*: https://www.visionlearning.com/en/library/Math-in-Science/62/Scientific-Notation-and-Order-of-Magnitude/250#top
1171	Bailey Declaration Example 1
1172	Bailey Declaration Example 2
1173	Bailey Declaration Python Script 1
1174	Bailey Declaration Python Script 2

Exhibit #	***Description***
1175	Bailey Declaration Python Script 3
1176	A. Ramachandran et al., *Processing and Integration of Functionally Oriented Prespacers in the Escherichia coli CRISPR System Depends on Bacterial Host Exonucleases*, 295 J. BIO. CHEM. 3403, 3412 (2020).
1177	Plevka, P., et al., "Maturation of flaviviruses starts from one or more icosahedrally independent nucleation centres," *EMBO Reports*, 12(6): 602-606 (2011)
1178	Rodrigues, A.F., et al., "Viral vaccines and their manufacturing cell substrates: New trends and designs in modern vaccinology," *Biotechnol. J.*, 10: 1329-1344 (2015)
1179	Souza, M.C.O., et al., "Production of yellow fever virus in microcarrier-based Vero cell cultures," *Vaccine*, 27: 6420-6423 (2009)
1180	Pereira, R.C., et al., "An Inactivated Yellow Fever 17DD Vaccine Cultivated in Vero Cell Cultures," *Vaccine*, 33: 4261-4268 (2015)
1181	Amended Articles of Incorporation of OCLC, Inc., revised June 23, 2017
1182	*Intentionally Left Blank*
1183	"Discussion Paper No. 2020-DP16: Recording the Mode of Issuance for Manifestations," Library of Congress, May 29, 2020
1184	*Intentionally Left Blank*
1185	Publisher's webpage for *Baronti¸ available at*: https://journals.asm.org/doi/full/10.1128/genomeA.00500-14
1186	PubMed Website, *available at*: https://pubmed.ncbi.nlm.nih.gov/ https://pubmed.ncbi.nlm.nih.gov/%20
1187	List of early citations to *Baronti*
1188	World Health Organization webpage for *Current Zika Pipeline*, *available at*: http://www.who.int/publications/m/item/current-zika-product-pipeline
1189	WorldCat website, *available at*: https://www.worldcat.org

Exhibit #	***Description***
1190	BLAST alignment of KU955593.1 to SEQ ID NO: 72
1191	BLAST alignment of FSS13025 NS2A protein and SEQ ID NO: 73 (annotated)
1192	BLAST alignment of MR-766 E protein and SEQ ID NO: 73 (annotated)
1193	Bailey Declaration Example 3
1194	*Intentionally Left Blank*
1195	Publisher's webpage for *Srivastava*, *available at*: https://www.sciencedirect.com/science/article/pii/S0264410X01002080?via%3Dihub
1196	*Intentionally Left Blank*
1197	Webpage for ScienceDirect, *available at*: https://www.elsevier.com/solutions/sciencedirect
1198	WorldCat webpage for *Vaccine*, *available at*: https://worldcat.org/title/10399916
1199	ScienceDirect webpage for *Vaccine*, *available at*: https://www.sciencedirect.com/journal/vaccine
1200	Directory of OCLC Members, *available at*: https://www.oclc.org/en/contacts/libraries.html
1201	*Intentionally Left Blank*
1202	National Library of Medicine Classification Schedule, "W General Medicine. Health Professions," *available at*: https://classification.nlm.nih.gov/schedules/w
1203	*Intentionally Left Blank*
1204	Publisher's webpage for *Thomas*, *available at*: https://www.ajtmh.org/view/journals/tpmd/88/1/article-p73.xml
1205	WorldCat webpage for *Thomas*, *available at*: https://worldcat.org/title/1724826
1206	Description of MARC Org Code DNLM, MARC Code List for Organizations

Exhibit #	***Description***
1207	MEDLINE/PubMed Data Element (Field) Descriptions, *available at*: https://www.nlm./nih.gov/bsd/mms/medlineelements.html
1208	List of early citations to *Thomas*
1209	List of early citations to *Srivastava*

I. INTRODUCTION

Takeda Vaccines, Inc. requests IPR of claims 1−15 and 21−25 of USPN 11,219,681 ("'681 patent") (EX1001), assigned to Valneva Austria GmbH. The challenged claims encompass Zika virus ("ZIKV") vaccines that the prior art would have rendered obvious or anticipated.

First, the challenged claims cannot claim priority to the earliest December 23, 2015 EP priority application, because that application *does not even mention ZIKV or ZIKV vaccines* and therefore cannot plausibly describe or enable the claimed ZIKV vaccines. Accordingly, the claims are not entitled to any filing date before March 18, 2016. But before then, it would have been obvious to develop the claimed vaccines.

Indeed, the World Health Organization ("WHO") had already declared ZIKV a "Public Health Emergency of International Concern." EX1025, 1. And it called for a "coordinated international response … to expedite the development of diagnostic tests and vaccines…." *Id.*, 2. Similarly, Dr. Anthony Fauci called for a "full-court press" to develop a ZIKV vaccine. EX1162, 1. The WHO's "Current Zika Product Pipeline" publication ("Zika Pipeline"; EX1143) identified eighteen ZIKV vaccine programs, "[m]ost [of which were] building on existing flavivirus vaccine technology and know-how." EX1143, 5.[1] ZIKV is a flavivirus, along with

[1] Cites are to the original page numbers of Zika Pipeline.

Yellow Fever virus ("YFV"), Japanese Encephalitis virus ("JEV"), Tick-Borne Encephalitis virus ("TBEV"), Dengue virus ("DENV"), and West Nile virus ("WNV"). EX1002, ¶50. Zika Pipeline stated, "[i]t is assumed that a ZIKV vaccine can be developed building on the same technologies that have been successfully used to develop human flavivirus vaccines…." *Id.*, 5. For example, Srivastava had developed a JEV vaccine using technology previously used to make a DENV vaccine. EX1163, 4558; EX1002, ¶151. In view of the Public Health Emergency and assumption that a ZIKV vaccine could be developed based on prior flavivirus vaccine technology, persons of ordinary skill in the art ("POSAs") would have had a reason to substitute ZIKV for JEV in Srivastava's vaccine technology to address the outbreak. Baronti disclosed the ZIKV strain H/PF/2013 from a recent outbreak, and published and deposited the H/PF/2013 sequence in GenBank. EX1160; EX1019. Additionally, POSAs would have had a reason to make a ZIKV vaccine that could stimulate neutralizing antibody ("NAb") titers much greater than 15 in at least 70% of vaccinated subjects, to provide long-term protection in a large portion of the vaccinated population. The art disclosed that flavivirus vaccines could stimulate NAb titers much greater than 15 in at least 70% of subjects, when administered using a multi-dose schedule. POSAs would have reasonably expected such titers with a ZIKV vaccine, because other flavivirus vaccines stimulated NAb titers in the thousands. Thomas disclosed suitable titer assays.

Second, the challenged claims are not entitled to the December 23, 2016 filing date of PCT/EP2016/082664 ("'664 PCT"), because the '664 PCT neither describes nor enables the full scope of vaccines encompassed by the claims. The claimed vaccines comprise a ZIKV having an RNA genome "correspond[ing to] SEQ ID NO: 72 or *a variant nucleic acid having at least 80% identity to SEQ ID NO: 72*."[2] EX1001, 445:35−37. As Takeda's expert Dr. Dan Barouch explains, the variant nucleic acids *are not limited to naturally occurring* ZIKV nucleic acids, and there are *many millions* of variant nucleic acids that have at least 80% identity to SEQ ID NO: 72. EX1002, ¶¶264−269. But, to make a vaccine, the variant nucleic acid must be capable of producing Zika virus that can replicate in the cells used for vaccine production. EX1002, ¶¶252−255. The '664 PCT provides no meaningful guidance as to *which of the many millions of variant sequences* can produce ZIKV that can replicate in cells and be made into a vaccine. And it provides no meaningful guidance as to *which of the many millions of variant sequences* would meet the claims' functional limitations specifying the vaccine "is capable of stimulating a neutralizing antibody titer greater than 15 in at least 70% of vaccinated subjects." EX1001, 445:37−41. *Juno Therapeutics, Inc. v. Kite Pharma*, 10 F.4th 1330, 1335 (Fed. Cir. 2021).

[2] Emphasis is added throughout.

At most, the ’664 PCT provides a narrow set of twelve naturally occurring ZIKV sequences and one working example of a ZIKV vaccine. But those disclosed species only abide in a miniscule corner of the claimed genus that encompasses many millions of potential vaccines, and do not represent the genus throughout its full scope. *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300 (Fed. Cir. 2014)

Further, Dr. Barouch shows that the claims’ structural language encompasses variant nucleic acids that *fail* to produce the ZIKV needed to make the claimed vaccines. In view of the claims’ large breadth of candidate ZIKV vaccines, the ’664 PCT’s narrow disclosure falls short. And given the “at least many, many [millions] of candidate [vaccines]” encompassed by the claims, the limited disclosure in the ’644 PCT, and unpredictability in the art regarding whether a given variant will yield ZIKV capable of replicating and being made into a vaccine—“each of which would require synthesis and … screening”—it would have required undue experimentation to make and use the full scope of the challenged claims. *Idenix Pharm. LLC v. Gilead Sciences Inc.*, 941 F.3d 1149, 1163 (Fed. Cir. 2019). Thus, the claims are not entitled to the ’664 PCT’s filing date, and intervening prior art (WO 2017/109225; “WO ’225” (EX1008)) anticipates the claims.

II. GROUNDS FOR STANDING (37 C.F.R. §42.104(a))

Petitioner certifies that the ’681 patent is available for IPR and Petitioner is not barred or estopped.

III. PRECISE RELIEF REQUESTED (37 C.F.R. §42.22(a))

The Board should institute IPR under 35 U.S.C. §§311−319 and 37 C.F.R. §§42.1−.80, 42.100−.123, and cancel claims 1−12, 15, and 21−25 as unpatentable under §103 and claims 1−15 and 21−25 as anticipated under §102(a)(1).

IV. POSA

A POSA developing the ZIKV vaccines of the ’681 patent typically would have had an M.D. and/or a Ph.D. degree, specializing in infectious diseases, virology, immunology, vaccinology, or a related discipline (e.g., biology, biochemistry, molecular biology, microbiology, structural biology, pathology), as well as typically at least 3 years of research and development experience specializing in developing and testing antiviral vaccines. EX1002, ¶47. A POSA would also have worked as part of a multi-disciplinary team and drawn upon not only his or her own skills, but also taken advantage of certain specialized skills of others in the team, to solve a given problem. *Id.*, ¶48. For example, such a team may be comprised of a bioinformatician, molecular biologist, epidemiologist, manufacturing specialist, and/or pharmaceutical formulator. *Id.*

V. SCOPE AND CONTENT OF THE ART BEFORE MARCH 18, 2016

A. ZIKV was a recognized global health threat, creating an urgent need to develop vaccines.

In 2013−2014, ZIKV caused a large epidemic in French Polynesia. EX1032; EX1002, ¶51. By 2015, ZIKV spread to Brazil, infecting an estimated 0.4−1.3 million people. EX1033, 2; EX1002, ¶51. ZIKV had eventually spread to at least 33 countries and territories in the Americas. EX1033, 1; EX1002, ¶51. The WHO recognized that (i) "Zika virus is highly likely to be a cause of microcephaly, [Guillain-Barré syndrome], and other neurologic disorders" and (ii) a "causal role for Zika virus" and birth defects was "highly likely," with the "most significant health risks [being] for pregnant woman." EX1033, 1, 6−8, 10; EX1002, ¶52.

Before March 18, 2016, the WHO declared ZIKV a "Public Health Emergency of International Concern," and a "coordinated international response [was] needed … to expedite the development of diagnostic tests and vaccines to protect people at risk, especially during pregnancy." EX1025, 1−2; EX1002, ¶53. Indeed, there was an "urgent need" to develop a ZIKV vaccine, and Dr. Fauci called for "all hands on deck." EX1034, 733; EX1002, ¶56; EX1162, 1.

The WHO also stated it was "assumed that a ZIKV vaccine can be developed building on the same technologies that have been successfully used to develop human flavivirus vaccines." EX1143, 2, 5; EX1002, ¶55. Dr. Fauci concurred: "you can translate the technologies that you've developed to hasten the

end game goal of what you want for a virus like Zika." EX1162, 1; EX1002, ¶56. Vaccine pioneer Stanley Plotkin, similarly noted, "Zika belongs to the flavivirus family, and vaccines exist for several of its relatives, including dengue, yellow fever, and Japanese Encephalitis." EX1052, 543; EX1002, ¶56. He did not "see any technical issues" in making a ZIKV vaccine, and the field recognized "a good shot at success" in developing a vaccine. EX1052, 543; EX1002, ¶56.

In its March 3, 2016 Zika Pipeline document,[3] the WHO announced eighteen ZIKV vaccine development programs, "[m]ost [of which were] building on existing flavivirus vaccine technology and know-how." EX1143, 5; EX1002, ¶57. The art recognized that an inactivated ZIKV vaccine had "the best chance of winning regulatory approval as a product that pregnant women might use," given the birth defects linked to ZIKV. EX1052, 543; EX1002, ¶58.

B. Aspects of ZIKV structure and maturation were known.

The genome and corresponding polyprotein sequences of at least four ZIKV strains were known in the art. EX1053; EX1054; EX1055; EX1019; EX1002, ¶60. Baronti sequenced the H/PF/2013 strain from the French Polynesia outbreak and confirmed that ZIKV, like other flaviviruses, contains an open reading frame

[3] Zika Pipeline, dated March 3, 2016, was publicly accessible by March 11, 2016. EX1097, ¶¶30−41.

("ORF") that is translated into a single polyprotein that is cleaved to produce three structural proteins (capsid, pre-membrane/membrane ("prM"), envelope ("E")) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5). EX1160, 1; EX1081, 2; EX1002, ¶60. The three structural proteins play important roles in the viral life cycle, affecting assembly, maturation, and fusion. EX1082, 14; EX1002, ¶61. Generally, a ZIKV has to be mature to be able to replicate and be made into an inactivated viral vaccine. EX1177, 602; EX1002, ¶63. All seven non-structural proteins are necessary for flavivirus replication. EX1081, 2; EX1002, ¶62. The flavivirus RNA genome also contains 5'- and 3'-noncoding regions that play key roles in regulating translation and genome replication. EX1048, 28−29; EX1050, 109−110; EX1002, ¶62.

C. NAb titers were used to assess the likelihood of protection.

To gauge the immune response stimulated in a vaccinated subject, researchers commonly measured a vaccine's ability to stimulate a neutralizing antibody ("NAb") titer. EX1002, ¶¶64−65; EX1042, 709; EX1045, 10−11; EX1042, 126. "[P]rotection is achieved when … the serum of the animal can be diluted 100-fold and 90% neutralization still be achieved *in vitro*." EX1042, 707−708; EX1045, 1; EX1002, ¶67. Two known methods of quantifying NAbs before March 18, 2016, were the plaque reduction neutralization test ("PRNT") and microneutralization ("MN") assays. EX1163, 4562−4563; EX1024, 458;

EX1164, 86; EX1002, ¶66. MN assays, such as Thomas's MN_{50} assay, were more high-throughput, less labor intensive, and generally more accurate than PRNT assays. EX1164, 86; EX1002, ¶73. MN and PRNT assays involve mixing a constant amount of virus with serial dilutions of a vaccinated subject's serum. EX1164, 75; EX1002, ¶¶69, 73. Analogous to $PRNT_{50}$, MN_{50} is the reciprocal number of the last dilution of serum that neutralizes ≥50% of the targeted virus. EX1164, 75; EX1002, ¶¶70, 73. Thomas disclosed that "[t]he precision of the assay was estimated to range from 39% to 59% depending on [virus] serotype." EX1164, 86; EX1002, ¶73.

The art further disclosed that NAb titers of 10, detected using PRNT or MN assays, evidenced the development of NAbs ("seroconversion") and were considered "the minimum protective level" against various flaviviruses. EX1047, 5209−5210; EX1041, 1327, 1330, 1334; EX1164, 86; EX1002, ¶68.

D. Various flavivirus vaccines were developed that stimulated NAbs.

Before March 18, 2016, there were at least twelve approved vaccines for four flaviviruses (YFV, TBEV, JEV, and DENV). EX1040, 171; EX1041, 1326−1327; EX1002, ¶74. The live-attenuated YFV-17D vaccine was used to develop chimeric flavivirus vaccines. EX1041, 1327; EX1002, ¶75. By 2001, Srivastava had developed a purified inactivated JEV vaccine following a technology used to make a DENV-2 vaccine. EX1163, 4558; EX1002, ¶75. By

2009, Srivastava's JEV vaccine product was approved as IXIARO®. EX1007, 1; EX1061, 10; EX1064, 3; EX1002, ¶75. These DENV and JEV vaccines produced high NAb titers (i.e., in the hundreds to thousands) as summarized below:

For DENV vaccines:

- Putnak disclosed:
  - $PRNT_{50}$ titers of 160−340 after one dose and 350−2,500 after two doses in 100% of vaccinated mice. EX1028, Table 4; EX1002, ¶¶79, 82.
  - $PRNT_{50}$ titers of 10−160 in 58% of vaccinated monkeys not previously exposed to DENV after one dose; 30−1,230 in 100% of monkeys after two doses. EX1028, Table 5; EX1002, ¶¶80, 82.
  - titers waned between the second and third doses, but rose to 20−1,680 after dose 3, before waning when assayed four weeks later. EX1028, Table 5; EX1002, ¶¶81−82.
- Thomas disclosed:
  - DENV vaccine MN_{50} titers of 11−2,430 after two doses. EX1164, 86, Table 8; EX1002, ¶¶84−86; and
  - NAb titers waned between the second and third doses. EX1164, Table 8; EX1002, ¶¶85−86.

- In additional studies of Thomas's vaccines:
  - MN_{50} titers were only >10 for each serotype in >70% of the vaccinated population and ranged from 14−2,430 in 100% of non-primed subjects for each serotype after two doses. EX1021, Table 6; EX1002, ¶88.
  - geometric mean titers ("GMTs")[4] were only >10 after two doses and ranged from 60.3−377.7 in 100% of subjects. EX1046, Table 6; EX1002, ¶89.
- Martinez disclosed:
  - only observing MN_{50} titers >10 after two doses and ranging from 11−1,868 in 100% of subjects. EX1024, Table 3; EX1002, ¶¶90−92.
  - titers dropped to <10 in ~40% of subjects two months after the second dose. EX1024, Table 3; EX1002, ¶¶91−92.

For JEV Vaccines:

- Srivastava reported $PRNT_{50}$ titers of 1,280−7,781 in 100% of mice receiving a two-dose schedule of a purified inactivated JEV vaccine ("**JE-PIV**"). EX1163, 4562−4563, Table 3; EX1002, ¶94.
- In 2007, Tauber assayed JE-PIV and observed it stimulated a GMT of

[4] EX1120, 141; EX1002, ¶88 n.17.

244 and titers of 5−19,783, with titers ≥10 observed in 98% of subjects, and ≥81−160 in ~90% of subjects (after two doses), which diminished over time. EX1049, 1848, 1850, FIG. 2; EX1065, 119, FIG. 2b; *see also* EX1060, 4386; EX1002, ¶¶96−97.

- Another JEV vaccine dosed twice provided $PRNT_{50}$ GMTs of ~391, ~263, and ~129 when administered at different dosages. EX1051, 5968, Table 3; EX1002, ¶99.[5] The titers waned at 6−12 months then, after a third dose, stimulated GMTs of ~9,057, ~5,834, and ~3,148. EX1051, 5968, Table 3; EX1002, ¶99.

VI. OVERVIEW OF THE '681 PATENT AND PROSECUTION HISTORY

The '681 patent issued from U.S. Appl. No. 16/813,862 ("'862 application"), filed March 10, 2020. The '862 application is a continuation of U.S. Appl. No. 16/063,007, which is the §371 entry of the '664 PCT, filed December 23, 2016 and published as WO '225 (EX1008) on January 29, 2017. The '664 PCT claims priority to multiple European patent applications (EX1015−EX1018), the earliest being EP15202585.4 ("EP '585"; EX1014), filed December 23, 2015, followed by EP16161068.8, filed March 18, 2016 (EX1015).

[5] EX1051 reports the GMTs in values of $\log_{10}$. EX1051, Table 3. These values have been converted into an integer value. EX1002, ¶59 n.14, ¶99 n.20.

During prosecution, the Examiner issued a first-action allowance, stating that the art—GenBank accession no. KJ776791.2 (EX1084) and Cox (EX1030)—did not "disclose, teach or suggest the instant invention." EX1004, 924−930.

In discussing the art, the Examiner did not focus on vaccines, but instead focused on Cox's disclosure that "lead candidates of treatment can likely be established using NS3 and NS5 inhibitors [i.e., small molecules] from other flaviviruses." *Id.*[6]

VII. CLAIM CONSTRUCTION

Terms not explicitly discussed below are plain on their face and should be given their ordinary meanings.

Claim 1 recites, in part, that the ZIKV virus genome has **"a variant nucleic acid having at least 80% identity to SEQ ID NO: 72**." EX1001, 445:34−37. Claims 21−23 recite at least 90%, 95%, and 99% identity to SEQ ID NO: 72, respectively. *Id.*, 448:11−18.

The '681 patent states:

> The terms "identical" or percent "identity" in the context of two or more nucleic acids or amino acid sequences

[6] The '681 patent's parent also received a cursory examination, receiving a restriction requirement followed immediately by an allowance, where the Examiner also focused on Cox's inhibitors. EX1104, 505−508, 941−946.

> refer to two or more sequences or subsequences that are the same. Two sequences are "substantially identical" if two sequences have a specified percentage of amino acid residues or nucleotides that are the same … over a specified region or over the entire sequence, when compared and aligned for maximum correspondence over a comparison window, or designated region as measured using one of the following sequence comparison algorithms or by manual alignment and visual inspection….
>
> Two examples of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms….

Id., 127:33−128:31; EX1002, ¶109.

POSAs, therefore, would have understood a "variant nucleic acid having at least [80%, 90%, 95%, or 99% identity]" to encompass variants having the specified percent identity to SEQ ID NO: 72 as determined, for example, using an algorithm such as BLAST, with the percent identity resulting from the maximum correspondence of the two sequences, and with the variant not being required to be identical to SEQ ID NO: 72 over any particular region and able to overlap with SEQ ID NO: 72, provided that specified percent identity is maintained. EX1002, ¶110.

VIII. IDENTIFICATION OF THE CHALLENGE (37 C.F.R §42.104(b))

Ground	AIA 35 U.S.C. §	Challenged Claims	References
1	§103	1−11, 15, and 21−25	**"Ground 1 Art":** Zika Pipeline (EX1143), Srivastava (EX1163), Baronti (EX1160), the H/PF/2013 Sequence (EX1019), and Thomas (EX1164)
2	§103	12	**"Ground 2 Art":** Zika Pipeline, Srivastava, Baronti, the H/PF/2013 Sequence, Thomas, and WO 2013/083726 (EX1083; "Möhlen")
3	§102(a)(1)	1−15 and 21−25	WO '225 (EX1008)

A. Claims 1−12, 15, and 21−25 lack priority to EP '585

The challenged claims recite a genus of ZIKV vaccines, but EP '585 *does not even mention* ZIKV or ZIKV vaccines. EP '585 is solely directed to Chikungunya virus, which (although having certain similarity to ZIKV) is not a ZIKV or even a flavivirus. EX1014, 3, 6; EX1002, ¶118. POSAs, therefore, would conclude that the inventors lacked possession of any ZIKV vaccine as of EP '585's December 23, 2015 filing date. EX1002, ¶¶119, 121. Devoid of any mention of ZIKV or ZIKV vaccines, EP '585 lacks written description support for the ZIKV vaccines of claims 1−12, 15, and 21−25. *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) (possession is shown by "describing the invention, … not that which makes it obvious."). Similarly, EP '585 does not enable claims 1−12, 15, and 21−25 because it provides zero guidance or working examples

regarding ZIKV vaccines. EP '585 fails to teach POSAs how to make and use even a single ZIKV vaccine, and it certainly does not enable the full scope of the challenged claims. *See, e.g.*, §VIII.E.1; EX1002, ¶¶120−121.

As such, claims 1−12, 15, and 21−25 cannot claim a priority date before **March 18, 2016**, the next date in the alleged priority chain. *Lockwood*, 107 F.3d at 1571−72.

B. Ground 1 Art: Zika Pipeline, Srivastava, the H/PF/2013 Sequence, Baronti, and Thomas render claims 1−11, 15, and 21−25 obvious.

The Ground 1 Art is prior art under §102(a)(1), because each reference became publicly available to POSAs exercising reasonable diligence before March 18, 2016:

Ground 1 Art	***Public Availability Date***
Zika Pipeline	by 3/11/2016 (EX1097, ¶¶30−41)
Srivastava	9/12/2001 (*Id.*, ¶¶50−71)
Baronti	6/5/2014 (*Id.*, ¶¶18−29)
H/PF/2013 Sequence	6/13/2014 (EX1002, ¶123)
Thomas	12/3/2012 (EX1097, ¶¶72−93)

1. Claim 1 recites obvious vaccines.

a. POSAs would have had a reason to make an inactivated ZIKV vaccine using known flavivirus vaccine technology.

Before March 18, 2016, ZIKV outbreaks caused serious neurological disorders, fetal malformations, and even death. EX1033, 1−2, 6, 10; EX1002, ¶140. Zika Pipeline declared ZIKV "a serious risk, necessitating further action as soon as possible" and stated, "WHO ha[d] initiated an emergency research and development plan" to respond to ZIKV. EX1143, 2; EX1002, ¶141. Zika Pipeline disclosed at least eighteen ZIKV vaccine programs, "[m]ost [of which were] building on existing flavivirus vaccine technology and know-how." EX1143, 5; EX1002, ¶141.

The urgent need for a ZIKV vaccine was also generally known in the art, e.g., in *Time* magazine ("Sifferlin"), Dr. Fauci "'made it clear that'" the U.S. "'want[ed] to put a full-court press'" and "'all hands on deck for Zika'" to develop a ZIKV vaccine. EX1162, 1; EX1002, ¶142. Similarly, the WHO had declared ZIKV a "public health emergency of international concern." EX1025, 1; EX1002, ¶142.

POSAs would thus have had a reason to develop a ZIKV vaccine to address the health threat ZIKV posed. EX1002, ¶143. Zika Pipeline directed POSAs to use known flavivirus vaccine technologies to make a ZIKV vaccine:

> It is assumed that a ZIKV vaccine *can be developed building on the same technologies* that have been *successfully used* to develop human flavivirus vaccines (Yellow Fever, Tick-Borne Encephalitis, Japanese Encephalitis, Dengue).

EX1143, 5; EX1002, ¶144. Srivastava disclosed one such known flavivirus vaccine technology, and POSAs would have been motivated to look to Srivastava based on the direction of Zika Pipeline. EX1002, ¶¶144−152.

POSAs would have also known from Srivastava and general knowledge in the art that flavivirus vaccines capable of stimulating high NAb titers (i.e., in the hundreds to thousands) had been successfully developed using known flavivirus strains. EX1002, ¶¶145−146; *see also* §V.D. POSAs would have been motivated to use known technologies for making purified inactivated flavivirus vaccines, because such vaccines were expected to be safer for pregnant women, which would have been of high importance due to the link between ZIKV infection and fetal disorders and death. EX1036, 3828; EX1037, 162; EX1002, ¶148.

Srivastava discloses that its JE-PIV was immunogenic and protective, stimulating NAb titers of 1,280−7,781 in 100% of mice after two doses. EX1163, Table 3; EX1002, ¶¶146, 149. JE-PIV later became IXIARO®, which Tauber in 2007 showed stimulated a NAb GMT of 244, with titers ≥81−160 in ~90% of subjects and as high as 19,783. EX1049, 1850; EX1007, 1; EX1061, 10; EX1064,

3; EX1001, 8:41−44; EX1041, 1329 (discussing IXIARO and citing Tauber (EX1049) as reference 38); EX1002, ¶147. Vaccines against DENV stimulated NAb titers of 350−2,500 in 100% of mice; 100−1,230 in 82% of monkeys; 139−2,430 in 83% of humans; and 107−1,868 in 70% of humans. EX1028, Tables 4, 5; EX1021, Table 6; EX1024, 456, Table 3; EX1002, ¶147.

Thus, POSAs making a ZIKV vaccine would have had a reason to follow Srivastava's inactivated vaccine technology, because it resulted in a vaccine ("JE-PIV") that was "more immunogenic and as effective as preventing encephalitis in mice" when compared to the then-existing FDA-approved JEV vaccine ("JE-Vax"). EX1163, 4557; EX1002, ¶149. POSAs would have understood good immunogenicity to be important because it would be indicative of the ability of a vaccine to stimulate high NAb titers. EX1002, ¶150. POSAs would have understood high NAb titers generally provide better protection and could counteract the waning of NAbs titers, which was generally known in the art. EX1045, 1; EX1042, 707−708; EX1002, ¶150; *see also* §V.D.

Consistent with Zika Pipeline's recommendation to use known, successful flavivirus vaccine technologies when making a ZIKV vaccine, Srivastava had done the same by following a technology used to make an inactivated DENV-2 vaccine. EX1163, 4558; EX1002, ¶¶151−152. Thus, POSAs would have reasonably

expected that Srivastava's technology for JE-PIV could be applied to ZIKV by swapping in ZIKV for JEV. EX1002, ¶152.

b. Srivastava discloses a safe, effective, and economical inactivated JEV vaccine.

Srivastava obtained active JEV virions[7] grown on Vero cells, completely formalin-inactivated the virions, purified them, and formulated them in 0.1% aluminum hydroxide ($Al(OH)_3$) and 0.01% thimerosal in PBS. EX1163, 4559−4561; EX1002, ¶¶153−154. Srivastava's "manufacturing process was efficient in generating a high yield of virus, essentially free of contaminating host cell proteins and nucleic acids." EX1163, 4557; EX1002, ¶154.

Srivastava's JE-PIV stimulated high NAb titers: 1,280−7,781 in 100% of mice after two 800-ng doses, with a GMT of 3,842. EX1163, Table 3; EX1002, ¶¶155−157. And JE-PIV had protective efficacy in mice. EX1163, 4557, 4563; EX1002, ¶157. Srivastava concluded, "the processes and materials used for production of the new JE-PIV will result in a product that is safe, effective and economical" and its "manufacturing methods are sufficiently robust, demonstrating good scalability, efficiency, and product yield." EX1163, 4564; EX1002, ¶158.

[7] Viruses exist outside of host cells as viral particles, i.e., virions. EX1095, 168, FIG. 2; EX1002, ¶61.

Srivastava identified advantages of its method: e.g., the ability to grow high virion titers, harvest a large production lot, increase safety due to lack of serum products, and purify virions using efficient, inexpensive methods. EX1163, 4564; EX1002, ¶158. POSAs would have understood that the identified advantages would have been applicable to ZIKV because they (i) flow from Srivastava's use of Vero cells, on which ZIKV also replicates, to propagate virions; and (ii) are independent from Srivastava's use of JEV, particularly because the technology was originally developed for DENV vaccine. EX1163, 4458; EX1002, ¶158.

c. POSAs would have had a reason to use Baronti's H/PF/2013 ZIKV strain.

POSAs would have substituted Baronti's H/PF/2013 ZIKV for JEV in Srivastava's successful technology, because Zika Pipeline suggested implementing technologies that had already been successfully used to develop other flavivirus vaccines. EX1143, 5; EX1002, ¶160. POSAs would have found Zika Pipeline's suggestion to be consistent with the general knowledge in the art: e.g., *Time* magazine reported Dr. Fauci's view that "[w]hen you are developing … vaccines … for viruses that are similar, you can *translate the technologies that you've developed to hasten the end game goal* of what you want for a virus like Zika." EX1162, 1; EX1002, ¶160. Srivastava's JEV vaccine (which became IXIARO, as the '681 patent acknowledges) was based on technology previously used to

produce a DENV-2 vaccine. EX1163, 4558; EX1007, 1; EX1061, 10; EX1064, 3; EX1001, 8:41−44; EX1002, ¶160.

POSAs would have been motivated to develop an inactivated ZIKV vaccine because it could be more safely administered, e.g., to pregnant women concerned about fetal abnormalities. EX1036, 3828; EX1037, 162; EX1002, ¶161. POSAs would have followed Srivastava's technology because Srivastava discloses it to be a safe, effective, and economical technology that had been applied to both JEV and DENV and had advantages flowing from its use of Vero cells. EX1163, 4564; EX1002, ¶162. And Srivastava's technology stimulated high NAb titers when dosed twice. EX1163, Table 3; EX1002, ¶162. POSAs, therefore, would have substituted a known ZIKV strain for JEV in Srivastava's technology. EX1002, ¶162.

Baronti discloses the H/PF/2013 strain of ZIKV isolated from a 2013 French Polynesia outbreak subject. EX1160, 1; EX1002, ¶163. Baronti harvested H/PF/2013 ZIKV virions from infected Vero cells, extracted the strain's RNA, and sequenced the genome. EX1001, 1; EX1002, ¶164. Baronti deposited the corresponding DNA sequence into GenBank as accession no. KJ776791 ("the H/PF/2013 Sequence"). EX1160, 1; EX1002, ¶164. The H/PF/2013 Sequence "includ[es] the virus complete open reading frame (ORF) sequence." EX1160, 1; EX1002, ¶164.

POSAs would have been motivated to use Baronti's H/PF/2013 ZIKV to make a ZIKV vaccine with Srivastava's technology because H/PF/2013 was a known, infectious ZIKV strain that had been passaged in Vero cells, like Srivastava's JEV (EX1160, 1), and H/PF/2013 was associated with "CNS malformations in children" (EX1033, 7−8). EX1002, ¶165. H/PF/2013 was "the closest strain to the one that emerged in Brazil," and it had 99.9% nucleotide and amino acid sequence identities with isolates circulating in Asia, the Pacific islands, and Americas. EX1058, 1887; EX1160, 1; EX1138, 1; EX1002, ¶165.

d. Baronti and the H/PF/2013 Sequence disclose a ZIKV strain having an RNA genome that is ≥80% identical to SEQ ID NO: 72.

Baronti discloses that the H/PF/2013 Sequence is 10,617 nucleotides long; and it has 99% identity to SEQ ID NO: 72 when aligned using BLAST, which the '681 patent identifies as a suitable alignment program (*see* §VII). EX1160, 1; EX1019, 2−5; EX1020, 3−11; EX1002, ¶166.[8] Thus, POSAs making a vaccine

[8] The H/PF/2013 Sequence is 100% identical to SEQ ID NO: 72 when compared using just the overlapping regions of the two sequences. EX1002, ¶166. In August 2016, Baronti updated its GenBank entry for H/PF/2013 and reported a sequence of 10,807 nucleotides long. EX1084, 1. Such an update is of no moment,

with H/PF/2013 would have arrived at a ZIKV with a genome having ≥80% identity, specifically, 99% identity, to SEQ ID NO: 72. EX1002, ¶167.

e. POSAs would have made a ZIKV vaccine capable of stimulating a MN_{50} of >15 in ≥70% of vaccinated subjects.

POSAs would have sought to make a ZIKV vaccine that stimulated a MN_{50} of >15 in ≥70% of vaccinated subjects because (1) higher titers generally led to better protection over longer time periods; and (2) high titers stimulated in a high percentage of subjects would have provided broader coverage in the relevant population. EX1002, ¶¶169, 172. POSAs would have known that flavivirus vaccines, such as Srivastava's JE-PIV, could stimulate high NAb titers after two doses. EX1002, ¶169; *see* §V.D. POSAs would also have had general knowledge from the art that protection is generally achieved when a subject's NAb titer is "relatively high" at the time of challenge with the target virus. EX1042, 708−709; EX1045, 1; EX1002, ¶169. POSAs, therefore, would have had a reason to make a ZIKV vaccine that would stimulate high MN_{50} titers, e.g., > 1000 when following Srivastava's technology, because it would have been reasonably expected to provide protection over a longer time period. EX1002, ¶¶169, 175−179.

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because Baronti simply characterizes an inherent property of the H/PF/2013 strain, and such a sequence still has >99% identity to SEQ ID NO: 72. EX1098, 3.

POSAs making a ZIKV vaccine would have been motivated to employ Thomas's MN_{50} assay when assessing NAb titers, because it was a known, rapid 4-day assay for assessing flavivirus vaccines. EX1002, ¶170. Thomas's assay has a "precision … estimated to range from 39% to 59%." EX1164, 86; EX1002, ¶170. POSAs thus would have used a MN_{50} of >15 as the baseline titer to be assured of seroconversion, i.e., NAb production, post-vaccination. EX1002, ¶¶170−171. This is because a 59% variability rate applied to the minimum NAb titer of 10 (which is just above Thomas's assay's limit of detection to assess seroconversion) would be a titer of 15.9. EX1164, 86; EX1047, 5209−5210; EX1041, 1327, 1330, 1334; EX1002, ¶170. Thus, a titer of >15 is just above the limit of detection, given the variability. EX1002, ¶¶170−171. *Id.*

POSAs would have sought to make a vaccine that stimulated high NAb titers in ≥70% of subjects to obtain protection in as much of the vaccinated population as possible. *See, e.g.*, EX1047, 5210 (recommending that new JEV vaccines achieve ≥75% seroconversion); EX1002, ¶¶131, 172. IXIARO reflects this practice by using a *two-dose* regimen, which seroconverted "essentially 100%" of subjects; high-dosage and normal-dosage *single-dose* regimens resulted in 60% and 20% seroconversion, respectively. EX1059, 2192; EX1002, ¶172.

f. POSAs would have used a MN assay.

POSAs would have known from the general knowledge in the art that

$PRNT_{50}$ assays were "labor intensive and therefore not readily amenable to high throughput, making it difficult to use for large-scale surveillance and vaccine trials." *See* §V.C, EX1043, 126; EX1164, 86 (stating PRNT has "limitations, such as its low throughput, unacceptable labor-intensive nature, and high degree of interassay variability"); EX1002, ¶174. POSAs thus would have used a MN assay to measure NAb titers, because MN assays provided high throughput and less interassay variability. EX1002, ¶174.

Thomas discloses a MN_{50} assay that provides higher throughput, less interassay variability, and sensitivity in detecting NAb titers compared to PRNT assays. EX1164, 86; EX1002, ¶174. POSAs making a ZIKV vaccine thus would have had a reason to use Thomas's MN_{50} assay to determine the resulting vaccine's ability to stimulate NAb titers in vaccinated subjects because Thomas's assay would have had the foregoing benefits and it had been used to asses NAb titers for a flavivirus vaccine. EX1002, ¶174.

g. POSAs would have had a reasonable expectation of success in arriving at the claimed ZIKV vaccine.

POSAs would have had a reasonable expectation of success in arriving at a purified inactivated ZIKV vaccine comprising the H/PF/2013 ZIKV strain, which would comprise a sequence in its RNA genome corresponding to the H/PF/2013 Sequence that is 99% identical to SEQ ID NO: 72, and capable of stimulating a

MN_{50} titer of >15 in ≥70% of vaccinated subjects after two doses when combining the Ground 1 Art. EX1002, ¶¶175−182.

First, Srivastava provides successful technology for making an immunogenic and protective inactivated vaccine with a known JEV strain, a flavivirus like ZIKV. *See* §VIII.B.1.b; EX1002, ¶176. Srivastava's JE-PIV stimulated NAb titers of 1,280−7,781 and a GMT of 3,842 after two doses. EX1163, 4562, Table 3; EX1002, ¶176. Srivastava's technology had been also used to make a DENV vaccine that stimulated high NAb titers after 2−3 doses. EX1163, 4558 (citing EX1028); EX1028, 1179; EX1002, ¶176. Baronti discloses a known ZIKV strain, H/PF/2013, which POSAs would have substituted for JEV in Srivastava's technology, for the reasons discussed above (§§VIII.B.1.b−VIII.B.1.c). EX1160, 1; EX1002, ¶176. And Thomas discloses a MN_{50} assay that detected NAbs stimulated by a flavivirus vaccine, and which provides high-throughput and less inter-assay variability. EX1164, 86; EX1002, ¶176.

Second, POSAs would have been aware of the general knowledge in the art that disclosed multiple other inactivated flavivirus vaccines capable of stimulating NAb titers in the hundreds to thousands in ≥70% of subjects after 2−3 doses. EX1002, ¶177. For example, Tauber reported that IXIARO, which JE-PIV became, stimulated NAb titers ≥81−160 in ~90% of subjects, reaching a maximum titer of 19,783, and a GMT of 244 after two doses. EX1049, 1850; EX1002, ¶177. Putnak

reported a DENV-2 vaccine that stimulated NAb titers of 350−2,500 in 100% of mice and 100−1,230 in 82% of monkeys after two doses, as well as 100−1,680 in 88% of monkeys after a third dose. EX1028, Table 4; EX1002, ¶177. Watanaveeradej reported a DENV vaccine that stimulated titers of 139−2,430 in 83% of subjects after two doses when assessed for NAbs to each serotype. EX1021, Table 6; EX1002, ¶177. Martinez's DENV-1 vaccine stimulated titers of 107−1,868 in 70% of subjects administered two 5-μg doses. EX1024, 456, Table 3; EX1002, ¶177.

Because Srivastava's JE-PIV and other flavivirus vaccines could stimulate high NAb titers in ≥70% of subjects after at least two doses, POSAs would have reasonably expected to successfully obtain a ZIKV vaccine made using Srivastava's technology and comprising the H/PF/2013 strain, that would stimulate a MN_{50} >15 in ≥70% of subjects, including mice and humans, after two doses. EX1002, ¶178. POSAs, moreover, would have determined the vaccine's ability to stimulate a NAb titer using a MN_{50} assay, such as Thomas's. *Id*.

Third, Zika Pipeline stated that ZIKV vaccines could be made "building on the same technologies that have been successfully used to develop human flavivirus vaccines." EX1143, 5; EX1002, ¶179. POSAs would further have had a reasonable expectation of success from the general knowledge in the art, which also stated that it was expected that a ZIKV vaccine could be developed

successfully based on other flavivirus vaccine technologies. EX1002, ¶179. Sifferlin's article in *Time* reflects Dr. Fauci's statement that "you can translate the technologies that you've developed [for other flavivirus vaccines] to hasten the end game goal of what you want for a virus like Zika." EX1162, 1; EX1002, ¶179. The art also reported that "[v]accine pioneer Stanley Plotkin" said he did not "see any technical issues" in making a ZIKV vaccine, and the field expected that there was "a good shot at success." EX1052, 543; EX1002, ¶179.

POSAs also would have a reasonably expected that an inactivated ZIKV vaccine comprising the H/PF/2013 strain and made following Srivastava's technology would have some degree of efficacy. EX1002, ¶180. A POSA would have reasonably expected a ZIKV vaccine made following Srivastava's technology to have efficacy, because a POSA would have expected it to stimulate MN_{50} NAb titers >15, and titers >10 were deemed protective for vaccines against the related JEV and YFV viruses. EX1047, 5209−5210; EX1002, ¶180. Also, Srivastava's technology for JE-PIV resulted in a vaccine that was efficacious and stimulated NAb titers >1000. EX1163, 4557, 4563, Table 3; EX1002, ¶180. POSAs, thus, would have reasonably expected some degree of efficacy for a vaccine made using the closely related ZIKV in Srivastava's technology. EX1002, ¶180.

In sum, POSAs would have had a reasonable expectation of success in combining the teachings of the Ground 1 Art to arrive at the claimed ZIKV

vaccine. Consequently, claim 1 would have been *prima facie* obvious. *Id.*, ¶¶24−39, 125−182.

2. Claims 2, 3, 24 and 25 encompass obvious vaccines with obvious MN_{50} values.

As discussed for claim 1, POSAs would have had a reason to combine the Ground 1 Art with a reasonable expectation of success.

POSAs also would have had a reason to make a ZIKV vaccine that stimulated an MN_{50} of >15 in ≥75% of subjects (**claim 3**), because the vaccine would have provided protection to more of the vaccinated population. *See* §VIII.B.1.e; EX1002, ¶185. POSAs would have had a reasonable expectation of success in making a vaccine that stimulates a MN_{50} of >15 in ≥75% of subjects (**claim 3**) for the same reasons outlined for ≥70% of subjects for claim 1. *See* §VIII.B.1.g; EX1002, ¶186.

POSAs would have also sought to target a MN_{50} of >90 (**claims 2, 24, and 25**), e.g., >1000, because high titers generally afford better protection for longer periods. *See* §VIII.B.1.e; EX1002, ¶187. And POSAs would have had a reasonable expectation of success in so doing because Srivastava discloses that its JE-PIV stimulated titers in the range of 1,280−7,781 in 100% of mice. EX1163, Table 3; EX1002, ¶188. IXIARO stimulated titers >161 in ≥75% of subjects. EX1049, 1851; EX1002, ¶188. And other flavivirus vaccines stimulated high NAb titers in ≥75% of subjects. *See* §V.D.

3. Claims 4 and 21−23 encompass obvious vaccines with obvious sequences.

Claim 4 recites that the ZIKV comprises an E protein having, *inter alia*, one of 56 amino acid sequences. EX1001, 445:48−53. Claims 21−23 recite that the RNA genome is a variant having ≥90%, ≥95%, or ≥99% identity to SEQ ID NO: 72, respectively. *Id*., 448:10−18.

As with claim 1, POSAs would have had a reason to combine the Ground 1 Art and arrive at a ZIKV vaccine comprising the H/PF/2013 strain, with a reasonable expectation of success. The H/PF/2013 genome comprises a sequence that is 99% identical to SEQ ID NO: 72, meeting the limitations of **claims 21−23**. EX1002, ¶194; *see* §VIII.B.1.

H/PF/2013 encodes a polyprotein that is 100% identical to SEQ ID NO: 73, which is encoded by SEQ ID NO: 72. EX1001, 121−124, 129:46−49; EX1071, 3−6; EX1002, ¶192. The E protein portion of SEQ ID NO: 73 is the same as SEQ ID NO: 47—one of the E proteins recited in **claim 4**. EX1001, 111−112, 129:52−54; EX1009 (alignment of SEQ ID NOs: 73 and 47); EX1002, ¶192. Thus, POSAs would have arrived at the vaccine of claim 4 with a reasonable expectation of success for the same reasons as claim 1; moreover, the E protein is a surface protein that would have been expected to be immunogenic and stimulate high NAb titers. EX1080, 2337; EX1048, 25−26; EX1002, ¶193.

As such, in addition to the reasons outlined for claim 1, claims 4 and 21−23 would have been *prima facie* obvious.

4. Claims 5−11 and 15 encompass obvious vaccines made by obvious methods.

Claims 5−11 and 15 recite obvious viral inactivation methods, or a pharmaceutically acceptable excipient. As discussed, POSAs would have combined the Ground 1 Art and arrived at claim 1's vaccine with a reasonable expectation of success by applying Srivastava's vaccine technology to the H/PF/2013 ZIKV strain. *See* §VIII.B.1. The Ground 1 Art also would have rendered obvious claims 5−11 and 15. Srivastava chemically inactivated (**claim 5**) its JEV by incubating the JEV virions in formalin (i.e., aqueous formaldehyde; EX1087, 695) (**claim 7**), at 22 °C (**claim 9**) for 10 days (**claim 8**), which was longer than required to completely inactivate the JEV as measured by plaque assay, as Srivastava reported complete inactivation occurred at day 6 as measured by plaque assay (**claim 6**). EX1163, 4559, 4561, Table 2; EX1002, ¶198. Srivastava also formulated the inactivated JEV virions with $Al(OH)_3$ (an adjuvant that is an aluminum salt) (**claims 10** and **11**), and thimerosal in PBS (pharmaceutical acceptable excipients) (**claim 15**). EX1163, 4560; EX1022, 149; EX1118, 294−295; EX1002, ¶¶204−205.

POSAs would have had a reason to replicate Srivastava's inactivation methodology because it completely inactivated JEV as measured by plaque assay.

EX1002, ¶199. POSAs would have reasonably expected Srivastava's inactivation process to also completely inactivate ZIKV as measured by plaque assay given its close relationship to JEV. *Id.* Formalin inactivation of virions, including flaviviruses, was also well-known in the art. EX1087, 695, 698; EX1002, ¶198. POSAs additionally would have sought to inactivate ZIKV for longer than required to completely inactivate the ZIKV as measured by plaque assay because it would have provided for an additional assurance of safety, e.g., for pregnant individuals. EX1002, ¶199.

POSAs would have also followed Srivastava's use of: (1) $Al(OH)_3$ because it was a known vaccine adjuvant for increasing immunogenicity; (2) thimerosal, a common vaccine additive for preventing microbial contamination, and (3) PBS, a well-known buffer for maintaining pH and stability. EX1083, 1:16−17; EX1022, 149; EX1118, 294−295; EX1002, ¶¶204−205. POSAs would have also followed Srivastava's technology because it provided a highly immunogenic and effective vaccine. EX1163, 4560, Table 3; EX1002, ¶¶199, 206.

POSAs would have had a reasonable expectation of success because Srivastava's technology worked for JEV and DENV, and the art suggested that technologies successfully used for other flavivirus vaccines would likely be successfully applied to ZIKV. EX1002, ¶¶200, 206; *see* §VIII.B.1.b.

C. Ground 2 Art: Zika Pipeline, Srivastava, Baronti, the H/PF/2013 Sequence, Thomas, and Möhlen render claim 12 obvious.

Claim 12 has an effective filing date no earlier than March 18, 2016. *See* §VIII.A. Möhlen became publically available in 2013 and is prior art under §102(a)(1). Claim 12 depends from claim 11 and recites that the adjuvant is an aluminum salt with <1.25 ppb copper based on a final pharmaceutical composition comprising the ZIKV. EX1001, 446:38−44.

As discussed for claim 11, POSAs would have arrived at using $Al(OH)_3$ in a ZIKV vaccine with a reasonable expectation of success in view of the Ground 1 Art. POSAs would have combined Möhlen with the Ground 1 Art because Möhlen discloses that heavy metals, e.g., copper, present in aluminum salt adjuvants can lead to oxidative degradation of viral antigens in formaldehyde-inactivated virus vaccines. EX1083, 5:1−5, 11:14−22, 16:1−11; EX1002, ¶¶210−211. POSAs would have also known that metal ions, e.g., copper, can cause degradation of biopharmaceuticals during storage. EX1077, 1173, 1177; EX1002, ¶210.

Möhlen discloses that a JEV vaccine comprising <3 ppb copper based on the weight of the composition was more stable than vaccines comprising >3 ppb copper. EX1083, 33:24−30, Tables 12−15; EX1002, ¶216. It was particularly preferred that the vaccine comprises copper at a level below the limit of detection, including being <1.25 ppb based on the weight of the composition. EX1083, 27:27−28:2; EX1002, ¶216. Möhlen notes, "[m]ethods for measuring the level of

one or more heavy metals in an aqueous solution are known in the art." EX1083, 28:18−25; EX1002, ¶217.

Srivastava teaches neutralizing formaldehyde used to inactivate virions with sodium bisulfite, which Möhlen teaches can then react with copper, degrading the virions. EX1163, 4559; EX1083, 11:14−22, 16:1−11; EX1002, ¶218. Accordingly, POSAs making an inactivated ZIKV vaccine following Srivastava's technology would have had a reason to ensure that the vaccine formulation contains $Al(OH)_3$ with any copper below the limit of detection (e.g., <1.25 ppb based on the weight of the composition), for quality assurance reasons. EX1002, ¶218. By doing so, POSAs would have reduced the chance that ZIKV antigen degradation would occur during long-term storage due to any residual bisulfite. *Id*. POSAs, further, would have known from Möhlen that well-known copper measurement techniques could be used to assess the composition's level of copper. EX1083, 28:18−25; EX1002, ¶219.

POSAs would, therefore, have had a reasonable expectation of success in making a ZIKV vaccine having <1.25 ppb copper based on a final vaccine composition. EX1002, ¶220. This is because $Al(OH)_3$ was a commonly used adjuvant and Möhlen discloses techniques to measure copper levels. EX1083, 28:18−25; EX1002, ¶220. POSAs would simply have changed the lot of $Al(OH)_3$ used if copper levels were too high. EX1002, ¶220. Möhlen, in fact, discloses

assaying lots of $Al(OH)_3$ for heavy metals, including copper, and finding lots with high or low amounts of heavy metals. EX1083, 26:7−13; EX1002, ¶220.

As such, in addition to the reasons outlined for claims 1 and 11, claim 12 would have been *prima facie* obvious.

D. No objective indicia of nonobviousness.

Here, a strong *prima facie* case of obviousness exists, and any potentially relevant objective indicia are insufficient to outweigh this strong case in view of both the Ground 1 and 2 Art. *Leapfrog Enterprises, Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007). Petitioner requests an opportunity to rebut any objective indicia arguments upon which Valneva may rely. *Amneal Pharm. LLC v. Supernus Pharm., Inc.*, IPR2013-00368, Paper 8, at 12-13 (P.T.A.B. Dec. 17, 2013).

1. No unexpectedly superior results.

The ’681 patent alleges that its data “indicate that immunogenicity was unexpectedly higher than the recently reported inactivated Zika virus vaccine candidate” of Larocca (EX1006). EX1001, 2:64−67. This is false.

First, Valneva seeks to compare (1) an MN_{50} of 90 obtained with a single working example of a vaccine that was dosed once with (2) Larocca’s MN_{50} of 15 obtained with a ZIKV vaccine dosed once. *Id.*, 136:22−27. But Valneva failed to perform a proper head-to-head comparison of the two vaccines because Valneva

did not test them in the same MN assay, in the same lab, or using a validated assay. *See, e.g.*, EX1047, 5209; EX1002, ¶226. Differences in laboratory conditions can lead to differences in results, rendering the data insufficient to be informative for such a comparison. EX1044, 963; EX1047, 5209; EX1002, ¶226.

Moreover, a titer of 15 compared to 90 from a single dose is merely a minor difference in degree, whereas unexpected results probative of nonobviousness are those that are "different in kind and not merely in degree." EX1002, ¶227; *Galderma Labs. L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013).

Second, consistent with prior art flavivirus vaccines that required two doses to achieve high NAb titers (*see* §V.D), two doses of Larocca's ZIKV vaccine stimulated a mean $\log_{10}$ MN_{50} titer of 3.66, i.e., 4,570, and titers in the thousands (with a maximum $\log_{10}$ MN_{50} titer of 3.86, i.e., 7,244) in 100% of monkeys.[9] EX1062, 1129, FIG. 1B. Thus, Larocca's vaccine stimulates titers much higher than 15 (and 90), and the patent's unexpected results assertion is incorrect. EX1002, ¶¶228−229.

Third, Valneva's results are not reasonably commensurate with the scope of

[9] Post-filing date evidence can demonstrate inherent properties of a product. *Monsanto Tech. LLC v. DuPont De Nemours & Co.*, 878 F.3d 1336, 1345 (Fed. Cir. 2018).

the claims. *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983). The challenged claims encompass millions of ZIKV vaccines (*see* §VIII.E.1.a.ii.b)), but Valneva presents data for only a single vaccine with no evidence that it represents the full scope of claimed variants. EX1001, 136:22−27; EX1002, ¶231.

Unexpected results must be compared to the closest prior art. Larocca is not prior art relative to a March 18, 2016 or December 23, 2015 filing date; Larocca's data was not added into the disclosures of the '681 patent's priority chain until filing of the '664 PCT in December 2016. *In re Baxter Travenol Lab'y*, 952 F.2d 388, 392 (Fed. Cir. 1991). Srivastava and other prior art disclosed flavivirus vaccines with NAb titers, including MN_{50} titers, >90 in ≥75% of subjects. *See* §V.D; EX1002, ¶230. Valneva's results are not unexpectedly superior to such prior art results. EX1002, ¶230.

2. Near-simultaneous invention.

"Simultaneous invention may serve as evidence of obviousness when considered in light of all of the circumstances," and it may "evidence [] the level of skill in the art" and "constitute[] objective evidence that [POSAs] understood the problem and a solution to that problem." *Regents of Univ. of Cali. v. Broad Inst., Inc.*, 903 F.3d 1286, 1295 (Fed. Cir. 2018).

Larocca's ZIKV vaccine comprises ZIKV having a genome having 98% identity to SEQ ID NO: 72 (and 99% identity when compared using just the

regions where the two sequences completely overlap), an E protein corresponding to SEQ ID NO: 40 (recited in claim 4), and $Al(OH)_3$ adjuvant. EX1006, 476, 479; EX1075; EX1076; EX1002 ¶236. Abbink reported that Larocca's vaccine stimulated a median MN_{50} of 4,570, and titers in the thousands (with a maximum MN_{50} of 7,244) in 100% of monkeys receiving two doses. EX1062, 1129, FIG. 1B; EX1002, ¶238.

Dr. Barouch, the senior author on Larocca and Abbink, explains that the data in Larocca were submitted to the publisher by May 30, 2016, within five months of their beginning work on it. EX1006, 477; EX1002, ¶235. He recalls that Abbink's data were submitted on or around July 21, 2016, and published on August 4, 2016, showing their development of a ZIKV vaccine within at most 2.5 months of Valneva—"a very short period of time in [the] field," evidencing near-simultaneous invention. EX1002, ¶¶235, 237.

3. No long-felt, but unmet, need or failure of others

A showing of a long-felt but unmet need requires that the need must have been a persistent one that was recognized by those of ordinary skill in the art. There is no evidence that there was a need that persisted for many years and went unmet. *Ecolochem, Inc. v. S. Cali. Edison Co.*, 227 F.3d 1361, 1377 (Fed. Cir. 2000). Once the field put on a "full-court press," Larocca, for example, obtained a vaccine within just a few months. EX1002, ¶240; EX1162, 1.

There also is no evidence of failure of others. Abbink showed that Larocca's ZIKV vaccine stimulated MN_{50} titers in the thousands in 100% of monkeys after two doses. *Id.*, ¶242. As Dr. Barouch explains, the lack of any approved ZIKV today is not the result of any failure, but is instead due to the reduced demand because ZIKV transmissions declined. EX1099, 2582; EX1002, ¶242.

E. Ground 3: WO '225 anticipates Claims 1−15 and 21−25.

Because, as discussed below in §VIII.E.1., claims 1−15 and 21−25 cannot claim priority to the December 23, 2016 filing date of the '664 PCT, they cannot be given a filing date before the March 10, 2020 actual filing date of the '681 patent. WO '225 is the publication of the '664 PCT; it published June 29, 2017, contains substantially the same disclosure as the '681 patent, and is anticipatory prior art under §102(a)(1). *See* §VIII.E.2.

1. Claims 1−15 and 21−25 lack priority to the '664 PCT

a. The '664 PCT does not provide written description support for the full scope of the challenged claims.

"To fulfill the written description requirement, a patent owner must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, [as demonstrated] by disclosure in the specification of the patent." *Idenix*, 941 F.3d at 1163. "[F]or a claim to a genus," such as the challenged claims here, the "patentee must disclose 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." *Amgen Inc. v. Sanofi, Aventisub LLC*, 872 F.3d 1367, 1373 (Fed. Cir. 2017).

Indeed, "[f]or genus claims using functional language, … the written description 'must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus.'" *Juno Therapeutics, Inc. v. Kite Pharma*, 10 F.4th 1330, 1335 (Fed. Cir. 2021). This requires that the specification discloses "a way to distinguish those [vaccine candidates] capable of" meeting a claim's functional requirements "from those incapable" of doing so. *Id.*, 1339. And "if the disclosed species only abide in a corner of the genus, one has not described the genus sufficiently to show that the inventor invented, or had possession of, the genus." *AbbVie*, 759 F.3d at 1300.

Factors to be considered when evaluating genus claims include "the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue." *Id.*, 1299. Another factor is "how large a genus is involved and what species of the genus are described in the patent." *Id.* The '664 PCT fails to support the full scope of the issued claims.

i. ZIKV must be able to replicate in production cells to make the claimed vaccines.

POSAs would have understood that, to make the claimed vaccines in December 2016, ZIKV must be able to replicate in the cell lines used for producing the ZIKV for the vaccine. EX1041, 1328−1329; EX1178, 1336; EX1002, ¶252. Cell culture-based technologies for making flavivirus vaccines, and cell lines for virion propagation, were known in the art. EX1139, Table 2; EX1028; EX1024; EX1163; EX1051; EX1140; EX1036; EX1141; EX1060; EX1002, ¶¶252−253. The ’681 patent likewise points to cell-culture technology (e.g., Vero cells) to practice the alleged invention. EX1001, 7:1−11; EX1002, ¶254.

POSAs would have known that cell-culture based viral vaccine production generally includes: (1) introducing viral genomes into production cells by infection or transfection; (2) allowing the virus to replicate in the cells and infect neighboring cells; (3) harvesting the virions; and (4) downstream processing (e.g., virion inactivation and purification, final product formulation). EX1163, 4558−4560; EX1002, ¶255. This process requires that the virus replicate in the production cells. EX1163, 4559; EX1028, 1177; EX1002, ¶255; *see* §V.B.

POSAs would have understood that ZIKV’s ability to replicate in a cell, and thus be made into a vaccine, is a function of a combination of, e.g., proper virion assembly, maturation, host cell entry, cytosolic genome release, and viral protein production. EX1048, 23−28; EX1002, ¶256. But as of December 23, 2016,

"significant gaps of knowledge in the assembly and maturation processes" of ZIKV existed, and those processes were "largely a black box." EX1091, 2; EX1092, 378−380; EX1002, ¶256. Even in 2020, the field still knew "little about the viral and host factors involved in the structural transition from immature to mature" virions. EX1091, 2; EX1092, 378; EX1002, ¶256.

Much of today's knowledge about ZIKV structure and function accumulated only *after* December 23, 2016. EX1002, ¶256. For instance, well after 2016, the field identified detailed aspects of how the ZIKV NS2A protein functions as "a central hub in the [virion] packaging process." EX1092, 378; EX1002, ¶257. In 2019, Zhang identified single amino acid NS2A mutants that were "completely defective in viral RNA synthesis," "impair[ed] [in] both viral RNA synthesis and virion production," and "block[ed] [in] virion assembly." EX1056, 591−592; EX1002, ¶257. Zhang's Figure 1B, reproduced below, identifies the phenotypes of various NS2A mutations:

Class	NS2A Mutations	Phenotypes
I	D4A, E22A, K31A, G47A, D53A, E67A, H76A, E122A, R146A, D148A, R163A, K186A, K188A, D210A	Mutants do not or weakly affect viral production
II	K56A , F83A, K84A, R86A, P87A, R96A, R102A, D124A, R207A	Mutants dramatically reduce viral production
III	G12A, N130A	Mutants abolish viral RNA synthesis
IV	D7A, R140A, R222A	Mutants abolish virus production by affecting RNA synthesis and viron assembly/release
V	K25A/K26A/R27A, G71A, D73A, E103A, R171A, K192A, K193A	Mutants abolish virion assembly

EX1056, FIG. 1B; EX1002, ¶257. Such ZIKV mutants would have had a compromised ability to replicate, but were not known by December 23, 2016. EX1002, ¶257.

In 2020, DiNunno disclosed single amino acid mutations in the ZIKV E protein preventing replication in Vero cells. EX1091, 5. DiNunno classified the mutations as "lethal for ZIKV" and "necessary [for ZIKV] to function in mammalian [] cells." EX1091, 4−5; EX1002, ¶258. In 2022, Ma disclosed additional ZIKV E protein residues that "nearly abolished [ZIKV] infectivity" due to defects in host cell entry, "advanc[ing the] understanding of the mechanism of flavivirus entry" (and ultimately its ability to replicate in production cells). EX1094, 1605, 1612, 1619, FIG. 6; EX1002, ¶259.

POSAs would not have known of any of these critical residues by December 23, 2016, and would have lacked critical knowledge concerning ZIKV replication and infectivity. EX1002, ¶260. Post-2016 research confirmed that even "single amino acid mutations have been shown to have [a] significant impact on ZIKV infection phenotypes." EX1089, 14; EX1002, ¶260. ZIKV structure and function, therefore, were unpredictable as of December 23, 2016. EX1002, ¶260.

ii. Claim 1

Claim 1 recites a genus of ZIKV vaccines having RNA genomes corresponding to variant sequences that are ≥80% identical to SEQ ID NO: 72 that

are functionally defined as being capable of stimulating a MN_{50} titer of >15 in ≥70% of vaccinated subjects, which requires that the ZIKV be capable of replicating in production cells to be made into a vaccine. EX1001, 445:34−41; EX1002, ¶262. For the reasons discussed below, POSAs would not have concluded that Valneva possessed the many millions of ZIKV vaccines encompassed by claim 1 as of the December 23, 2016 filing date of the '664 PCT.

a) Claim 1 encompasses many millions of functionally defined candidate ZIKV vaccines—an unwieldy number

POSAs would have understood the term "variant nucleic acid having at least 80% identity to SEQ ID NO: 72" to encompass nucleic acid sequences that are not required to be identical to SEQ ID NO: 72 over any particular region and can overlap with SEQ ID NO: 72, as long as the "at least 80%" level of identity is maintained. *See* §VII.

Neither the specification nor claim 1 specifies which of the 10,773 nucleotides of SEQ ID NO: 72 should be substituted; thus, any of the nucleotides could be substituted as long as ≥80% identity is maintained. EX1002, ¶¶263−264. As Dr. Barouch explains, calculating the number of sequences having ≥80% identity to just a 20-nucleotide-long sequence shows that there would be 424,995 different sequences. EX1002, ¶265. Given the 10,773-nucleotide length of SEQ ID NO: 72, Dr. Barouch states that his calculation on a 20-mer indicates that the

number of possible sequences having ≥80% identity to SEQ ID NO: 72 will be *unwieldy* and POSAs would need the aid of a computer algorithm to calculate the exact number. *Id.* Dr. Scott Bailey used such an algorithm and determined that the number of variants having ≥80% identity to SEQ ID NO: 72 is **$3.88 \times 10^{3,366}$**. EX1078, ¶¶25−43; EX1002, ¶266. Determining the number of variant polyprotein sequences encoded by $3.88 \times 10^{3,366}$ variant nucleic acid sequences would require super-computer resources not normally available to POSAs or a bioinformatician, but the minimal number of variant polyprotein sequences remains in at least the millions. EX1078, ¶¶48−49. Dr. Bailey illustrated this point by performing a conservative analysis: he determined the number of full-length variant polyprotein sequences if one permitted up to 5 substitutions in only the first 33 nucleotides of SEQ ID NO: 72's open-reading frame. Such variants would be at least *99.95%* identical to SEQ ID NO: 72, yet encode 6,032,020 polyprotein sequences, given genetic code degeneracy and after disregarding polyproteins having premature stop codons. Even when making a conservative calculation based on a subset of the variants encompassed by the claims, the analysis reveals that claim 1 encompasses millions of variant sequences—an unwieldy number for POSAs to synthesize and empirically test. EX1078, ¶¶44−49; EX1002, ¶¶267−268.

In short, claim 1 represents a vast genus of candidate ZIKV vaccines because of the many millions of variant nucleic acid sequences encompassed by

the claim's structural language (which includes sequences encoding virions that would not replicate). EX1002, ¶269.

b) The '664 PCT does not demonstrate possession.

The '664 PCT does not provide (1) a representative number of species or (2) any structural features common to the claimed genus that would permit POSAs to visualize ZIKV vaccines that would achieve the claimed function, nor was any structure-function correlation known in the art. EX1002, ¶¶270−282. The '664 PCT, therefore, does not demonstrate that the inventors possessed the full scope of the challenged claims as of December 23, 2016. *Id.*

i) The '664 PCT does not provide sufficient representative species.

In contrast to the millions of candidate ZIKV vaccines, the '664 PCT discloses only:

(1) a single working example using the H/PF/2013 strain having an RNA genome comprising a sequence corresponding to SEQ ID NO: 72; and

(2) twelve naturally-occurring ZIKV sequences isolated from infected subjects that are all closely related to SEQ ID NO: 72, but not used in making a ZIKV vaccine.

EX1008, 75:20−87:14, SEQ ID NOs: 2−13; EX1002, ¶271. Besides those natural sequences, no other variants, or vaccines made therefrom, are specifically disclosed or exemplified. EX1002, ¶271.

The ’664 PCT’s single example employs the naturally occurring H/PF/2013 strain. EX1008, 76:16−23; EX1002, ¶272. This is the only vaccine shown to be capable of stimulating NAbs in the ’664 PCT. EX1008, 84:20−28, 85:19−20, 85:25−28. The twelve, naturally occurring ZIKV sequences disclosed represent—at best—a very narrow sliver of the claimed variants: (1) SEQ ID NOs: 2−10 and 13 correspond to Asian ZIKV strains that are all ≥98% identical to SEQ ID NO: 72; and (2) SEQ ID NOs: 11 and 12 correspond to African ZIKV strains that are each 89% identical to SEQ ID NO: 72 and 99% identical to each other. EX1002, ¶¶273−274, Appx. A.

Claim 1, however, is not limited to vaccines made from naturally occurring ZIKV genomes; it encompasses millions of variant genomes having as little as 80% identity to SEQ ID NO: 72, with sequence variations anywhere in the genome. *Id.*, ¶275. Variants that meet the structural requirements of claim 1 include, e.g.,: (1) Zhang’s NS2A mutants, which are all ≥97% identical to SEQ ID NO: 72; and (2) DiNunno’s E protein mutants, which are 88% identical to SEQ ID NO: 72. *Id.*, ¶275, Appx. B.

Because the '664 PCT's disclosed sequences (SEQ ID NOs: 2−13 and 72) are all naturally occurring, they are not representative of the full scope of variants of claim 1. *Id.*, ¶275. This is because, while virions comprising the naturally occurring sequences would be able to replicate in cell culture, so as to be propagated for making a vaccine, certain non-naturally occurring variants, like in Zhang and DiNunno, would not. *Id.*, ¶276. SEQ ID NOs: 2−13 and 72, therefore, only represent a small "corner of the genus" and are not a representative number of species sufficient to support this broad functionally defined genus. *AbbVie*, 759 F.3d at 1300.

The '664 PCT "fails to provide sufficient blaze marks" through SEQ ID NOs: 2−13 and 72 that would "direct a POSA to the specific subset" of sequences among the millions of other sequences having ≥80% identity to SEQ ID NO: 72 that will provide ZIKV virions that can be propagated, while also being capable of stimulating a MN_{50} of >15 in ≥70% of subjects, versus those that would not. *Idenix*, 941 F.3d at 1164; EX1002, ¶277. The '664 PCT therefore "fails to disclose a way to distinguish those [variants] *capable* of" replicating and being made into a vaccine "from [variants] *incapable* of" replicating and being made into a vaccine. *Juno*, 10 F.4th at 1339; EX1002, ¶277. Yet, post-December 2016 art demonstrated that "single amino acid mutations have been shown to have [a] significant impact on ZIKV infection phenotypes." EX1089, 14; EX1056, 591−592; EX1002, ¶277.

Given the art's limitations, merely disclosing that a ZIKV comprises a sequence corresponding to "a variant genome that is at least 80% … identical to any one of SEQ ID NOs: 2−13 or 72" (EX1008, 56:48−51) does not show possession of the full scope of claim 1 at the '664 PCT's filing date. EX1002, ¶¶277−278. Valneva merely disclosed a small set of highly similar species abiding in a miniscule corner of the genus that are not representative of the whole and left it to others to explore the genus's unknown contours. *AbbVie*, 759 F.3d at 1301 (finding a lack of written description when the specification "d[id] not describe representative examples to support the full scope of the claims").

ii) The '664 PCT failed to describe any structure-function correlation.

The '664 PCT fails to disclose structural features common to the claimed genus that correlate with the claimed function, and the prior art does not fill the gaps. EX1002, ¶¶279−282. Making the claimed vaccines require virions capable of replication. *Id.*, ¶279. The '664 PCT, however, does not disclose: (1) structural features common to the claimed ZIKV variants that produce virions that can replicate or (2) how to distinguish the genomes capable of producing such virions from those incapable of doing so. *Id.*; *Juno*, 10 F.4th at 1339.

The '664 PCT discloses that the ZIKV can have an RNA genome corresponding to the sequences provided by "any one of SEQ ID NO: 2−13 or 72" or a sequence ≥80% identical to those sequences; this allows for significant

variability, encompassing variants that cannot replicate (e.g., Zhang's and DiNunno's post-2016 mutants). EX1001, 103:15−104:16; EX1002, ¶280. The '664 PCT, however, does disclose which structural features of ZIKV produce virions that can replicate. EX1002, ¶280.

The '664 PCT states that the ZIKV can comprise SEQ ID NO: 73 or the E protein of SEQ ID NO: 47 or sequences having ≥95% identity to those two amino acid sequences. EX1001, 129:46−56; EX1002, ¶280. The '664 PCT, however, does not disclose which variant sequences will form virions that can replicate, and consequently, it fails to establish any correlation between a sequence variant and ZIKV's capability to be made into a vaccine. EX1002, ¶280.

Nor was any correlation established in the art by December 23, 2016. *Id.* The art reported "significant gaps of knowledge in the assembly and maturation process" of ZIKV existed and those processes were "largely a black box." EX1091, 2; EX1092, 378; EX1002, ¶¶256−260. Residues known to be important for ZIKV replication were not known until after December 2016. EX1002, ¶¶256−260; *see* §VIII.E.1.a.i. The '664 PCT, moreover, does not disclose what structural characteristics can be modified, and in what way, to arrive at ZIKV vaccines capable of stimulating a MN_{50} titer substantially >15 in ≥70% of a variety of vaccinated subjects. EX1002, ¶281. The '664 PCT at most provides a starting point and direction for further research into which of the millions of candidate

ZIKV vaccines encompassed by claim 1 could be made into vaccines capable of stimulating the claimed NAb titers. *Id.*

In sum, the '664 PCT does not provide written description support for claim 1, and thus claim 1 is not entitled to the '664 PCT's December 23, 2016, filing date. *Id.*, ¶282; *AbbVie*, 759 F.3d at 1300−01 (the "patents [at issue] d[id] not describe representative examples to support the full scope of the claims"); *Idenix*, 941 F.3d at 1164 (lack of written description where "a POSA is deprived of any meaningful guidance into what compounds beyond the examples and formulas, if any, would provide" the claimed function).

iii. Claims 2, 3, 24, 25

Claims 2, 3, 24, and 25 do not further structurally define the claimed vaccines and thus do not narrow the claimed number of candidate variant genomes. EX1002, ¶285. While the claims recite MN_{50} ranges with higher lower limits (claims 2, 24, and 25) or observing NAb titers in a higher percentage of subjects (claim 3) than claim 1, the scope of candidate variant genomes remains unwieldy. *Id.*

As with claim 1, POSAs would not have known which of the millions of variants would be capable of replicating in production cells, so as to be used to make a vaccine meeting the claims' functional limitations. *Id.*, ¶286. Claims 2, 3,

24, and 25 therefore lack written description support in the ’664 PCT for the same reasons as claim 1. *Id.*

iv. Claim 4

Claim 4’s recitation of various E protein sequences and variants thereof also does not materially narrow the many millions of candidate ZIKV genome sequences claimed, given that (1) there are at least **2.17×10^{74}** amino acid sequences encompassed by the variants having ≥95% identity to any one of the 56 claimed E protein sequences; and (2) claim 1’s ≥80% identity language allows for additional variations outside of the E protein, adding to the claim’s breadth. EX1002, ¶¶288−292; EX1078, ¶¶50−58.

The ’664 PCT does not indicate which of the many millions of variant sequences recited in claim 4 would be able to pack a virulent ZIKV virus, as required by claim 4. EX1002, ¶293. Nor would POSAs have known which variants would be capable of replicating in production cells, so as to be used to make a vaccine meeting the claim’s functional limitations. *Id.*

Claim 4 therefore lacks written description support in the ’664 PCT for the same reasons as claim 1. *Id.*

v. Claims 5−15

Claims 5−15 do not narrow the claimed number of candidate variant genomes. For the same reasons discussed for claim 1, POSAs would not have

known the full scope of variants that would be capable of replicating in production cells, so as to be used to make a vaccine meeting the claims' functional limitations. *Id.*, ¶¶294−299. Claims 5−15 therefore lack written description support in the '664 PCT for the same reasons as claim 1. *Id.*

vi. Claims 21−23

Claims 21−23 recite that the RNA genome corresponds to a variant nucleic acid sequence having at least 90%, 95%, and 99% identity to SEQ ID NO: 72, respectively. EX1001, 448:10−18. While claims 21−23 narrow the scope of candidate variant genomes, they still encompass **$4.45 \times 10^{2,032}$**, **$7.91 \times 10^{1,182}$**, or **1.57×10^{310}** variant sequences, respectively. EX1078, ¶43; EX1002, ¶¶301, 304.

As with claim 1, POSAs would not have known the full scope of variants that would be capable of replicating in production cells, so as to be used to make a vaccine meeting the claims' functional limitations. EX1002, ¶¶302, 305−306. Claims 21−23 therefore lack written description support in the '664 PCT for the same reasons as claim 1. *Id.*

b. The '664 PCT does not enable the full scope of the challenged claims.

"A claim is not enabled when, 'at the effective filing date of the patent, one of ordinary skill in the art could not practice their *full scope* without undue experimentation.'" *Idenix*, 941 F.3d at 1154; *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). "'Undue experimentation can include undue experimentation in identifying,

from among the many concretely identified [embodiments] that meet the structural requirements, th[ose] that satisfy the functional requirement.'" *Amgen Inc. v. Sanofi, Aventisub LLC*, 987 F.3d 1080, 1087 (Fed. Cir. 2021); *Idenix*, 941 F.3d at 1163 (a specification that requires POSAs to engage in a trial-and-error process to practice the claimed invention is not enabling); *Wyeth & Cordis Corp. v. Abbott Lab'ys*, 720 F.3d 1380, 1385–86 (Fed. Cir. 2013) (same).

i. The breadth of the challenged claims is vast.

The challenged claims encompass millions of candidate ZIKV vaccines, including variants that meet the claims' structural limitations but not the functional limitations, e.g., ZIKV variants identified by Zhang in 2019 and DiNunno in 2020 that could not be made into vaccines. EX1002, ¶¶308−309; *see* §VIII.E.1.a.i. POSAs would not have been able to determine the full scope of embodiments that would meet *both* the structural and functional limitations of the claims without undue experimentation, because the full scope of operable embodiments is not *a priori* determinable. EX1002, ¶¶309−310, 318−319. As such, *Wands* factor 1 weighs strongly against enablement.

ii. The nature of the alleged invention and unpredictability in the art necessitate making and screening each claimed variant, even for a highly skilled artisan.

Wands Factors 2−5 also weigh strongly against enablement. The claimed vaccine candidates would have had to be made and screened to identify the full

scope of ZIKV variants that can replicate in production cells, and be made into the claimed vaccines. *See* §VIII.E.1.a.i; EX1002, ¶¶310, 318−319. The art was undeveloped, however, with the requirements for ZIKV assembly and replication being largely "a black box." EX1092, 378; EX1002, ¶310. And post-2016 studies revealed that "single amino acid mutations have been shown to have [a] significant impact on ZIKV infection phenotypes." EX1089, 14; EX1056, 591−592, FIG. 1B; EX1091, 5; EX1094, 1605; EX1002, ¶310. Whether a given ZIKV variant could produce replicating virions would have been unpredictable, necessitating empirical testing. EX1002, ¶310. Moreover, given the unpredictability in using non-naturally-occurring variant ZIKV sequences, even a highly skilled POSA would have had to engage in undue experimentation to practice the full scope of the claims. EX1002, ¶314. As of December 23, 2016, there were "significant gaps" of knowledge regarding ZIKV virion assembly and maturation. EX1091, 2; EX1002, ¶314; *see* §VIII.E.1.a.i.

iii. Little to no direction and insufficient working examples.

The '664 PCT provides a single working example of a ZIKV vaccine, which is insufficient to support the unwieldy genus of candidate vaccines claimed. §VIII.E.1.a.ii. The '664 PCT also fails to disclose any correlation between a variant nucleic acid sequence and its ability to produce replicating virions capable of being formulated into a vaccine. EX1002, ¶¶315−316. The '664 PCT, therefore,

provides no direction from which POSAs could determine which of the millions of candidate variant nucleic acid sequences would meet the claim's functional language. *Id.* This situation mirrors *Wyeth*, where POSAs "having to synthesize and screen each of at least tens of thousands of candidate compounds constitute[d] undue experimentation." 720 F.3d at 1385. Here, POSAs would have to produce and screen many millions of ZIKV variants to identify the full scope of vaccines meeting the claims' functional limitations. Just as in *Wyeth*, the claims are broad, yet the '664 PCT specification provides "only a starting point, a direction for further research." *Id.* at 1386; EX1002, ¶¶314−319.

The '664 PCT thus leaves it up to POSAs "to discover undisclosed claimed embodiments … through … 'trial and error, by making changes to the disclosed [vaccine] and then screening those [vaccines] for the desired … propert[y].'" *Amgen*, 987 F.3d at 1088; *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1372−74 (Fed. Cir. 1999). As such, *Wands* factors 6 and 7 weigh strongly against enablement.

iv. The quantity of experimentation is extensive and undue.

The quantity of experimentation to make and use the claimed vaccines would have been undue given the '664 PCT's limited disclosures and the state of the art. EX1002, ¶¶317−319. Making variants and growing and isolating them to make vaccines is a process that generally requires extensive and iterative

experimentation. EX1100, 73; EX1002, ¶¶311−312. Larocca's single ZIKV vaccine would not have obviated the need for iterative empirical testing across the full claim scope. EX1006, 475−476; EX1002, ¶313. POSAs, therefore, would have had to engage in trial and error by synthesizing each and every candidate variant sequence, cloning each sequence into an expression vector, transfecting production cells with the virus, develop growth and purification protocols for viable virions, and propagating, harvesting, and purifying viable virions to formulate and test them in a vaccine. *Id.*, ¶318. Making and testing the millions of variant nucleic acid sequences embraced by the full scope of the claims, would have been an impossibly laborious and time-intensive undertaking. *Id.*, ¶319. As such, *Wands* factor 8 weighs strongly against enablement.

v. Undue experimentation would have been required.

Weighing the *Wands* factors, POSAs would have concluded that the '644 PCT would not have enabled POSAs to make and use the full scope of the challenged claims without undue experimentation. *Id.*, ¶¶320−327. POSAs would have known that the claims encompass many millions of candidate ZIKV vaccines, not all of which could be used to make a vaccine, yet the '664 PCT discloses only a single working example and lacks sufficient guidance. *Id.* POSAs seeking to practice the claims' full scope would have had to synthesize and empirically screen

each of the millions of ZIKV vaccine candidates to determine which embodiments achieve the claimed functionality. *Id.* This would have been undue.

Consequently, the challenged claims are not entitled to the ’664 PCT’s filing date because “the required experimentation ‘would take a substantial amount of time and effort.’” *Amgen*, 987 F.3d at 1087−88. The ’644 PCT thus “discloses only a starting point for further iterative research,” requiring undue experimentation. *Wyeth*, 720 F.3d at 1386.

2. WO ’225 anticipates claims 1−15 and 21−25.

WO ’225 discloses each and every element of claims 1−15 and 21−25, arranged as claimed and in a manner enabling to POSAs. EX1002, ¶¶328−350. Prior art publications are presumed enabled. *Fresenius Kabi USA LLC v. Chugai Seiyaku Kabushiki Kaisha*, IPR2021-01336, Paper 27, at 23−24 (P.T.A.B. Feb. 23, 2022). WO ’225’s working example discloses a species of the challenged claims. WO ’225 provides sufficient detail to enable POSAs to make and use that specific example without undue experimentation. EX1002, ¶329. This is because WO ’225 discloses methods for propagating ZIKV in Vero cells, performing formaldehyde inactivation, purifying the inactivated virions, and formulating the purified inactivated ZIKV with $Al(OH)_3$ and PBS. *Id.*; EX1008, 76:20−82:35. Those techniques also were well-known in the art. EX1002, ¶329. As discussed below, WO ’225’s single species is sufficient to anticipate the challenged claims. *Titanium*

Metals Corp. of Am. v. Banner, 778 F.2d 775, 782 (Fed. Cir. 1985) (stating that prior art disclosure of single species can anticipate a genus).

a. Claims 1−3, 21−25

WO ’225 discloses the same working example as the ’681 patent, which is a ZIKV vaccine comprising H/PF/2013 and SEQ ID NO: 72. EX1008, 75:20−85:28; EX1001, 128:35−136:27; EX1002, ¶332. Claims 21−23 encompass ZIKV vaccines comprising SEQ ID NO: 72 because they include all the limitations of claim 1. *See* 35 U.S.C. §112(d). WO ’225 discloses administering 1 μg of that vaccine to mice and observing a MN_{50} of 90. EX1008, 84:20−28; EX1002, ¶334. WO ’225 further discloses “a virus vaccine comprising an optimally inactivated particle, wherein the virus particle in an appropriate dose is able to seroconvert a subject that is administered the virus vaccine with at least a 70% probability, preferably an 80% probability.” EX1008, 5:26−28; EX1002, ¶335. A MN_{50} of >15 would be indicative of seroconversion. EX1002, ¶335; *see* §V.C.

Thus, WO ’225’s exemplified vaccine reportedly is capable of stimulating a MN_{50} of 90 in ≥80% of vaccinated subjects. EX1002, ¶¶335−336. WO ’225, therefore, anticipates claims 1−3 and 21−25. *Id.*, ¶¶331−340.

b. Claim 4

The example in WO ’225 uses the H/PF/2013 ZIKV strain, which has an E protein sequence of SEQ ID NO: 47, just as recited in claim 4. EX1008, 77:5−8;

EX1002, ¶¶341−342. Thus, WO ’225 discloses each and every element of claim 4 arranged as claimed and in a manner enabling to POSAs, anticipating claim 4. *Id.*

c. Claims 5−9

The example in WO ’225 discloses chemically inactivating H/PF/2013 virions by incubating them in formaldehyde for ten days at +22° C (**claims 5, 7−9**). EX1008, 81:10−12; EX1002, ¶¶343−344. Table 7 of WO ’225 discloses that the ZIKV virions were completely inactivated as measured using a plaque assay on day 5 of the inactivation protocol because no plaque forming units above the limit of detection were observed. EX1008, Table 7; EX1002, ¶344. WO ’225’s 10-day inactivation process, therefore, is longer than is required to completely inactivate the ZIKV as measured by plaque assay (**claim 6**). EX1002, ¶344. WO ’225 anticipates claims 5−9. *Id.*, ¶345.

d. Claims 10, 11, 15

The example in WO ’225 discloses that the ZIKV vaccine comprises $Al(OH)_3$ (**claims 10, 11**) and a pharmaceutically acceptable excipient, PBS (**claim 15**). EX1008, 82:29−32; EX1002, ¶347. Thus, WO ’225 discloses each and every element of claims 10, 11, and 15 in a manner enabling to POSAs, anticipating claims 10, 11, and 15. *Id.*, ¶¶346−347, 350.

e. Claims 12−14

WO ’225 states, “[a] preferred aluminium salt is the aluminium hydroxide with reduced Cu content, e.g., lower than 1,25 ppb based on the weight of the Zika

composition" (**claim 12**). EX1008, 20:19−22; EX1002, ¶348. WO '225 additionally discloses that $Al(OH)_3$ can be used in combination with "IC31®, i.e. $KLKL_5KLK$," an antibacterial peptide, "and the nucleic acid sequence $(dIdC)_{13}$," an I-ODN (**claims 13, 14**). EX1008, 20:24−33; EX1002, ¶348.

WO '225 makes clear that $Al(OH)_3$ with the claimed copper content and IC31 are contemplated as part of its invention because its example discloses using $Al(OH)_3$ as the adjuvant. EX1008, 82:29−32; EX1002, ¶348. WO '225 further states that its invention includes using IC31 and $Al(OH)_3$ in combination and it is preferred to use $Al(OH)_3$ with copper content <1.25 ppb copper based on a final pharmaceutical composition comprising the ZIKV. EX1008, 20:19−33; EX1002, ¶348. Thus, POSAs would have at once envisaged using the claimed adjuvants in WO '225's example.[10] Before March 10, 2020, POSAs would have been able to use the claimed adjuvants in WO '225's example without undue experimentation because (1) IC31 was well-known (EX1066, Abstract); and (2) the level of copper

[10] "[A] reference can anticipate a claim even if it 'd[oes] not expressly spell out' all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would 'at once envisage' the claimed arrangement or combination." *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015).

in $Al(OH)_3$ could be measured using well-known techniques (EX1083, 28:18−25). EX1002, ¶349. POSAs, therefore, would have been able to assess the lot of $Al(OH)_3$ for its copper content and use a different lot if the copper level were too high. *Id.*

Thus, WO '225 discloses each and every element of claims 12−14 in a manner enabling to POSAs, anticipating claims 10−15. *Id.*, ¶¶346−350.

IX. DISCRETIONARY DENIAL IS NOT WARRANTED

The '681 patent is not involved in any related proceeding that implicates *Apple v. Fintiv,* IPR2020-00019 (P.T.A.B. Mar. 20, 2020), or *General Plastic v. Canon Kabushiki Kaisha,* IPR2016-01357 (P.T.A.B. Sept. 6, 2017). The Board also should not deny institution under §325(d) or *Advanced Bionics v. MED-EL Elektromedizinische,* IPR2019-01469 (P.T.A.B. Feb. 13, 2020).

Regarding Ground 3: the Office has not previously considered whether the challenged claims lack priority to the '664 PCT and are anticipated by WO '225, which is intervening art. In view of the millions of candidate ZIKV vaccines encompassed by the claims and their lack of §112 support in the '664 PCT, the Examiner materially erred by not denying priority to the '664 PCT and not rejecting the claims over WO '225.

Regarding Grounds 1 and 2: while Srivastava, Baronti, and the H/PF/2013 Sequence (EX1004, 944, 946) were listed in an IDS, no art was applied in a

rejection because the Examiner issued a first-action allowance. *Id.*, 924−930. The Examiner materially erred by misapprehending or overlooking the '664 PCT's International Preliminary Report on Patentability ("IPRP"), which was cited in an IDS and stated EP '585 "does not relate to Zika virus at all." EX1086, 5. The Examiner materially erred by failing to appreciate that EP '585 cannot plausibly constitute an effective filing date for the claims. The Examiner thus erred by failing to assess patentability over the prior art cited herein.

Proper review of the IPRP should have led the Examiner to make a rejection over Srivastava because, as the IPRP notes, Srivastava discloses "how to produce a successful Flavivirus vaccine. Hence … the skilled person looking to develop a [ZIKV] vaccine would turn to [Srivastava] to find a strategy for the development of a Flavivirus vaccine with a reasonable expectation of success without the exercise of inventive skill." *Id*., 6−7. The Examiner therefore materially erred by not rejecting the claims over Srivastava, and by overlooking the high titers shown in ≥70% of subjects for multiple flavivirus vaccines. *See* §§VIII.B.1.g., V.D. The Examiner further erred by deeming Cox the closest prior art. EX1004, 929. While Cox briefly discusses flavivirus vaccines, it is in the context using the ZIKV prM and E proteins in a YFV-backbone-based *chimeric* vaccine. EX1030, 119−120. Cox, however, directs POSAs away from such a chimeric vaccine, stating that residues in the ZIKV prM and E proteins may affect their presentation in the

chimera. *Id.* Cox concludes by directing POSAs to use known small molecule inhibitors, i.e., fundamentally different technology, of NS3 and NS5 because of similarity of those proteins in ZIKV with their DENV, WNV, and JEV counterparts. *Id.*, 124. It is this disclosure that the Examiner focused on in allowing the claims. EX1004, 929. The Examiner overlooked the extensive prior art related to known (non-chimeric) flavivirus vaccines that, as discussed above, would have motivated POSAs to develop a ZIKV vaccine using known flavivirus technology that resulted in vaccines that stimulated high NAb titers. The Examiner erred in issuing a first-action allowance. This Petition presents new evidence and facts demonstrating unpatentability.

X. MANDATORY NOTICES (37 C.F.R. §42.8)

Real party-in-interest (37 C.F.R. §42.8(b)(1)): Takeda Vaccines, Inc.

Related matters (37 C.F.R. §42.8(b)(2)): Petitioner is not aware of any judicial matters that would affect or be affected by a decision in this proceeding; but pending Appl. No. 17/548,721 claims priority to U.S. Patent Appl. No. 16/813,862, which issued as the '681 patent.

Lead and Back-Up Counsel (37 C.F.R. §42.8(b)(3)):

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Service information (37 C.F.R. §42.8(b)(4)): Please direct all correspondence to the above addresses and PTAB@sternekessler.com. Petitioner consents to service by email.

Power of attorney: This Petition is filed in accordance with 37 C.F.R. §42.106(a). Concurrently filed herewith are a Power of Attorney and Exhibit List

under 37 C.F.R. §42.10(b) and §42.63(e), respectively. The required fee is paid through Deposit Acct. No. 19-0036 (Customer ID No. 45324). The Office is authorized to charge any fee deficiency, or credit any overpayment, to Deposit Acct. No. 19-0036 (Customer ID No. 45324).

Respectfully submitted,
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CERTIFICATION OF WORD COUNT (37 C.F.R. §42.24(d))

Petitioner certifies that this Petition is 13,994 words in length, as determined by Microsoft Word® word count feature, excluding any table of contents, mandatory notices under §42.8, certificate of service or word count, or appendix of exhibits or claim listing.

Respectfully submitted,
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CERTIFICATION OF SERVICE (37 C.F.R. §§42.6(e), 42.204(a))

The undersigned hereby certifies that on December 27, 2022, true and correct copies of the foregoing **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 11,219,681** and all associated exhibits were served in their entireties on the following parties via FedEx® Express:

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APPENDIX A

Claim listing:

Claim:	**Claim Limitation:**
Claim 1	A Zika virus vaccine comprising
	a Zika virus having an RNA genome corresponding to the DNA sequence provided by SEQ ID NO: 72 or a variant nucleic acid having at least 80% identity to SEQ ID NO: 72,
	wherein said Zika virus vaccine is capable of stimulating a neutralizing antibody titer greater than 15 in at least 70% of vaccinated subjects, wherein the neutralizing antibody titer is determined using a microneutralization assay (MN_{50}).
Claim 2	The Zika virus vaccine according to claim 1, wherein said MN_{50} is greater than 20, 25, 30, 35, 40, or 45.
Claim 3	The Zika virus vaccine according to claim 1, wherein the Zika virus vaccine is capable of stimulating a MN_{50} titer greater than 15 in at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, or at least 99% of vaccinated subjects.
Claim 4	The Zika virus vaccine according to claim 1, wherein the Zika virus comprises an E protein having an amino acid sequence provided by any one of SEQ ID NOs: 14-69, or a variant amino acid sequence that is at least 95% identical to any one of SEQ ID NOs: 14-69 and able to pack a virulent Zika virus.
Claim 5	The Zika virus vaccine according to claim 1, wherein the Zika virus is inactivated by chemical inactivation, thermal inactivation, pH inactivation, or UV inactivation.
Claim 6	The Zika virus vaccine according to claim 5, wherein the chemical inactivation comprises contacting the Zika virus with a chemical inactivation agent for longer than is required to completely inactivate the Zika virus as measured by plaque assay.
Claim 7	The Zika virus vaccine according to claim 5, wherein the chemical inactivation comprises contacting the Zika virus with formaldehyde.

Claim:	**Claim Limitation:**
Claim 8	The Zika virus vaccine according to claim 7, wherein the chemical inactivation comprises contacting the Zika virus with formaldehyde for between 2-10 days.
Claim 9	The Zika virus vaccine according to claim 5, wherein the chemical activation is performed at about +4° C. or about +22° C.
Claim 10	The Zika virus vaccine according to claim 1, further comprising an adjuvant.
Claim 11	The Zika virus vaccine according to claim 10, wherein the adjuvant is an aluminium salt adjuvant.
Claim 12	The Zika virus vaccine according to claim 11, wherein said aluminium salt adjuvant is aluminium hydroxide with less than 1.25 parts per billion (ppb) copper (Cu) based on a final pharmaceutical composition comprising the Zika virus.
Claim 13	The Zika virus vaccine according to claim 10, wherein the adjuvant comprises a peptide and a deoxyinosine-containing immunostimulatory oligodeoxynucleic acid molecule (I-ODN).
Claim 14	The Zika virus vaccine according to claim 13, wherein the peptide comprises the sequence $KLKL_5KLK$ (SEQ ID NO: 71) and the I-ODN comprises oligo-$d(IC)_{13}$ (SEQ ID NO: 70).
Claim 15	The Zika virus vaccine according to claim 1, further comprising one or more pharmaceutically acceptable excipients.
Claim 21	The Zika virus vaccine according to claim 1, wherein said variant nucleic acid has at least 90% identity to SEQ ID NO: 72.
Claim 22	The Zika virus vaccine according to claim 1, wherein said variant nucleic acid has at least 95% identity to SEQ ID NO: 72.
Claim 23	The Zika virus vaccine according to claim 1, wherein said variant nucleic acid has at least 99% identity to SEQ ID NO: 72.
Claim 24	The Zika virus vaccine according to claim 2, wherein said MN50 is greater than 50, 55, 60, 65, 70, 75, 80, or 85.
Claim 25	The Zika virus vaccine according to claim 2, wherein said MN50 is greater or equal to 90.