

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

VALNEVA AUSTRIA GMBH,
Petitioner

v.

TAKEDA VACCINES, INC.,
Patent Owner

Case IPR2025-00776
U.S. Patent No. 11,730,802

PATENT OWNER'S SUPPLEMENTAL PRELIMINARY RESPONSE

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PATENT OWNER'S UPDATED EXHIBIT LIST

Exhibit No.	Description
2001	Declaration of Dr. Dan H. Barouch in Support of Patent Owner's Discretionary Denial Brief
2002	<i>Curriculum vitae</i> of Dr. Dan H. Barouch
2003	Larocca, R.A., et al., "Vaccine Protection Against Zika Virus from Brazil," <i>Nature</i> , 536: 474–478 (2016)
2004	Abbink, P., "Protective Efficacy of Multiple Vaccine Platforms Against Zika Virus Challenge in Rhesus Monkeys," <i>Science</i> , 353(6304) 1129–1132 (2016)
2005	Statutory Disclaimer for U.S. Patent No. 11,730,802, filed June 11, 2025
2006	Sumathy et al., "Protective efficacy of Zika vaccine in AG129 mouse model," <i>Scientific Reports</i> , 7:46375, 1–9; April 12, 2017 (Sumathy)
2007	Wressnigg et al., "A randomized, placebo-controlled, blinded phase 1 study investigating a novel inactivated, Vero cell-culture derived Zika virus vaccine," <i>Journal of Travel Medicine</i> , 1–10; (2022) (Wressnigg)
2008	Burton, D.R., "Antibodies, Viruses and Vaccines," <i>Nature Review Immunology</i> , 2: 706–713 (2002)
2009	Roehrig, J.T., et al., "Guidelines for Plaque-Reduction Neutralization Testing of Human Antibodies to Dengue Viruses," <i>Viral Immunology</i> , 21(2): 123–132 (2008)
2010	Martinez, L.J., et al., "Safety and Immunogenicity of a Dengue Virus Serotype-1 Purified-Inactivated Vaccine: Results of a Phase 1 Clinical Trial," <i>Am. J. Trop. Med. Hyg.</i> , 93(3): 454–460 (2015) (Martinez)
2011	Srivastava, A.K., et al., "A Purified Inactivated Japanese Encephalitis Virus Vaccine Made in Vero cells," <i>Vaccine</i> , 19(3): 4557–4565 (2001)
2012	Thomas, S. J., et al., "A Phase II, Randomized, Safety and Immunogenicity Study of a Re-derived, Live-attenuated Dengue Virus Vaccine in Healthy Adults," <i>Am. J. Trop. Med. Hyg.</i> , 88(1): 73–88 (2013) (Thomas II)

Exhibit No.	Description
2013	Shan, C., “Zika Virus: Diagnosis, Therapeutics, and Vaccine,” <i>ACS Infectious Diseases</i> , 2: 170–172 (2016)
2014	Burrell, Christopher J., “Fenner and White’s Medical Virology,” 155–167 (5th ed. 2016)
2015	Monath, T, et al., “An Inactivated Cell-Culture Vaccine against Yellow Fever,” <i>N Engl J Med</i> , 364:1326-33 (2011) (Monath)
2016	Label for IXIARO® (Japanese Encephalitis Vaccine, Inactivated, Adsorbed), (Jul. 23, 2017), available at: https://wayback.archive-it.org/7993/20170722072912/https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142569.pdf (last accessed June 2, 2025)
2017	Schöndorf, I., et al., “Tick-borne encephalitis (TBE) vaccination: Applying the most suitable vaccination schedule,” <i>Vaccine</i> , 25:1470–1475 (2007) (Schöndorf)
2018	Legrand, N., et al., “Humanized Mice for Modeling Human Infectious Disease: Challenges, Progress, and Outlook,” <i>Cell Host & Microbe</i> , 6:5–9 (2009)
2019	Rasmussen, S.A., “Vaccines and Pregnancy: Past, Present, and Future,” <i>Seminars in Fetal & Neonatal Med.</i> , 19: 161–169 (2014) (Rasmussen)
2020	Rasmussen, S.A., et al., “Zika Virus and Birth Defects — Reviewing the Evidence for Causality,” <i>N Engl J Med</i> , 374:1981–87 (2016) (Rasmussen II)
2021	Davis, M., “A Prescription for Human Immunology,” <i>Immunity</i> , 29:835–838 (2008)
2022	McNeela, E. A. & Mills, K. H., “Manipulating the immune system: humoral versus cell-mediated immunity,” <i>Adv Drug Deliv Rev.</i> , 51(1–3):43–54 (2001)
2023	Manikandan, S., “Measures of central tendency: The mean,” <i>Journal of Pharmacology and Pharmacotherapeutics</i> , 2(2):140–142 (2011)
2024	Shedlock, et al., “Monkeying around with HIV vaccines: using rhesus macaques to define 'gatekeepers' for clinical trials,” <i>Nature Reviews Immunology</i> , 9:717–728 (2009)

Exhibit No.	Description
2025	Paul A. Offit, “Pandora’s Lab: Seven Stories of Science Gone Wrong,” 213–240 (April 4, 2017)
2026	Declaration of Dr. Dan H. Barouch in Support of Patent Owner’s Discretionary Denial Brief
2027	Tao, L. & Reese, T.A., “Making Mouse Models That Reflect Human Immune Responses,” <i>Trends in Immunology</i> , 38(3):181–193 (March 2017)
2028	Declaration of Mina Ching, Records Request Processor at the Internet Archive, dated June 21, 2025
2029	Khun, K.A. & Stappenbeck, T.S., “Peripheral Education of the Immune System by the Colonic Microbiota,” <i>Seminars in Immunology</i> , 25:364–369 (2013)
2030	Beura, L.K., et al., “Normalizing the Environment Recapitulates Adult Human Immune Traits in Laboratory Mice,” <i>Nature</i> , 532:512–518 (2016)
2031	Miner, J.J., et al., “Zika Virus Infection during Pregnancy in Mice Causes Placental Damage and Fetal Demise,” <i>Cell</i> , 165:1081–1091 (2016)
2032	Cugola, F.R., et al., “The Brazilian Zika virus strain causes birth defects in experimental models,” <i>Nature</i> , 534:267–273 (2016)
2033	Adams Waldorf, K.M., et al., “Fetal brain lesions after sub-cutaneous inoculation of Zika virus in a pregnant nonhuman primate,” <i>Nature Medicine</i> , 22(11):1256–1261 (2016)
2034	Walpole, S.C., et al., “The weight of nations: an estimation of adult human biomass,” <i>BMC Public Health</i> , 12(439):1–6 (2012)
2035	Good, K.L., et al., “Decreased expression of Kruppel-like factors in memory B cells induces the rapid response typical of secondary antibody responses,” <i>PNAS</i> , 104(33):13420–13425 (2007)
2036	Murphy, K., “Janeway’s Immunobiology,” (8th ed., 2012), Chapter 11

Exhibit No.	Description
2037	Sallusto, F., et al., “From vaccines to memory and back,” <i>Immunity</i> , 33:451–463 (2010)
2038	Sörman, A., et al., “How antibodies use complement to regulate antibody responses,” <i>Molecular Immunology</i> , 61:79–88 (2014)
2039	“Body Weight Information for BALBc,” The Jackson Laboratory, accessible at https://www.jax.org/jax-mice-and-services/strain-data-sheet-pages/body-weight-chart-000651 (last accessed July 10, 2025)
2040	Teixeira, F. M. E., et al., “Maternal-Fetal Interplay in Zika Virus Infection and Adverse Perinatal Outcomes,” <i>Frontiers in Immunology</i> , 11(175):1–15 (2020)
2041	Babe, I. B., et al., “Interim Guidance for Interpretation of Zika Virus Antibody Test Results,” <i>Morbidity and Mortality Weekly Report, CDC</i> , 65(21):543–546 (2016)
2042	Wren, L., et al., “Influence of Cytokines on HIV-Specific Antibody Dependent Cellular Cytotoxicity Activation Profile of Natural Killer Cells,” <i>PLOS One</i> , 7(6):1–9 (2012)
2043	Raghupathy, Raj, “Cytokines as Key Players in the Pathophysiology of Preeclampsia,” <i>Medical Principles and Practice</i> , 22(Suppl. 1):8–19 (2013)

Per the Board's authorization via email on July 30, 2025, Takeda files this Supplemental Patent Owner Preliminary Response. Valneva newly points to Schuller (EX1036) that discloses a study of Valneva's IC51.¹ Paper 8, 2-3. Valneva omitted Schuller from its Petition, but now claims that Schuller contradicts Dr. Barouch's conclusions that a POSA would not have arrived at the methods of the challenged claims with a reasonable expectation of success. *Id.*, 2. Valneva also alleges that Takeda, its counsel, and Dr. Barouch violated their duty of candor having cited Schuller previously in IPR2023-00345. *Id.*, 2-4, 12-19; EX3101. Valneva is incorrect, and its assertions of a failure to comply with the duty of candor are unfounded.

To support Takeda's POPR, Dr. Barouch noted that inactivated flavivirus vaccines known in the art before November 3, 2017, failed to achieve in humans the seroconversion rates recited in claims 11, 39, 60-62, and 65-67 after a single dose. Paper 7, 12-18, 44-46; EX2026, ¶¶53-55, 108-112. He also noted that Dr. Guirakhoo "fail[ed] to identify any inactivated flavivirus vaccines with single-dose administration schedules for humans." EX2026, ¶111. Those two conclusions are

¹ Schuller is authored by individuals at Intercell AG, which merged with Vivalis to form Valneva in 2013. See https://valneva.com/wp-content/uploads/2019/08/2013_05-28_PR_ENG.pdf (last visited August 6, 2025).

consistent with the state of the art, including Schuller, and Dr. Barouch's testimony in this proceeding and in IPR2023-00345. As discussed below, Schuller tested and *failed* to develop a single-dose inactivated flavivirus vaccine.

Schuller conducted a clinical study of IC51. EX1036, 2188. To determine whether IC51 could be administered as a single-dose vaccine, Schuller set the "primary immunogenicity endpoint [as] demonstrat[ing] non-inferiority of SCR ['seroconversion rate'] for the single, high-dose vaccination regimen (1×12μg) compared to the standard regimen (2×6μg) *on Day 56.*" *Id.*, 2189 (emphasis added throughout unless indicated). A study's primary endpoint is generally considered "[t]he main result that is measured at the end of a study *to see if a given treatment worked.*"² Schuller's single-dose regimen failed to meet this endpoint: "*Non-inferiority* of the single, high-dose (1×12μg) regimen compared to the standard (2×6μg) vaccination regimen *could not be demonstrated* for SCR *on Day 56.*" *Id.*, 2190. At the study's primary endpoint at Day 56, Schuller reported a SCR of only **41.2%** for the 1×12μg dose. *Id.* In other words, Schuller's attempt to provide IC51 *as a single-dose vaccine failed to meet Schuller's own standards.* Moreover, Schuller concluded that "...*a second immunization is required* to maintain

² <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/primary-endpoint> (last visited August 6, 2025) (emphasis added).

protective antibody tit[er]s, *confirming a large body of published evidence* that for inactivated vaccines, a 2-dose schedule is preferable to attain the maximum induction of neutralizing antibodies....” *Id.* Schuller’s failed single-dose regimen prompted Schuller to then propose testing “an accelerated **2-injection ... regimen** (e.g., 14 days between the 2 injections)” to possibly provide a solution for travelers. *Id.*, 2193. Schuller is therefore entirely consistent with Dr. Barouch’s testimony that Dr. Guirakhoo failed to identify any inactivated flavivirus vaccine that had a single-dose schedule in humans. EX2026, ¶111. Schuller is also consistent with Dr. Barouch’s testimony that one cannot simply arrive at a single-dose vaccine merely by increasing the dose. *Id.*, ¶106.

And Schuller is consistent with Dr. Barouch’s statement that “inactivated flavivirus **vaccines** investigated in human subjects before November 3, 2017 required more than one dose to achieve a seroconversion rate of at least 60% in the vaccinated human population.” EX2026, ¶¶55, 60-61, 106, 111-112. Dr. Barouch’s testimony must be read in the context of his entire Declaration, which was directed to discussing clinically useful inactivated flavivirus **vaccines** and a POSA’s lack of a reasonable expectation of successfully arriving at the presently claimed methods directed to “vaccinating against Zika virus disease” or “vaccinating against Zika virus infection” in humans. *See, e.g., id.*, ¶¶39-40, 42-49, 53-55, 58-61, 70-80, 91-98, 104-112; EX1001, claims 9, 11, 32-58, 60-62, 64-67. Schuller points to Day 56

as the primary endpoint for assessing the clinical immunogenicity of IC51, at which point the SCR for the single-dose regimen was merely **41.2%**. While Schuller reported a *point estimate* SCR of 65.8% at Day 28 for the 1×12μg dose group, that data point was extremely transient (lasting < 7 days) and ***not sufficient for Schuller to conclude that IC51 could be used as a single-dose vaccine.***

EX1036, 2190-2191. Not only did the SCR for the 1×12μg dose quickly drop to 58.8% at Day 35 and to 41.2% at Day 56 (the primary endpoint), the low mean titers in this group also dropped. *Id.* Yet, in the two-dose group, the SCR remained at 97.3% at Day 35 and Day 56, along with high titers. *Id.* ***Schuller therefore rejected its investigational single-dose regimen in favor of two doses, as the single-dose regimen failed to meet the primary endpoint of Schuller's clinical study.*** EX1036, 2190, 2192-2193. Schuller's single data point at Day 28 for its experimental single-dose regimen was thus not clinically meaningful: the single-dose regimen provided extremely transient seroconversion (< 7 days) and low titers, ***failing to lead to a single-dose vaccine.*** *Id.* Schuller thus would not have provided a POSA a reasonable expectation of successfully achieving a single-dose inactivated flavivirus ***vaccine.***

Accordingly, Schuller is not inconsistent with the positions Takeda has taken, and Takeda was not required to cite Schuller in this IPR or serve it on Valneva under Rule 42.51(b)(1)(iii). The Board therefore should reject Valneva's

serious, but completely unfounded and unsupported, allegations that Takeda and Dr. Barouch “expressly mischaracteriz[ed] the state of the art” or “intentionally fail[ed] to disclose ... Schuller.” Paper 8, 2. Takeda, its counsel, and Dr. Barouch take seriously their duty of candor and did not violate that duty here. Valneva’s unfounded allegations of any intent to mislead the PTAB should be rejected.

Valneva also wrongly states that Dr. Barouch opined that a POSA “would not have understood that the dose amount is a result effective variable.” Paper 8, 4. Dr. Barouch made no such statement. The burden of proof as to unpatentability falls squarely on Valneva, and Dr. Barouch correctly observed that Dr. Guirakhoo cited *no evidence* that supported Dr. Guirakhoo’s conclusory allegation that dose is a result effective variable. EX2026, ¶¶109-112. Schuller does not support Valneva. Its experimental single-dose regimen failed in its clinical trial, prompting Schuller to propose an “accelerated 2-injection ... regimen” instead. EX1036, 2190, 2193.

Valneva was well aware of Schuller before filing its petition. It is Valneva’s own study. Valneva should not be allowed to belatedly rely on Schuller to salvage the Petition’s failure to provide supporting evidence. As raised in Takeda’s POPR, the Petition did not identify where the claimed seroconversion rate was present in the relied-upon art as required by Rule 42.104(b)(4). Paper 7, 29, 49. The Board should deny institution and reject Valneva’s allegations regarding the duty of candor.

Respectfully submitted,

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

I certify that the above-captioned **PATENT OWNER'S**
SUPPLEMENTAL PRELIMINARY RESPONSE was served in its entirety on
August 6, 2025, upon the following parties via electronic mail:

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