

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 11,730,802

PETITIONER'S BRIEF AGAINST DISCRETIONARY DENIAL

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PETITIONER’S LIST OF EXHIBITS

Previously Filed:

Exhibit No.	Description
1001	U.S. Patent 11,730,802 (“the ‘802 patent”)
1002	Declaration of Farshad Guirakhoo, Ph.D.
1003	Selected file history of the ‘802 patent
1004	Thomas PCT/US2017/035046 (WO2017/210215)
1005	Barbero Calzado PCT/EP2016/082662 (WO2017/109223)
1006	Murata et al, Plaque purification as a method to mitigate the risk of adventitious-agent contamination in influenza vaccine virus seeds, Vaccine, 2011 Apr 12;29(17):3155-61
1007	Faucette et al., Immunization of pregnant women: Future of early infant protection, Human Vaccines & Immunotherapeutics 11:11, 2549-2555; November 2015
1008	PCT/US2018/059233 (published as WO2019/090238)
1009	Provisional application No. 62/592,995
1010	Provisional application No. 62/581,500
1011	Version 8 of Clinical Trial NCT02952833
1012	Liu, et al., Clinical and Vaccine Immunology, Vol. 19, No. 1 (January 2012) pp. 73-78
1013	Declaration of Robert Paarlberg
1014	U.S. NAT’L LIBRARY OF MED., NAT’L INST. OF HEALTH, Press Release: National Institutes of Health Launches “ClinicalTrials.gov” (February 29, 2000), https://www.nlm.nih.gov/archive/20040831/news/press_releases/clntr_lpr00.html

Exhibit No.	Description
1015	U.S. NAT'L LIBRARY OF MED., NAT'L INST. OF HEALTH, ClinicalTrials.gov, Clinical Trial Reporting Requirements, https://clinicaltrials.gov/policy/reporting-requirements#InternationalCommittee (last accessed March 4, 2025)
1016	U.S. National Institutes of Health, ClinicalTrials.gov, About ClinicalTrials.gov, https://web.archive.org/web/20081013222556/www.clinicaltrials.gov/ct2/info/about (Oct. 13, 2008)
1017	U.S. NAT'L LIBRARY OF MED., NAT'L INST. OF HEALTH, ClinicalTrials.gov, History, Policies, and Laws, https://clinicaltrials.gov/ct2/about-site/trends-charts (last accessed March 4, 2025)
1018	U.S. NAT'L LIBRARY OF MED., NAT'L INST. OF HEALTH, https://clinicaltrials.gov (last accessed March 4, 2025)
1019	ClinicalTrials.gov, Protocol Data Element Definitions, https://web.archive.org/web/20090411233717/http://prsinfo.clinicaltrials.gov/definitions.html (April 11, 2009)
1020	Registering Clinical Trials with ClinicalTrials.gov, https://web.archive.org/web/20090410230211/http://prsinfo.clinicaltrials.gov/registering.pdf (April 10, 2009)
1021	ClinicalTrials.gov, Disclaimer, https://clinicaltrials.gov/about-site/disclaimer (last accessed March 4, 2025)
1022	FAQ: ClinicalTrials.gov - Submission and Review of Information, https://web.archive.org/web/20090511070156/http://nlm.nih.gov/services/ctmaintain.html (May 11, 2009)
1023	ClinicalTrials.gov, How to Edit Your Study Record, http://clinicaltrials.gov/submit-studies/prs-help/how-edit-record (last accessed March 4, 2025)
1024	ClinicalTrials.gov, Background, https://web.archive.org/web/20170315024655/http://www.clinicaltrials.gov/ct2/about-site/background (March 15, 2017)

Exhibit No.	Description
1025	Study Details A Phase 1, First-in-human, Double-blinded, Randomized, Placebo-controlled Trial of a Zika Virus Purified Inactivated Vaccine (ZPIV) With Alum Adjuvant in Healthy Flavivirus-naive and Flavivirus-Primed Subjects, https://clinicaltrials.gov/study/NCT02963909?term=NCT02963909&rank=1
1026	ClinicalTrials.gov Glossary Terms ClinicalTrials.gov, https://clinicaltrials.gov/study-basics/glossary
1027	Record History NCT02963909 ClinicalTrials.gov, https://clinicaltrials.gov/study/NCT02963909?term=NCT02963909&rank=1&tab=history
1028	Study Details ZIKA Vaccine in Naive Subjects ClinicalTrials.gov, https://clinicaltrials.gov/study/NCT02952833?term=NCT02952833&rank=1
1029	Record History NCT02952833 ClinicalTrials.gov, https://clinicaltrials.gov/study/NCT02952833?term=NCT02952833&rank=1&tab=history
1030	Record History ver. 1-8: 2016-11-01 NCT02952833 ClinicalTrials.gov, https://clinicaltrials.gov/study/NCT02952833?term=NCT02952833&rank=1&tab=history&a=1&b=8#version-content-panel
1031	Record History ver. 8-10: 2017-06-29 NCT02952833 ClinicalTrials.gov, https://clinicaltrials.gov/study/NCT02952833?term=NCT02952833&rank=1&tab=history&a=8&b=10#version-content-panel
1032	Record History ver. 18: 2018-12-06 NCT02952833 ClinicalTrials.gov, https://clinicaltrials.gov/study/NCT02952833?term=NCT02952833&rank=1&a=18&tab=history#version-content-panel

Exhibit No.	Description
1033	Study Details Zika Virus Purified Inactivated Vaccine (ZPIV) Accelerated Vaccination Schedule Study ClinicalTrials.gov, https://clinicaltrials.gov/study/NCT02937233?term=NCT02937233&rank=1
1034	Record History NCT02937233 ClinicalTrials.gov, https://clinicaltrials.gov/study/NCT02937233?term=NCT02937233&rank=1&tab=history

Filed Herewith:

Exhibit No.	Description
1035	Declaration of Dan H. Barouch, M.D., Ph.D. in IPR2023-00354, dated December 15, 2022
1036	Schuller 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, Intercell AG, Campus Vienna Biocenter 2, 1030 Wien, Austria
1037	Barouch et al., Prospects for a Zika Virus Vaccine, Immunity 46, February 21, 2017 ^a 2017 Elsevier Inc.

I. INTRODUCTION

In response to Valneva's Petition demonstrating invalidity of the claims of the '802 patent by at least a preponderance of evidence, Patent Owner admitted invalidity based at least on Thomas, statutorily disclaimed, and dedicated to the public around 50% of the claims (claims 1-8, 10, 12-31, 59 and 62). Patent Owner's statutory disclaimer also implicitly concedes that Thomas (which was not cited by the Examiner during prosecution) is more material to patentability than Barbero (which was cited by the Examiner during prosecution), at least with respect to the subject matter of the statutorily disclaimed claims. Accordingly, Petitioner demonstrated that the Examiner erred in a manner material to the patentability of the limitations of the claims statutorily disclaimed based at least on Thomas. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6, at *10 (PTAB Feb. 13, 2020) (precedential) ("*Advanced Bionics*") ("[I]f the record of the Office's previous consideration of the art is not well developed or silent, then a petitioner may show the Office erred by overlooking something persuasive under factors (e) and (f).").

Patent Owner's Brief in Support of Discretionary Denial ("Patent Owner's Brief") on the remaining claims set forth in Grounds II (single dose claims) and VII-XI (adoptive transfer claims) does not argue *Fintiv* or *General Plastic* discretionary factors. Rather, Patent Owner argues based on the *Advanced Bionics* framework of

the *Becton* factors that: (1) Thomas was previously presented to the office or is substantially the same as art previously presented to the office; (2) Valneva cannot identify any error by the Office that is material to patentability; and (3) Valneva's petition with respect to the challenged claims is legally and substantively deficient.

However, Thomas was not applied by the Examiner during prosecution and Valneva has demonstrated material error by the Office in view of Thomas' teaching both 100% seroconversion in humans after a single dose and adoptive transfer of antibodies from mother to fetus. Patent Owner, through its statutory disclaimer, has implicitly conceded this material error of the Patent Office in not applying Thomas during prosecution. Further, Patent Owner wrongly argues an anticipation standard, *i.e.*, Thomas must have experimental data in humans for all of the claim limitations, in arguing against invalidity of the claims, rather than the correct standard for obviousness, which is a motivation to modify with a reasonable expectation of success, as set forth in the Petition.

Both Patent Owner and its expert Dr. Barouch have violated their duty of candor to this Board (1) by expressly mischaracterizing the state of the art, and (2) by intentionally failing to disclose the prior art Schuller reference known to them which refutes, or is inconsistent with (i) their position of lack of motivation to modify with a reasonable expectation of success in asserting patentability and (ii) their suggestion that the art does not support vaccine dose being a result-effective

variable. Particularly, both Patent Owner and Dr. Barouch argue that “[i]n *fact*, as discussed above in §II.C., before November 3, 2017, inactivated flavivirus vaccines known in the art did not provide greater than a 60% seroconversion rate in a population of human subjects after a single dose.” Patent Owner’s Brief, p. 42, *citing* Ex. 2001, ¶109. Schuller contradicts this alleged “fact” by teaching that a single 12µg dose of a JEV vaccine (IXIARO) achieved a 65.8% seroconversion rate in humans. Based on their false alleged “fact”, both Patent Owner and Dr. Barouch assert that “a POSA would not have reasonably expected to arrive at an inactivated ZIKV vaccine that could achieve the claimed seroconversion rates in a population of human subjects after a single dose.” *Id.*, p. 13, *citing* Ex. 2001, ¶¶44-45. A POSA, of course, would have expected to arrive at an inactivated ZIKV vaccine achieving a seroconversion rate of greater than 60% in humans after a single dose because Schuller teaches such was actually achieved with the JEV vaccine. Further, both Patent Owner and Dr. Barouch also ignore that this same Schuller reference, which they failed to disclose to this Board clearly discloses that vaccine dose is a variable affecting antibody generation, *i.e.* a result-effective variable for seroconversion. *Id.*, p. 42, *citing* Ex. 2001, ¶110.

Patent Owner and Dr. Barouch cited to the Board in IPR2023-00354 involving another Zika virus vaccine patent, the Schuller prior art listed on the face of the ‘802 patent as evidence of the state of the art. *See Takeda Vaccines, Inc. v. Valneva*

Austria GmbH, IPR2023-00354, Paper 2, at *25 (PTAB Dec. 27, 2022); Ex. 1035, ¶172, *citing* Ex. 1036, pp. 2188-2192. In fact, Schuller teaches that the single 12 µg dose of the IXIARO JEV vaccine resulted in 65.8% seroconversion in a population of 115 humans at day 28, directly contradicting their alleged “fact” and nonobviousness position with respect to the single dose claims in this IPR. *See* Ex. 1036, Table 2. Schuller also teaches that a single 12 µg dose achieved higher seroconversion rates than the 6 µg dose at all time points tested. *Id.*, p. 2191. This teaching demonstrates that more antigen resulted in higher seroconversion rates, and thus contradicts Patent Owner’s and Dr. Barouch’s position in this IPR that one of skill would not have understood that the dose amount is a result effective variable. Having violated their duty of candor to disclose information known to them which contradicts positions taken in this IPR, Patent Owner and Dr. Barouch’s positions are entitled to little, if any, weight.

II. BACKGROUND – RELEVANT PROSECUTION HISTORY.

Patentee either cancelled or declined to prosecute pending claims 1-64 prior to substantive prosecution. Petition, pp. 5-7. Patentee amended pending claim 65 to recite a human subject and administering a dose of from about 1 µg to about 40 µg of an antigen from a Zika virus, wherein the antigen is an inactivated whole virus. Ex. 1003, p. 147. The Patentee also added new dependent claim 75 which recited “administration of the vaccine or immunogenic composition induces 14 and/or 28

days after the boost administration a seroconversion rate of at least 80%, or at least 90%, or at least 95%, or 100% in a population of at least 20 Zika virus seronegative subjects.” *Id.*, p. 148. New claims 74-124 were also added. *Id.*, pp. 148-154.

The Examiner rejected claims 65, 66-72, 78, 79, 80-90 and 96 as being anticipated by Barbero WO2017/109223. *Id.*, p. 87. Claims 73-74, 89, 92-93, 94, 95, 103-106, 121-122 were rejected as being obvious over Barbero. However, the Examiner indicated that the subject matter of claims 75, 76, 77, 97-102, 107-119 and 123-124 “would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.” *Id.*

III. THE *ADVANCED BIONICS* FRAMEWORK IS NOT MET

Patent Owner bears the burden of proof with respect to the request for exercising discretionary denial. *Geotab USA, Inc. v. Omega Patents, LLC*, IPR2023-00504, Paper 11, at *16 (PTAB July 25, 2023) (citing 37 C.F.R. § 42.20(c)). The Board uses the *Advanced Bionics* two-part framework to determine whether discretionary denial is merited under § 325(d):

- (1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and
- (2) if either condition of first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

Advanced Bionics, Paper 6, at *8. To determine whether a previously presented reference is “substantially the same” as a reference applied in a Petition under part one of *Advanced Bionics*, the Board weighs *Becton, Dickinson* factors (a), (b), and (d), which include:

(a) the similarities and material differences between the asserted art and the prior art involved during examination;

(b) the cumulative nature of the asserted art and the prior art evaluated during examination;

. . . .

(d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;

Becton, Dickinson & Co. v. B. Braun Melsungen AG, IPR2017-01586, Paper 8, at *17-18 (PTAB Dec. 15, 2017); *Advanced Bionics*, Paper 6, at *10.

Discretionary denial of institution is inappropriate as Patent Owner’s statutory disclaimer (Ex. 2005) implicitly concedes that Thomas is not cumulative of Barbero or any other art evaluated during examination with respect to the numerous limitations in both the disclaimed and remaining claims. Thus, Patent Owner cannot meet its burden with respect to the first part of the *Advanced Bionics* framework. *JUUL Labs, Inc. v. NJOY, LLC*, IPR2024-00160, Paper 10, at *11-13 (PTAB May 24, 2024) (citation of a reference in an IDS does not automatically satisfy part 1 of the *Advanced Bionics* framework and failure to meet part 1 of the *Advanced Bionics*

framework eliminates any need to consider of part 2); *Verizon Connect Inc. v. Omega Patents., LLC*, IPR2023-01162, Paper 12, at *14 (PTAB Feb. 21, 2024) (finding that the same art or arguments were not previously presented to the office in view of combinations of prior art references even when one of the references in the combination was previously presented to the office). Further, Patent Owner neither explains how the Board relied on the same disclosures of Barbero (or any other art) during examination in the same manner as the petition relies on Thomas nor presents any analysis of the similarities of Thomas and Barbero sufficient to demonstrate that Barbero or any other art applied during examination discloses the same relevant information as Thomas. *Geotab USA*, Paper 11, at *16.

Becton, Dickinson factors (c), (e), and (f) are used to analyze whether the Office erred in a manner material to the patentability of challenged claims. *Advanced Bionics*, Paper 6, at *10. Those factors include:

- (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
- (e) whether petitioner has pointed out sufficiently how the examiner erred in its evaluation of the asserted prior art; and
- (f) the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments.

Id., at *9; *Becton, Dickinson*, Paper 8, at *17-18. These factors favor institution because the Office materially erred by allowing the claims of the ‘802 patent set

forth in Grounds II and VII-XI. At the very least, the examiner erred in failing to identify and apply Thomas, which alone or in combinations cited in the petition discloses nearly every limitation of the claims. *Quasar Sci. LLC v. Colt Int'l Clothing, Inc.*, IPR2023-00611, Paper 10, at *12-13 (PTAB Oct. 10, 2023) (declining to deny institution on finding that even if part 1 of the *Advanced Bionics* framework could be satisfied, material error existed from the failure to consider combinations and teachings of the prior art cited in the petition).

Patent Owner would have the Board believe that the Examiner considered Thomas and found Thomas no more relevant than Barbero. *See* Patent Owner's Brief, p. 28 discussing "examiner's silence." However, this "examiner's silence" argument is rebutted by the Petition's demonstration of the material teaching of Thomas that the Examiner failed to appreciate or at least overlooked, i.e. 100% seroconversion after a single dose in a human, and adoptive transfer from pregnant mother to fetus/newborn, as discussed further herein. Accordingly, Patent Owner's reliance on the "examiner's silence" in view of Petitioner's demonstrated error by the Examiner does not justify discretionary denial.

IV. THE FACTS AND LAW WEIGH AGAINST DISCRETIONARY DENIAL OF THE CLAIMS OF GROUND II (SINGLE DOSE CLAIMS)

The second part of the *Advanced Bionics* framework does not support discretionary denial of institution under § 325(d). *Becton* Factors (c), (e), and (f) favor institution because the Office erred in a manner material to the patentability of

the challenged claims by failing to appreciate the persuasive teachings of Thomas. *Advanced Bionics*, Paper 6, at *10 (“[I]f the record of the Office's previous consideration of the art is not well developed or silent, then a petitioner may show the Office erred by overlooking something persuasive under factors (e) and (f).”).

Although Thomas was cited in an IDS (Ex. 1003, p. 106), the Examiner did not issue a rejection in view of Thomas even though Thomas expressly teaches the subject matter of claim 75, as demonstrated in the Petition. Petition, pp. 15-16. *Becton Factor* (c) supports institution. *Mylan Pharm. Inc. v. Merck Sharp & Dohme Corp.*, IPR2020-00040, Paper 21, at *18 (PTAB May 12, 2020) (“The Examiner never discussed WO ’498 or made a rejection based on it. Indeed, the Examiner entered no prior art rejection against the claims of the ’708 patent. *See supra* Section I(E). Because the Examiner gave no reasons for allowance, we are left to guess at why the Examiner regarded the ’708 patent’s claims as novel and nonobvious.”); *Medacta USA, Inc., et al. v. RSB Spine, LLC*, IPR2020-00264, Paper 24, at *17 (PTAB May 22, 2020) (“because the examiner did not apply Fraser ’106’s Figure 8 during examination, *Becton*’s factor (c) weighs against exercising our discretion to deny institution under 35 U.S.C. § 325(d).”).

Single dose independent claim 11 differs from statutorily disclaimed claim 1 insofar as the administered vaccine or immunogenic composition “induces 14 and/or 28 days after *a single dose or prime administration* a seroconversion rate of **at least**

60% in a population of at least 20 Zika virus seronegative subjects.” Ex. 1001, Claims 1 and 11(emphasis added). Claims 60, 61 and 62 depend from claim 11 and recite seroconversion rates of 80%, 90% and 95%, respectively. *Id.*, 127:24-128:9.

Claim 11 corresponds to pending dependent claim 76 during prosecution which recites the above limitation and which the Examiner indicated was allowable if amended to include the subject matter of claims 65 and 68 which were both rejected as being anticipated by Barbero. Ex. 1003, pp. 86-87. The Examiner provided no explanation of why claim 76 reciting a single dose and a 60% seroconversion rate in a population of at least 20 Zika virus seronegative human subjects was allowable over Barbero.

According to Patent Owner, Barbero teaches “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, i.e., is able to confer seroprotection in at least 70% of vaccinated subjects ...” Patent Owner’s Brief, p. 17. According to Patent Owner, Barbero also teaches “the therapeutically effective amount is sufficient to seroconvert a subject with at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or at least 99% probability.” *Id.*

However, Barbero does not teach the claimed at least 60% seroconversion rate “in a population of at least 20 Zika virus seronegative [human] subjects” as required by claim 11. Barbero provides no teaching that its recited seroconversion rates are

determined within any specific population of Zika virus seronegative human subjects. Patent Owner conveniently fails to address this claimed population feature when arguing that Thomas is substantially similar to Barbero.

Further, the teachings of Barbero relied upon by Patent Owner make no mention of a point emphasized by Patent Owner in its brief that the vaccinated subjects experiencing such seroconversion are human subjects, as required by claim 11. In Barbero, the subjects can be mice or monkeys.

Provided herein are methods for administering a dose of a therapeutically effective amount of a Zika virus vaccine to a subject in need thereof. In some embodiments, the subject is a mammalian subject, such as a human, non-human primate, rodent, rabbit, sheep, dog, cat, horse, or cow. In some embodiments, the subject is a mouse. In some embodiments, the subject is a human subject, such as a child, an adult, or an elderly adult. In some embodiments, the subject is a female subject. In some embodiments, the subject is pregnant or planning on becoming pregnant. In some embodiments, the

Ex. 1005, 21:28-33. Barbero provides no teaching to one of skill that the specific seroconversion rates apply to human subjects.

According to Patent Owner, Barbero teaches that “[i]n some embodiments, a subject that is administered any of the Zika virus vaccines or compositions described [t]herein with, prior to, or after administration of an adjuvant may only require a single administration of the Zika virus vaccine or composition to be seroconverted (*produce a level* of anti-Zika virus antibodies).” Patent Owner’s Brief, p. 17 (emphasis added). However, this teaching of Barbero relied upon by Patent Owner for a single dose approach only produces “*a level*” of anti-Zika virus antibodies,

which can be any level. Barbero fails to teach either a *human subject* or a *particular population of seronegative human subjects*. In fact, the *single dose disclosure fails to teach the claimed at least 60% seroconversion rate*.

Thomas cures these deficiencies of Barbero, and Patent Owner admits as much. Patent Owner correctly quotes Thomas as teaching

‘a *single immunization* of the vaccine can be shown to *provide 100% complete protection* in susceptible mammals against challenge with ZIKV’ and ‘[i]deally, only one dose is needed to effect protection against Zika infection for mammals, *including humans*.’

Patent Owner’s Brief, p. 18.

In this single quotation, Patent Owner admits that Thomas teaches that a *single dose in humans* can provide 100% complete protection, i.e., *an upper limit seroconversion rate of 100% in humans*. If Thomas teaches 100%, then Thomas teaches greater than 60% to POSA. Thomas further teaches actual seroconversion rates of greater than 60% in a population of at least 20 Zika virus seronegative *humans*. See e.g., Ex. 1004, 42:4-7; Ex. 1002, ¶84.

Patent Owner, however, in its Brief and citing as support Dr. Barouch’s declaration (Ex. 2001, ¶¶44-45), knowingly mispresents the prior art state of single dose administration in order to reach a conclusion of no reasonable expectation of success:

“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. EX2001, ¶¶44-45. Given that, a POSA would not have reasonably expected to arrive at an inactivated ZIKV vaccine that could achieve the claimed seroconversion rates in a population of human subjects after a single dose. *Id.*”

Patent Owner. Brief, p. 13; *See also*, p. 42 (“***In fact***, as discussed above in §II.C., before November 3, 2017, inactivated flavivirus vaccines known in the art did not provide greater than a 60% seroconversion rate in a population of human subjects after a single dose.”) (emphasis added). Patent Owner and Dr. Barouch make similar misrepresentations of lack of single dose teaching and lack of motivation with reasonable expectation of success throughout the Brief. *See e.g.*, Patent Owner’s Brief, p. 13, 15, 27, 45, and 53. Only this false statement allows Patent Owner and Dr. Barouch to conclude that “a POSA would not have reasonably expected to arrive at an inactivated ZIKV vaccine that could achieve the claimed seroconversion rates in a population of human subjects after a single dose.” Patent Owner, Brief, p. 13, *citing* Ex. 2001, ¶¶44-45.

Not only is this a material misrepresentation of fact, but both Patent Owner and Dr. Barouch knew at the time of the filing of the present Patent Owner’s Brief and Expert Declaration that Schuller directly contradicted their factual assertion. Particularly, Schuller is listed on an IDS in the ‘802 patent and is an investigational

study of Japanese encephalitis vaccine IC51 (same as the IXIARO JEV vaccine referenced by Patent Owner) which reports that *a single dose of 12 µg* in a population of 115 humans achieved a *seroconversion rate of 65.8% 28 days after vaccination*.

Table 2
Seroconversion rates and GMTs of all treatment groups (PP population).

Parameter	Standard dose IC51 2 × 6 µg (N= 115)	Single, standard-dose IC51 1 × 6 µg (N= 119)	Single, high-dose IC51 1 × 12 µg (N= 115)
SCR (95% CI)			
Day 10	21.1% (13.6%; 28.5%) (114)	29.4% (21.2%; 37.6%) (119)	53.9% (44.8%; 63.0%) (115)
Day 28	39.8% (30.8%; 48.8%) (113)	42.7% (33.8%; 51.7%) (117)	65.8% (57.1%; 74.5%) (114)
Day 35	97.3% (94.4%; 100.0%) (113)	37.9% (29.1%; 46.8%) (116)	58.8% (49.7%; 67.8%) (114)
Day 56	97.3% (94.4%; 100.0%) (113)	25.6% (17.7%; 33.6%) (117)	41.2% (32.2%; 50.3%) (114)
GMT (95% CI)			
Day 10	8.41 (6.79; 10.42) (114)	9.34 (7.58; 11.51) (119)	16.74 (13.53; 20.71) (115)
Day 28	11.24 (8.90; 14.19) (113)	13.05 (10.37; 16.40) (117)	22.82 (18.10; 28.78) (114)
Day 35	265.82 (214.9; 329.89) (113)	11.29 (9.12; 13.97) (116)	17.62 (14.21; 21.85) (114)
Day 56	218.04 (179.81; 264.41) (113)	8.05 (6.66; 9.74) (117)	11.21 (9.25; 13.58) (114)

CI= confidence interval; GMT= geometric mean antibody titre; N= number of subjects in treatment group; SCR= seroconversion rate.

This study also recorded immunogenicity data at Days 10, 28 and 35 post-vaccination, to determine the kinetic profile of immunogenicity after vaccination with IC51 (Figs. 2 and 3). At Day 10, the SCR was 21% with the standard regimen, and 54% with the single, high-dose (1 × 12 µg) regimen. By Day 28, immunogenicity had increased in both groups to 40% (standard) and 66% (1 × 12 µg), which also represented the peak for the single, high-dose (1 × 12 µg) regimen. At Day 35, however, the standard regimen had achieved its peak SCR (97%), the same as that observed at Day 56, whereas the single, high-dose (1 × 12 µg) regimen was lower (59%). Thus, the standard regimen confers the maximum immunogenicity already at Day 35. The single, standard-dose (1 × 6 µg) regimen had a similar immunogenicity kinetic as the single, high-dose (1 × 12 µg) regimen although generally at a lower level (PP, Fig. 2) with statistically significant differences at all time points assessed ($p < 0.001$ at days 10 and 28; $p = 0.01$ at day 35; $p = 0.011$ at day 56).

Ex. 1036, Table 2, p. 2191 (emphasis added). Patent Owner and Dr. Barouch were both well aware of Schuller when each falsely represented to this Board as a matter of fact that no prior art flavivirus vaccine achieved a seroconversion of at least 60% in a human population after a single dose before November 3, 2017. Schuller directly contradicts this conclusion because Schuller achieved the claimed seroconversion rate (i.e., 65.8%) after a single dose of 12 μ g in a population of 115 human seronegative subjects.

Schuller was not identified to this Board by either Patent Owner or Dr. Barouch. Not only was Schuller, which was published in 2009, cited by Patent Owner on an IDS during prosecution of the '802 patent, but as detailed below, Schuller was well-known to Patent Owner and Dr. Barouch as it was cited in a recent IPR petition filed by Takeda (and represented by its current counsel) and the Expert Declaration of Dr. Barouch in support of that petition attempting to invalidate a ZIKV vaccine patent owned by Valneva. *See* IPR2023-00354, Paper 2, at *25; Ex. 1035, ¶172.

In his declaration submitted in support of that Petition, Dr. Barouch, opining on the state of the art regarding what a POSA would have sought to make expressly acknowledged the Schuller reference, (specifically citing as support for his POSA opinion the Schuller pages relied upon (“EX1059, 2188-2192”), which includes the portions of Schuller excerpted above:

172. A POSA would have also sought to make a vaccine that stimulated high titers in greater than 70% of vaccinated subjects, so as to obtain protection in as much of the vaccinated population as possible. *See* ¶131, above. In fact, IXIARO reflects this practice by using a two-dose regimen that “conferred essentially 100% seroconversion already 7 days after the second immunization,” instead of using a single-dose regimen that resulted in 60% seroconversion when IXIARO was administered using a higher dose than normal or 20% seroconversion when administered using a single dose of the standard dosage. EX1059, 2188–2192.

Ex. 1035, ¶172 (emphasis added). Patent Owner’s and Dr. Barouch’s conclusion of a lack of reasonable expectation of success fails to consider the true state of the art of which Dr. Barouch and Patent Owner were well aware. When considering Schuller as the correct state of the prior art, neither Patent Owner nor Dr. Barouch can conclude a lack of motivation and lack of a reasonable expectation of success of using a single dose ZIKV vaccine to achieve a seroconversion rate of at least 60% in a population of at least 20 humans, because Schuller achieved just that.

Under 37 C.F.R. § 42.11(a), Patent Owner and Dr. Barouch each have “a duty of candor and good faith to the Office during the course of a proceeding.” Likewise, under 37 C.F.R. § 42.51(b)(1)(iii), Patent Owner and Dr. Barouch have a duty of candor to identify relevant information that is inconsistent with its positions advanced in its Brief.

Patent Owner and Dr. Barouch have each repeatedly violated their duty of candor by advancing many times the misrepresentation that “[i]n fact, as discussed above in §II.C., before November 3, 2017, inactivated flavivirus vaccines known in the art did not provide greater than a 60% seroconversion rate in a population of human subjects after a single dose.” Patent Owner’s Brief, p. 42; Ex. 2001, ¶45 (emphasis added). This alleged “fact” is clearly contradicted by Schuller, which was known to both Patent Owner and Dr. Barouch before filing Patent Owner’s Brief and Dr. Barouch’s declaration. Despite their specific knowledge of Schuller’s contrary teaching, and having specifically cited that contrary teaching in another IPR proceeding, Patent Owner and Dr. Barouch failed to disclose Schuller to this Board in this IPR proceeding.

It is well established that parties and individuals involved in any proceeding before the Board “have a *duty of candor and good faith* to the Office during the course of a proceeding” 37 C.F.R. § 42.11(a)¹ (emphasis added); *see also Patent Quality Assurance, LLC v. VLSI Tech. LLC*, IPR2021-01229, Paper 102, at *23 (PTAB Dec. 22, 2022) (precedential) (quoting same); *OpenSky Indus., LLC v. VLSI Tech. LLC*, IPR2021-01064, Paper 102, at *17 (PTAB Oct. 4, 2022) (precedential)

¹ See also 37 C.F.R. §11.103 and 37 C.F.R. § 1.56 with respect to the duty of candor and good faith.

(quoting same). That duty of candor and good faith in conformance with Rule 42.11 attests compliance with 37 C.F.R. §11.18(b)(2) in papers presented to the Board such as such petitions, responses, written motions, or other papers. 37 C.F.R. § 42.11(c). In pertinent part, 37 C.F.R. §11.18(b)(2) states that:

(2) *To the best of the party's knowledge, information and belief*, formed after an inquiry reasonable under the circumstances,

(i) The paper is not being presented for any improper purpose,

...

(iii) The *allegations and other factual contentions have evidentiary support* or, if specifically so identified, are likely to have evidentiary support after a reasonable opportunity for further investigation or discovery; and

(iv) The *denials of factual contentions are warranted on the evidence*, or if specifically so identified, are reasonably based on a lack of information or belief.

37 C.F.R. § 11.18(b)(2) (emphasis added).

The Patent Owner and Dr. Barouch have thus far both clearly demonstrated their lack of candor and good faith in their positions and arguments advanced in this proceeding and accordingly their positions and arguments should be given little, if any, weight. Patent Owner's and Dr. Barouch's misrepresentation of the state of the art by failing to include the highly material Schuller reference negates Patent Owner's attempt to argue discretionary dismissal based on the merits. Accordingly,

Valneva requests denial of Patent Owner's request for discretionary denial and such other further relief as the Board deems suitable.

Notwithstanding Patent Owner's lack of candor and good faith, Petitioner has demonstrated in its Petition that the Examiner erred in a manner material to the patentability by missing that Thomas cures the deficiencies of Barbero by teaching (1) a single dose providing 100% complete protection in humans, and (2) seroconversion rates determined in a population of at least 20 Zika virus seronegative human subjects. In fact, Patent Owner fails to offer any comparative analysis of Barbero and Thomas with respect to the claimed human subjects or the claimed population of at least 20 Zika virus seronegative human subjects, or the claimed single dose providing at least 60% seroconversion in humans that shows where Barbero teaches these limitations. Patent Owner's analysis that ignores these claim limitations is woefully deficient and therefore fatally flawed.

Had the Examiner not missed the teachings of Thomas as set out by Dr. Guirakhoo, the Examiner would have rejected claim 76 based on Thomas, rather than indicating allowability. Claim 76 was amended to include the subject matter of dependent claim 68 and independent claim 65 leading to allowability of claim 76 as issued claim 9 and its issued dependent claims 60, 61 and 62. Accordingly, *Becton Factor* (e) supports institution. *Advanced Bionics*, Paper 6, at *8 (Board will not exercise discretionary denial under § 325(d) where "petitioner has demonstrated that

the Office erred in a manner material to the patentability of challenged claims”); *Vudu, Inc. v. Ideahub, Inc.*, IPR2020-01689, Paper 16, at *18-20 (PTAB Apr. 19, 2021) (where prior art references were cited but not substantively discussed during prosecution, “Petitioner sufficiently demonstrate[d] that the Office erred in a manner material to the patentability of the challenged claims by overlooking [the teachings of those references] and not applying [the references] in a rejection”); *Amber.io, Inc. d/b/a Two Tap v. 72Lux, Inc. d/b/a Shoppable*, IPR2020-00015, Paper 8, at *20-21 (PTAB Apr. 1, 2020) (concluding that if the office previously considered two prior art references listed on IDS forms there was clear material error to patentability from the office’s conclusion that those prior art references did not disclose certain claim limitations); *Medacta*, Paper 24, at *17; *Mylan Pharm.*, Paper 21, at *19 (“By not citing such teachings in WO ’498, we find “the Examiner erred in the evaluation of the prior art ... [and] overlooked specific teachings in the relevant prior art such that error by the Office was material to the patentability of the challenged claims.” *Advanced Bionics* at 21.”).

Further, Petitioner has provided the Board with the benefit of the expert declaration of Dr. Guirakhoo demonstrating that Thomas renders claims 9, 60, 61 and 62 obvious. Accordingly, *Becton* Factor (f) supports institution. *Medacta*, Paper 24, at *17 (finding that expert declaration explaining overlooked teachings in previously submitted prior art is additional evidence against discretionary denial);

Mylan Pharm., Paper 21, at *20 (“The Examiner’s apparent oversight with respect to the highly material teachings in WO ’498 (and the ’871 patent), along with Dr. Chorghade’s testimony about the significance of those teachings (*see*, e.g., Ex. 1002 ¶¶ 67–70, 72–80), which was not before the Examiner, convinces us that the Office’s reconsideration of the prior art or arguments is justified.”).

V. THE FACTS AND LAW WEIGH AGAINST DISCRETIONARY DENIAL OF THE CLAIMS OF GROUNDS VII-XI (ADOPTIVE TRANSFER CLAIMS)

For the reasons discussed above with respect to the Examiner’s failure to issue a rejection based on Thomas and the Guirakhoo Declaration supporting invalidity, *Becton* Factors (c), (e), and (f) support institution of the adoptive transfer claims of Grounds VII-XI.

The adoptive transfer claims of Grounds VII-XI all share the common feature “wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn.” *See*, e.g., Ex. 1001, 123:28-32. During prosecution, the Examiner rejected claim 74 as being obvious over Barbero. Claim 74 is presented below (emphasis added).

74. (New) A method of vaccinating against Zika virus disease in a fetus or newborn in need thereof, the method comprising administering to a pregnant human subject a vaccine or immunogenic composition comprising a dose of from about 1 µg to about 40 µg of an antigen from a Zika virus, wherein the antigen is an inactivated whole virus, and

wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn.

Ex. 1003, p. 148 (emphasis added).

The Examiner did not indicate that Barbero taught the claimed adoptive transfer of neutralizing antibodies from a pregnant human subject to a fetus or newborn. Instead, the Examiner placed the burden on the applicant to show “a novel or unobvious difference between the claimed” vaccine and the vaccine of Barbero. *Id.*, p. 89. The Patent Owner offered no such difference to support patentability over Barbero alone.

The Examiner indicated that dependent claim 100 (below) reciting a first and second administration would be allowable if amended into independent form to include the subject matter of claim 74. *Id.*, p. 87.

100. (New) The method of claim 74, wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration.

Id., p. 151.

Claim 100 is identical to claim 70 (below) which the Examiner stated was taught by Barbero.

70. (Previously Presented) The method of claim 65, wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration.

Id., p. 147.

Accordingly, claim 100 was believed to be allowable by the Examiner only because of the combination of the adoptive transfer feature of claim 74 (which was not taught by Barbero but nonetheless deemed obvious based on similarity between the claimed and prior art vaccines) and the first and second administration of claim 100. Patent Owner amended claim 74 to include the subject matter of claim 100, leading to allowed claim 9.

This clear back and forth during prosecution shows that the Examiner and applicant did not believe that Barbero taught “*wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn.*” Thomas cures this deficiency of Barbero. First, Thomas teaches that the human subject can be a fetus or newborn. Ex. 1002, ¶¶400-402; Ex. 1004, 2:13-24 (need for a Zika virus vaccine that protects pregnant women and fetuses). Thomas also teaches *vaccine induced immunity* from mother to fetus or child, i.e. that the mechanism of action administering a vaccine to a pregnant woman “could include ... protecting the fetus during maternal infection (infection during pregnancy occurs but vaccine induced immunity prevents fetal infection from taking hold.)” Ex. 1004, 3:2-12; *See also*, Ex. 1004, 2:13-24, 4:2-7, 18:26-30, 39:15-16; Ex. 1002, ¶¶408, 413, 415; Petition, p. 47-48.

While Thomas does not provide experimental data where the pregnant human adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn, Thomas does teach adoptive transfer studies in rhesus monkeys and in mice similar to that described in the '802 patent. Ex. 1002, ¶409. Particularly, Thomas teaches that “[a]doptive transfer studies are conducted demonstrating that the ZIKV PIV created antibodies and these antibodies protect against infection.” Ex. 1004, 33:8-10. Thomas further states that “taken together, these data demonstrate that purified IgG from ZIKV PIV vaccinated rhesus monkeys provided passive protection following adoptive transfer in both rodents and primates.” Ex. 1004, 38:24-26. Thomas then concludes that “[t]he adoptive transfer studies demonstrate that vaccine-elicited antibodies are sufficient for protection against ZIKV challenge. Moreover, passive protection in mice and rhesus monkeys is observed at relatively low antibody titers (Figs. 11, 12). Such antibody titers are likely achievable by these vaccine platforms in humans, thus raising optimism for the development of a ZIKV vaccine for humans.” Ex. 1004, 38:30-39:2; *See also* Ex. 1002, ¶409, Ex. 1004, 33:21-25, 38:17-22. Accordingly, Thomas teaches with respect to the adoptive transfer data in mice and rhesus monkeys that “taken together, these data are reasonably predictive for how ZIKV vaccines will perform in humans.” Ex. 1004, 39:15-16; *See also* Ex. 1002, ¶¶410-411; Ex. 1004, 8:24-26, 26:26-30, 38:5-22, 38:30-39:2. It is undisputed by Patent Owner that Thomas also

teaches the additional limitation of claim 9, namely wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration. *See* Ex. 1002, ¶421, *citing* Ex. 1004, 4:20-22, 7:32-33, 41:7-8.

Accordingly, the Examiner erred in a manner material to the patentability by failing to understand that Thomas cures the deficiencies of Barbero by teaching (1) vaccine induced immunity from mother to fetus or child to prevent fetal infection from taking hold, (2) adoptive transfer in both rodents and primates, (3) “taken together, these data are reasonably predictive for how ZIKV vaccines will perform in humans,” and (4) administration as a first (prime) and second (boost) administration. Further, Patent Owner admits that the state of the art recognized “[a]ntibodies transferred from mother to fetus during gestation persist in newborns for a period of time after birth. EX2019, 161; EX2001, ¶78.” Patent Owner’s Brief p. 2, n. 1. The adoptive transfer claims only require that *a vaccine effective amount* of neutralizing antibodies be transferred to the fetus or newborn. *See*, e.g., Ex. 1001, 123:28-32. The claims do not require any particular level of immune response in the fetus or newborn. *Id.* This is consistent with the limited teachings of the ‘802 patent that describe the vaccines or immunogenic compositions at a minimum *merely induce or stimulate an immune response* but do not describe any particular level of immune response or the amount of antibodies required to provide such a particular response. *See*, Ex. 1001, 33:34-38 (“Such vaccines and immunogenic

compositions may be useful, for example, for ... inducing an immune response ...); 36:3, 38:3-4, 54:40-44, and 65:21-24. Accordingly, Thomas still cures the deficiencies of Barbero since adoptive transfer was a recognized result of vaccinating a pregnant human, and the claims do not require that a vaccine effective amount result in any particular level of immune response in the fetus or newborn.

Patent Owner fails to offer any comparative analysis of Barbero and Thomas with respect to the claimed adoptive transfer. Accordingly, Patent Owner's analysis is again woefully deficient and therefore fatally flawed. Further, Patent Owner's arguments regarding any substantially similar teachings in Faucette or Murata and the art considered by the office (*See*, Patent Owner's Brief, pp. 21-23) does not address the material error made by the Office (and argued by Petitioner) in failing to appreciate Thomas's non-cumulative and substantially more robust teachings with respect to Barbero. Thomas cures the deficiencies of Barbero by teaching (1) vaccine induced immunity from mother to fetus or child to prevent fetal infection from taking hold, (2) adoptive transfer in both rodents and primates, (3) "taken together, these data are reasonably predictive for how ZIKV vaccines will perform in humans," and (4) administration as a first (prime) and second (boost) administration.

Had the Examiner not missed the teachings of Thomas as set out by Dr. Guirakhoo, the Examiner would have rejected claim 100 (issued claim 9) and any

other claims reciting adoptive transfer, rather than indicating allowability. Thus, Becton Factor (e) supports institution. *Advanced Bionics*, Paper 6, at *8 (Board will not exercise discretionary denial under § 325(d) where “petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims”); *Vudu*, Paper 16, at *18-20 (where prior art references were cited but not substantively discussed during prosecution, “Petitioner sufficiently demonstrate[d] that the Office erred in a manner material to the patentability of the challenged claims by overlooking [the teachings of those references] and not applying [the references] in a rejection”); *Amber.io*, Paper 8, at *20-21 (concluding that if the office previously considered two prior art references listed on IDS forms there was clear material error to patentability from the office’s conclusion that those prior art references did not disclose certain claim limitations); *Medacta*, Paper 24, at *17; *Mylan Pharm.*, Paper 21, at *19 (“By not citing such teachings in WO ’498, we find “the Examiner erred in the evaluation of the prior art ... [and] overlooked specific teachings in the relevant prior art such that error by the Office was material to the patentability of the challenged claims.” *Advanced Bionics* at 21.”).

VI. VALNEVA’S INVALIDITY POSITIONS IN GROUNDS II AND VII-XI ARE STRONG

Notwithstanding Patent Owner’s protestations to the contrary, the use of expert witness testimonial evidence by petitioners in PTAB proceedings has long been recognized as useful by the Board in explaining complex technologies and how

one of ordinary skill in the art would understand them (*see, e.g.*, Consolidated Trial Practice Guide, November 2019, at pp. 34-36) and is expressly contemplated by statute: “[a] petition filed under section 311 may be considered only if ... the petition identifies ... the evidence that supports the grounds for the challenge to each claim, **including ... affidavits or declarations of supporting evidence and opinions, if the petitioner relies on expert opinions.**” 35 U.S.C. § 312(a) (emphasis added). This is particularly true in assessing obviousness, which necessarily considers whether “the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.” 35 U.S.C. § 103.

That Patent Owner has submitted a Declaration from Dr. Barouch that disagrees with Dr. Guirakhoo’s opinions neither favors discretionary denial nor is evidence of weak invalidity positions. To the extent that resolution of any disagreement between opinions of experts is important to any dispute, that dispute should be resolved only after the parties have developed the record through the Board’s procedures.

A. Dr. Guirakhoo’s Expert Testimony Provides Detailed Explanations of Where the Prior Art Teaches Claim Limitations and Why the “Single Dose” Claims of Ground II are Obvious

With respect to Ground II, Dr. Guirakhoo’s declaration in this case (Ex. 1002) is provided exactly for the purposes specified in the Trial Practice Guide. His

declaration supports the Petition because it provides detailed explanations of Thomas's teachings and suggestions of a seroconversion rate in a human population after a single dose, which meets each of the claimed seroconversion rates in humans. His declaration also explains why a person of ordinary skill in the art would have found the specific claimed seroconversion rates obvious based on the teachings and suggestions of the Thomas prior art.

With respect to the Single Dose claims of Ground II, Patent Owner only challenges whether Thomas teaches the specific claimed seroconversion rates of at least 60%, 70%, 80%, 90% and 95% respectively in humans after a single dose:

“Dr. Guirakhoo does not identify where the claimed seroconversion rates of at least 60% (claims 11 and 39), at least 70% (claim 65), at least 80% (claims 60 and 66), at least 90% (claims 61 and 67), and at least 95% (claim 62) after a single dose or prime administration in a population of human subjects can be found in the prior art. EX1002, ¶¶162–201; EX1001, 123:40–52, 125:25–29, 127:24–128:26.”

“Dr. Guirakhoo cannot demonstrate where the claimed seroconversion rates in a population of human subjects are found in the asserted art...”

Patent Owner's Brief, p. 34. This is not true. Dr. Guirakhoo cites to Thomas expressly teaching an upper limit of 100% seroconversion in humans encompassing the claimed seroconversion rates in a human population after a single dose:

“[t]he purified, inactivated ZIKV can be used to immunize mammals (including humans) to elicit high titers of virus neutralizing antibodies and protect the immunized mammal from disease caused by ZIKV. For example, **a single immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against challenge with ZIKV.** Another example is wherein two doses are administered (e.g., a first dose, followed by a second dose 4 weeks later). **A booster dose (second dose or more) may be useful for persons with recurrent infection risk.**”

Ex. 1004, 4:15-22 (emphasis added); *See, e.g.,* Ex. 1002, ¶¶170, 174, 176, 178, 183, 185, 190, 192, 198, 200, 455, 457, and 459.

“Booster doses may be used, if needed ... Ideally, **only one dose is needed to effect protection against Zika infection for mammals, including humans.**”

Ex. 1004, 7:11-32 (emphasis added); *See, e.g.,* Ex. 1002, ¶¶170, 174, 176, 183, 190, 198, 455, and 457.

Patent Owner’s argument fails to address what Thomas actually teaches and suggests to one of ordinary skill in the art and erroneously conflates the law of obviousness with anticipation.²

² Patent Owner’s Brief also contains citations conflating holdings directed to obviousness with inaccurate parentheticals describing anticipation. *See, e.g.,* Patent

Anticipation under 35 U.S.C. § 102 requires that the prior art reference disclose each and every limitation. *Biogen MA Inc. v. EMD Serono, Inc.*, 976 F.3d 1326, 1331–32 (Fed. Cir. 2020). Obviousness of the claims in Ground II does not require that Thomas disclose the specific claimed seroconversion rates of at least 60%, 70%, 80%, 90%, and 95% in humans after a single dose; but rather only requires that one of ordinary skill in the art would have been motivated to achieve, and had a reasonable expectation of success in achieving, those specific claimed seroconversion rates in humans after a single dose. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). The obviousness of these claims is particularly apparent here given Thomas’ undisputed teaching and suggestion of 100% seroconversion in human subjects after a single dose. *In re Applied Materials, Inc.*, 692 F.3d 1289, 1298 (Fed. Cir. 2012). (“A reference must be considered for everything that it

Owner’s Brief, p. 49 containing the following citation and parenthetical “*Bungie, Inc. v. Acceleration Bay, LCC*, IPR2017-01601, Paper 11 at 13 (P.T.A.B. Jan. 9, 2018) (denying institution because the petitioner had not shown that the prior art **disclosed all of the limitations** of the challenged claims)”(emphasis added) where the actual holding from *Bungie Inc.* is “Petitioner has not shown sufficiently that the combination of Gilbert and Francis teaches or suggests **all of the limitations** of independent claim 19.” (emphasis added).

teaches, not simply the described invention or a preferred embodiment.”); *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1368 (Fed. Cir. 2012) (“if prior art discloses a portion of the claimed range, the entire claim is invalid.”); *In re Aller*, 220 F.2d 454, 456 (CCPA 1955)(“[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.”); *In re Wertheim*, 541 F.2d 257 (CCPA 1976) (claimed ranges that overlap or lie inside a range disclosed by the prior art are considered to be obvious over the prior art unless the range produces unexpected results).

This admitted teaching of Thomas (*see* Patent Owner’s Brief, p. 18) is cited extensively by Petitioner and in Dr. Guirakhoo’s opinions describing the teachings of Thomas and why one of ordinary skill would be motivated by this teaching to explore and have a reasonable expectation of achieving the specific claimed (or any other) seroconversion rate in at least 20 human subjects after a single dose by routine optimization of either the dosage amount or the amount/identity of the adjuvant. Petition, pp. 26-29; Ex. 1002, ¶¶170-178, 182-185; 189-192, and 196-200. Contrary to Patent Owner’s assertion, Dr. Guirakhoo identifies each claim element in the prior art. Dr. Guirakhoo’s testimony does not “fill-in” any gap in the prior art with testimony alone to teach or suggest the specific claimed seroconversion rates in a human population after a single dose. *Advanced Micro Devices, Inc. v. Realtek*

Semiconductor Corp., IPR2023-00789, Paper 9, at *39 (PTAB Oct. 26, 2023) (finding Petitioner’s citation of prior art and argument constituting sufficient support and rejecting Patent Owner’s assertions of improper gap filling with expert testimony); *In re Applied Materials*, 692 F.3d at 1298 (“The mere fact that multiple result-effective variables were combined does not necessarily render their combination beyond the capability of a person having ordinary skill in the art.”); *Senju Pharm. Co. v. Lupin Ltd.*, 780 F.3d 1337, 1353 (Fed. Cir. 2015) (invalidating a claim directed to “a product of routine optimization that would have been obvious to one of skill in the art.”)

Further, the law recognizes that determining an optimized dose as taught by Thomas is a matter of routine skill. *Genentech, Inc. v. Sandoz Inc.*, 55 F.4th 1368, 1376-1378 (Fed. Cir. 2022) (finding that “varying doses in response to the occurrence of [patient response] would seem to be a well-established, hence obvious, practice. Thus, claiming it as an invention would appear to be at best a long shot.”).

1. Patent Owner Ignores the Actual Teachings of Thomas Relied on by Petitioner and Dr. Guirakhoo

Patent Owner’s attacks on the obviousness of the claims in Ground II as supported by Dr. Guirakhoo’s opinions ignore the actual teachings of Thomas and do not withstand serious scrutiny. Instead, Patent Owner’s attacks improperly focus on requiring Thomas to expressly anticipate the claims. *Illumina Cambridge Ltd. v. Intelligent Bio-Systems, Inc.*, 638 F. App’x 999, 1005 (Fed. Cir. 2016) (“The lack of

prior art disclosures of actually achieving higher efficiency yields does not render the teachings about increasing efficiency irrelevant; obviousness is not a question of novelty.”) *citing EWP Corp. v. Reliance Universal Inc.*, 755 F.2d 898, 907 (Fed. Cir. 1985) (“A reference must be considered for everything it teaches by way of technology and is not limited to the particular invention it is describing and attempting to protect.”).

Patent Owner ignores the entirety of what Thomas teaches and what is actually relied on by Dr. Guirakhoo and Petitioner:

- That “[t]he purified, inactivated ZIKV can be used to immunize mammals (including humans) to elicit high titers of virus neutralizing antibodies and protect the immunized mammal from disease caused by ZIKV. For example, a single immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against challenge with ZIKV. Another example is wherein two doses are administered (e.g., a first dose, followed by a second dose 4 weeks later). A booster dose (second dose or more) may be useful for persons with recurrent infection risk.” Ex. 1002, ¶¶170, 174, 176, 178, 183, 185, 190, 192, 198, 200, 455, 457, and 459, citing Ex. 1004, 4:15-22;
- That a booster dose, if needed, may be used but that “[i]deally, only one dose is needed to effect protection against Zika infection for mammals,

including humans.” Ex. 1002, ¶¶170, 174, 176, 183, 190, 198, 455, and 457, citing Ex. 1004, 7:11 and 7:30-32;

- Thomas describes an exemplary dosage schedule containing a booster but also notes that “someone skilled in the art would be able to determine without undue experimentation **if** and when any second dose is needed.” (emphasis added) *See*, e.g., Ex. 1002, ¶170, citing Ex. 1004, 7:32-8:2;
- That based on knowledge for other flavivirus vaccines, “extrapolation to human use is reasonable for safe and effective dosages (e.g., **a single dose**, or a booster dose at 4 weeks as described below).” (emphasis added) *See*, e.g., Ex. 1002, ¶¶170, 176, 178, 183, 185, 190, 192, and 200, *citing* Ex. 1004, 18:17-20;
- Thomas then continues in Example 5 to teach a seroconversion rate of 92% in at least 20 humans 28 days after a boost (second) administration of a specific vaccine using a specific dose with a specific adjuvant. Ex. 1002, ¶¶169, 172, 174, 176, 183, 190, 197, and 198, *citing* Ex. 1004, 42:4-23; and
- Thomas’ description and actual data also shows the commonly understood idea that vaccine dose and/or adjuvant are well-known result-effective variables affecting seroconversion rate. Ex. 1002,

¶¶171-172, 183-184, 190-191, and 198-199, *citing* Ex. 1004, 28:19-22, 42:4-23.

These Thomas teachings provide more than ample support for Dr. Guirakhoo's opinions that the claimed specific seroconversion rates are obvious to one of ordinary skill in the art. As discussed below, Patent Owner's specific arguments are weak attempts at misdirection and fail to undermine the strength of Petitioner's invalidity positions.

2. Thomas' Teaching of 100% Seroconversion is Not Limited to Mice

On multiple occasions, Patent Owner's motion argues that Thomas' teaching of 100% seroconversion is limited to only mice because Thomas' experiments only show protection for mice from a single dose and that Petitioner's and Dr. Guirakhoo's reliance on this teaching of "mouse" data is improper. *See* Patent Owner's Brief, pp. 38, 41. However, the cited portions of Dr. Guirakhoo's opinions (Ex. 1002, ¶¶174, 178) clearly show that Dr. Guirakhoo's opinions are based on the teachings of Thomas as a whole and are not limited to extrapolation from "mouse" data. Ex. 1002, ¶¶174, 178. For example, in both of these cited paragraphs, Dr. Guirakhoo's opinions are based on Thomas' actual teaching that the 100% seroconversion is not limited to only mice but rather is directed to "mammals (including humans)":

One composition can be a purified-inactivated vaccine (PIV) for ZIKV. The vaccines comprise, consist essentially of, or consist of one or more of the purified-inactivated ZIKV as described herein. The purified, inactivated ZIKV
15 can be used to immunize mammals (including humans) to elicit high titers of virus neutralizing antibodies and protect the immunized mammal from disease caused by ZIKV. For example, a single immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against
20 challenge with ZIKV. Another example is wherein two doses are administered (e.g., a first dose, followed by a second dose 4 weeks later). A booster dose (second dose or more) may be useful for persons with recurrent infection risk.

Ex. 1004, 4:15-22. One of skill would understand that Thomas as a whole teaches a single dose vaccine administration achieving 100% seroconversion in humans. *In re Applied Materials*, 692 F.3d at 1298 (“A reference must be considered for everything that it teaches, not simply the described invention or a preferred embodiment.”).

Patent Owner and Dr. Barouch protest loudly in their Brief and Expert Declaration that animal data is “lousy” relying on the generic thoughts of others. Patent Owner’s Brief, p. 39. But, Thomas teaches that Zika vaccine studies in animals are useful to design Zika vaccine studies in humans. Particularly, Thomas teaches that:

[a]n animal efficacy study is designed to demonstrate that the vaccine is safe and has the potential for clinical benefit in human populations. Animal models may be infection models or disease models. If the animal experiences disease similar to humans this is a disease model and is desired. In the event animals do not experience disease

manifestations after exposure but viral replication (viremia) is measurable it is possible to extrapolate animal results to potential outcomes in humans (prevent viremia = prevent disease). Therefore, if vaccination does not cause any adverse events in the animal and induces an effective immune response (neutralizing antibodies) which protects against a live virus challenge in comparison to a placebo or another control this is typically supportive data to advance to human trials. This testing may be necessary before a vaccine can progress to a clinical trial. Typically, such experiments are best performed in a non-human primate infection model (e.g., rhesus macaques) with the primary endpoints being the measurement of virus neutralizing antibodies after vaccination and the measurement of protection against challenge with an attenuated or wild type ZIKV strain. Protection can be assessed by a disease surrogate such as circulating virus (viremia) after virus challenge with a near-wild-type (low passage) strain of ZIKV. Various vaccine doses and immunization schedules can also be tested in the experiment.

Ex. 1004, pp. 26:20-27:5.

Thomas tested the purified, inactivated Zika virus vaccine using alum as the adjuvant in mice and concluded based on the reported data that a single dose of the vaccine provided complete protection. *Id.*, pp. 32:23-24, 32:27-33:2. Thomas also tested the ZIKV PIV vaccine in rhesus monkeys and concluded that the data confirms and extends the previous conclusions to non-human primates. *Id.*, pp. 36:26-37:29, 37:33-38:4.

From these mice and non-human primate studies, Thomas then further teaches that the consistency and antibody-based correlates of vaccine protection “are reasonably predictive for how ZIKV vaccines will perform in humans.” *Id.*, p. 39:9-16. Thomas then tested the ZIKV PIV vaccine in humans and reported high seroconversion rates. *Id.*, p. 42:4-7. Leading to the conclusion that Thomas’ compositions are immunogenic and that vaccines comprising inactivated ZIKV are protective against infection with ZIKV. *Id.*, pp. 42:20-43:1. This is the very conclusion in human studies that was reached in animal studies. Accordingly, the preclinical mouse and monkey data disclosed by Thomas is far from “lousy” as argued by Dr. Barouch. Thomas demonstrated it to be predictively valid in humans.

In fact, Dr. Barouch recognized the predicative validity of preclinical ZIKA vaccine animal studies for developing a ZIKA vaccine in humans before Thomas. In one of his peer reviewed articles, Dr. Barouch stated:

- “[p]romising data from preclinical vaccine studies in mice and monkeys suggest that an effective vaccine will likely be possible, but important scientific challenges remain;”
- “[p]reclinical vaccine studies in mice and monkeys have suggested that multiple ZIKV vaccine platforms may be highly efficacious;”
- “[o]ur group demonstrated the initial proof-of-concept that vaccines can protect against ZIKV challenge in both mice (Larocca et al., 2016)

and rhesus monkeys (Abbink et al., 2016)” and that “these findings raise considerable optimism that the development of a ZIKV vaccine for humans will likely be possible;” and

- “[p]reclinical ZIKV vaccine studies have provided a strong proof-of-concept that the development of an effective ZIKV vaccine should be possible.”

Ex. 1037, Abstract, pp. 176-177; *See also* Ex. 2003, Abstract (“Our findings suggest that the development of a ZIKV vaccine for humans is likely to be achievable.”); Ex. 2004, Abstract (“These data support the rapid clinical development of ZIKV vaccines for humans.”). Accordingly, Dr. Barouch’s present expert opinion for purposes of this IPR that animal studies are “lousy” is contradicted by his own prior published and peer reviewed opinions with respect to development of a Zika vaccine for humans.

Patent Owner’s and Dr. Barouch’s cherry-picking of prior art for positions that denigrate animal studies as “lousy models” (Patent Owner’s Brief, p. 39) is disingenuous and misleading in view of Dr. Barouch’s own prior opinions and the many animal studies and results achieved therefrom that helped to guide vaccine development in the ‘802 patent towards human trials. Dr. Barouch states that “many of those in the field of vaccinology have shared this perspective before November 3, 2017.” Patent Owner’s Brief, p. 39, *citing* Ex. 2001, ¶104. Apparently, Dr. Barouch

did not share this perspective with respect to his own efforts in ZIKA vaccine development. Certainly, Thomas did not share this perspective. Thomas expressly teaches that results in mice for the Zika vaccine can be expected to produce similar results in humans. Further, none of the references relied on by Dr. Barouch describe a Zika vaccine. Accordingly, Dr. Barouch's cherry-picked references are less relevant to the issue of reasonable expectation of success in humans based on mouse data than Thomas, or his own prior opinions.

3. The Teachings of Thomas Support Dr. Guirakhoo's Opinion That "Dose" or "Adjuvant" Are Result-Effective Variables That Could Be Readily Optimized To Achieve the Specific Claimed Seroconversion Rates

As detailed below, Dr. Guirakhoo relied on the express teachings of Thomas on dose amount, dose frequency and adjuvant effect and his experience in the field to conclude that both dose and adjuvant effect antibody generation and are therefore result effective variables based on the law.

a. Dr. Guirakhoo's Opinions on The Result Effective Variables Are Supported by Thomas' Own Teachings

Contrary to Patent Owner, Dr. Guirakhoo's opinions regarding result effective variables are not simply conclusory. Patent Owner's reliance on *Xerox* is misplaced as it does not support the Patent Owner's argument in the present case. *Xerox* focused on whether the expert testimony cites to "supporting evidence or provide[s] any technical reasoning." *Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Paper 9,

at *15 (PTAB Aug. 24, 2022). Expert testimony is afforded less weight if it “adds little to the conclusory assertion for which it is offered to support.” *Id.* Here however, Dr. Guirakhoo’s opinion is fully supported and includes “additional supporting evidence [and] provide[s] ... technical reasoning to support his statement.” *Id.* In forming his opinions, Dr. Guirakhoo indicated that he relied on his “education, experience, and knowledge in the field of vaccine development, manufacture and use,” including his knowledge of “recognition in the prior art that a property is affected by the variable is sufficient to find the variable result-effective.” Ex. 1002, ¶¶3, 37; *B/E Aero., Inc. v. C&D Zodiac, Inc.*, 962 F.3d 1373, 1380 (Fed. Cir. 2020) (“After KSR, we recognized that **courts must consider** common sense, common wisdom, and common knowledge in analyzing obviousness.”) (emphasis added. quotes omitted). Further, Patent Owner ignores the cited evidence in Thomas and technical reasoning supporting Dr. Guirakhoo’s opinions. *See e.g.*, Patent Owner’s Brief, p. 33, *citing* Ex. 1002, ¶178, and p. 42, *citing* Ex. 1002, ¶177. That evidence and technical reasoning ignored by the Patent Owner supports Dr. Guirakhoo’s opinion³ and explains how Thomas teaches to one of ordinary skill that dose and adjuvant are result-effective variables:

³ For ease of understanding, Petitioner has limited its response to paragraphs expressly dealing with Dr. Guirakhoo’s opinions on claim 11. However, similar

- Thomas teaches a seroconversion rate of 92% for 55 humans at day 57 after a boost administration. Thus, Thomas teaches a seroconversion rate of at least 60% in a human population of at least 20 subjects (See e.g., Ex. 1002, ¶169, 176, *citing* Ex. 1004, 42:4-7, Table at 42:19);
- Thomas teaches that while a single dose is ideal, a booster dose may be need for certain subjects (*See e.g.*, Ex. 1002, ¶¶170, 174, 176, 178, *citing* Ex. 1004, 4:15-28, 7:11, 7:30-8:2, 18:17-20);
- Thomas teaches that a single antigen dose can provide 100% seroconversion in mammals (including humans) (*See e.g.*, Ex. 1002, ¶¶170, 174, 176, 178, *citing* Ex. 1004, 4:15-28, 7:11, 7:30-8:2);
- Thomas teaches that with the same adjuvant seroconversion is increased in response to increased dosage (*See e.g.*, Ex. 1002, ¶¶172, 174, 176, *citing* Ex. 1004, 42:4-23, Table at 42);
- Adjuvants are well-known substances used in vaccines to enhance, accelerate or prolong antigen response (e.g., seroconversion) (*See e.g.*, Ex. 1002, ¶¶171, *citing* Ex. 1004, 28:19-22); and

detailed explanation for the other claims in Ground II is also present in Dr. Guirakhoo's declaration. Ex. 1002, ¶¶181-186, 188-193, and 195-200.

- Thomas itself teaches that “An exemplary dosage schedule entails an initial dose, then a second (booster) dose about 4 weeks later. However, this schedule is exemplary only, and someone skilled in the art would be able to determine without undue experimentation if and when any second dose is needed.” (*See e.g.*, Ex. 1002, ¶¶170, *citing* Ex. 1004, 4:24-28; 7:32-8:2, 18:17-20).

Thus, Dr. Guirakhoo has clearly provided “additional supporting evidence” and “technical reasoning to support his statement” that “the amount of antigen and/or adjuvant or the type of adjuvant make the vaccine dose a result-effective variable.” *Xerox*, Paper 9, at *15; Ex. 1002, ¶¶172, 177, 178.

Patent Owner’s implication that the vaccine dose is not a result-effective variable in view of the state of the art is simply not credible. Both Patent Owner and Dr. Barouch withheld the state of the art Schuller reference which contradicts their position that the art did not recognize vaccine dose being a result effective variable and that the art lacked motivation to administer a single dose to achieve a seroconversion of greater than 60%. Ex. 1036, p. 2191. Table 2 of Schuller discloses data demonstrating that raising the single dose from 6 µg to 12 µg results in a higher seroconversion at all time points tested, with a maximum of 65.8% at day 28 in a population of 115 humans. Ex. 1036, Table 2. This data further supports Dr. Guirakhoo’s opinions based on the teachings of Thomas as well as his education,

knowledge, and experience that vaccine dose is result effective in terms of seroconversion and would have motivated one of skill to administer a single dose and to increase single dosage amount to increase seroconversion rates.

b. Lack of an Anticipatory Teaching is Immaterial to the Obviousness of the Single Dose Claims of Grounds II

As discussed above, Ground II is directed to the obviousness of the Single Dose Claims. Thus, an anticipatory teaching of the specific claimed seroconversion rate in humans after a single dose in any one piece of prior art is neither necessary nor required. *See, Illumina Cambridge*, 638 F. App'x at 1005 (“The lack of prior art disclosures of actually achieving higher efficiency yields does not render the teachings about increasing efficiency irrelevant; obviousness is not a question of novelty.”) *citing EWP Corp.*, 755 F.2d at 907 (“A reference must be considered for everything it teaches by way of technology and is not limited to the particular invention it is describing and attempting to protect.”); *In re Applied Materials*, 692 F.3d at 1298 (“A reference must be considered for everything that it teaches, not simply the described invention or a preferred embodiment.”). Further, all that is required to be taught by Thomas is a reasonable expectation of success, not an absolute prediction of success. *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988) (“Obviousness does not require absolute predictability of success ... [A]ll that is required is a reasonable expectation of success.”). Even if one were to accept Patent Owner's premise that Thomas teaches information in addition to or differing

from other prior art references, that premise does not require one of ordinary skill to ignore Thomas' teachings. *In re Young*, 927 F.2d 588, 591 (Fed. Cir. 1991) (each reference must be considered on its own "for its power to suggest solutions to an artisan of ordinary skill.").

Patent Owner's arguments that Dr. Guirakhoo's opinions based on Thomas are conclusory and "contrary" to the teachings of other pre-selected references that pre-date Thomas is inapposite. Patent Owner's Brief, pp. 42-45, *citing* Ex. 2001, ¶¶44-45 and Exs. 2010, 2015-2017. These cherry-picked references relied on by Patent Owner pre-date Thomas by years (some by nearly 10 years) and plainly ignore additional years of understanding in the technology field that Thomas describes. Thomas's publication date is much closer in time to the '802 patents' earliest claimed priority date than each of the older cherry-picked references relied upon by the Patent Owner. Thus, Thomas is the more relevant prior art and more instructive of Zika virus vaccines at the pertinent time for determining obviousness.

Further and as discussed above in Section IV above, Patent Owner and Dr. Barouch knowingly misrepresented to this Board that "before November 3, 2017, inactivated flavivirus vaccines known in the art did not provide greater than a 60% seroconversion rate in a population of human subjects after a single dose." Patent Owner's Brief, p. 42. Particularly, when they were a Petitioner in an IPR attacking Valneva's patent, Patent Owner and Dr. Barouch relied upon and specifically cited

the earlier Schuller reference's teaching of a greater than a 60% seroconversion rate in a population of human subjects after a single dose. Now that they are on the Patent Owner's side in this IPR, they have no issue withholding this information which contradicts the positions they are advancing to save the '802 patent. In view of this breach of the duty of candor, neither Patent Owner nor Dr. Barouch have any credibility and their arguments and testimony should be treated as such. Accordingly, Patent Owner's and Dr. Barouch's criticism of Dr. Guirakhoo's opinions, while knowingly misrepresenting the state of the art before November 3, 2017 based on their cherry-picked pre-Thomas prior art references, has no substantive merit. Notwithstanding any other prior art teaching or Patent Owner or Dr. Barouch's characterization or omission of those teachings, Thomas itself remains highly relevant for what it teaches and suggests to one of ordinary skill in the art at the time when obviousness is to be determined. As discussed in Section VI.A.1, the admitted, indisputable teaching and suggestion of Thomas, as extensively cited in the Petition and by Dr. Guirakhoo, is that Thomas expressly teaches to one skilled in the art an upper limit encompassing the claimed seroconversion rates in a human population after a single dose:

“[t]he purified, inactivated ZIKV can be used to immunize mammals (including humans) to elicit high titers of virus neutralizing antibodies and protect the immunized mammal from disease caused by ZIKV. For example, **a single immunization of the vaccine can be shown to**

provide 100% complete protection in susceptible mammals against challenge with ZIKV.”

Ex. 1004, 4:15-22 (emphasis added).

“Booster doses may be used, if needed...Ideally, only one dose is needed to effect protection against Zika infection for mammals, including humans.”

Ex. 1004, 7:11-32 (emphasis added). Additionally, Thomas is more relevant than Patent Owner’s cherry-picked prior art references because Thomas relates to a Zika virus vaccine. That Patent Owner’s earlier cherry-picked references do not teach or suggest what Thomas discloses does not negate the fact that Thomas provides this very teaching and suggestion to one skilled in the art and thereby renders claims of the ‘802 patent invalid for obviousness.

Patent Owner’s argument that Example 5 of Thomas did not achieve mean titers greater than 1:10 after a single dose or prime administration (Patent Owner’s Brief, pp. 35-36) does not mean one of skill would have understood that higher titers were not possible with a single dose, taking the teachings of Thomas as a whole. Thomas’ specific example used a 5 µg dose, but also taught to vary dosage to achieve 100% seroconversion in a single dose. *See e.g.*, Ex. 1002, ¶174, *citing* Ex. 1004, 4:15-22. Thomas also taught that adjuvants affected seroconversion. *Id.* While Thomas’ specific example used a second 5 µg dose, one of skill would not

understand from Thomas that only a second 5 µg dose was required in all circumstances to achieve higher seroconversion.

Patent Owner also argues that Valneva's own data teaches against the single dose approach, citing Wressnigg (Ex. 2007). Patent Owner's Brief, pp. 47-48, *citing* Ex. 2007. However, Ex. 2007 is dated 2022 and reports data generated after the filing date of the '802 patent and so is not prior art. Ex. 2007 is irrelevant to what one of skill would have understood as of the priority date of the '802 patent.

Patent Owner further argues that Thomas would have directed Dr. Guirakhoo to the studies identified by Dr. Barouch in his Declaration on which he relies for his factual statement that no vaccine achieved 60% seroconversion in humans after a single dose. Patent Owner's Brief, pp. 45-46. If true, then Thomas would also have directed a POSA to Schuller, which was withheld by Dr. Barouch and directly contradicts the many statements made by Dr. Barouch that a single dose did not achieve a seroconversion of 60% in humans. This entire line of argument by Patent Owner is not credible in view of Patent Owner's and Dr. Barouch's withholding of Schuller's contrary teachings.

Patent Owner's suggestion that an Article III court is more capable than the Board in reviewing expert declarations and making decisions on validity is also not well-founded. Patent Owner's Brief, p. 49. First, there is no lawsuit pending between Patent Owner and Petitioner, and so there is nothing for an Article III court

to decide. Second, the IPR process was created expressly as an alternative to an Article III court and there is no requirement that limits potential petitioner to only those with Article III court standing. 35 U.S.C. § 311(a) (“**[A] person who is not the owner of a patent** may file with the Office a petition to institute an inter partes review of the patent”) (emphasis added); *Cuozzo Speed Techs., LLC v. Lee*, 579 U.S. 261, 279 (2016); *OpenSky*, Paper 102, at *36 (precedential) (the Director noted the propriety of filing a petition when there are “circumstances in which a petitioner has not yet been sued”).

B. Dr. Guirakhoo’s Expert Testimony Provides Detailed Explanation of the Motivations to Combine and Reasonable Expectation of Success for the “Adoptive Transfer” Claims in Grounds VII-XI

Petitioner has demonstrated motivation to combine and reasonable expectation of success of the adoptive transfer claims in Grounds VII-XI.

The Petition and Dr. Guirakhoo’s opinions based on the knowledge and understanding of one of ordinary skill in the art, describe a very predictable and logical basis for how Thomas and Faucette build on each other:

- Thomas teaches all of the claim limitations of the broadest independent claims in Grounds VII-XI (as well as the specific limitations of the dependent claims in Ground VII) including examples of adoptive transfer in animals other than humans; that a purified inactivated whole Zika virus is advantageous for pregnant women; that a method of

vaccine could include protection of a fetus through adoptive transfer; and, taken together its examples of adoptive transfer in other animals are reasonably predictive of what will happen in humans. However, Thomas does not expressly provide human experimental data for adoptive transfer from mother to fetus. *See*, e.g., Ex. 1002, ¶¶407-413; and

- Second, Faucette teaches methods of adoptive transfer from human mothers to fetuses in a number of inactivated virus vaccines such as inactivated Zika virus vaccine described in Thomas; Ex. 1002, ¶¶414-418.

Accordingly, one of ordinary skill would have a strong motivation to combine Thomas with Faucette. Thomas teaches adoptive transfer in animals and that such teachings are reasonably predictive of human performance and support advancement to human trials. Thomas also teaches the need for a vaccine to protect pregnant human women and fetuses. Faucette is in the same field of endeavor as Thomas. Faucette teaches the making, testing and using of the same type of vaccine (e.g., a purified, inactivated whole virus antigen vaccines) described in Thomas for adoptive transfer from pregnant women to fetuses/newborns, with a reasonable expectation of success. *See*, e.g., Ex. 1002, ¶¶412-419. One of skill would have looked to Faucette to confirm adoptive transfer from pregnant mother to fetus/newborn.

Contrary to Patent Owner’s argument, there is no improper reliance on hindsight. For when the prior art suggests that one approach is or may be effective, it is not impermissible hindsight to base an unpatentability argument on this approach. *See, e.g., Mylan Pharm. Inc. v. Janssen Oncology, Inc.*, IPR2016-01332, Paper 84, at *30-31 (PTAB Jan. 17, 2018) (finding allegations of hindsight bias unpersuasive where at least “some research” was focused on the claimed cancer treatment and thus petitioner’s “reasoning incorporates and relies on the knowledge of [a POSA].”).

Patent Owner initially argues that “[a] POSA would not have selected Thomas’s inactivated ZIKV vaccine to vaccinate a pregnant individual, when Thomas’s vaccine required two doses, given four weeks apart, to achieve significant seroconversion in a population of human subjects and when quick seroconversion, with as few administrations as possible, would have been important for pregnant individuals.” Patent Owner’s Brief, p. 31; *See also* Patent Owner’s Brief, pp. 52-53. However, adoptive transfer claim 9 requires a first (prime) and a second (boost) administration and requires no particular timing in between to achieve adoptive transfer between pregnant mother and fetus/newborn. Accordingly, Patent Owner’s position that one of skill would not have selected Thomas because Thomas discloses two doses four weeks apart is contradicted by claim 9 itself, which allows the very same administration as claimed.

Patent Owner’s first argument (see, Patent Owner’s Brief, Section IV(B)(1), pp. 51-54) is that a person of ordinary skill would not reasonably expect success or be motivated to combine Thomas with Faucette for the adoptive transfer claim limitations of the claims set forth in Grounds VII-XI. This argument, based on Patent Owner’s similar arguments discussed *supra*, ignores what Thomas teaches as a whole and thus improperly limits Thomas’ teachings to a specific embodiment --- a vaccine schedule that requires multiple doses, spaced 28 days apart in human subjects and disputes Thomas teachings that dosage is a result effect variable. *See, e.g.*, Patent Owner’s Brief, p. 52 (“Valneva does not explain why a POSA would have had a reason to use Thomas’s vaccine – which required two doses, spread 28 days apart, to induce significant seroconversion in a population of human subjects – to transfer a vaccine effective amount of neutralizing antibodies against ZIKV to a fetus or newborn.”).

However, only two claims in Grounds VII-XI contain the “Single Dose” seroconversion rate limitations (e.g., claims 39 and 67). With respect to these claims, Thomas is not so limited and renders obvious the single dose seroconversion rate limitation. *See supra* Section VI.A. As to the remainder of the claims, Patent Owner’s argument is legally improper as a patentee cannot import non-existent limitations into a claim as a basis for nonobviousness. *See Am. Piledriving Equip., Inc. v. Geoquip, Inc.*, 637 F.3d 1324, 1330–31 (Fed. Cir. 2011) (holding that it is

improper to read limitations into the claim to obviate factual questions of validity); *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1340 (Fed. Cir. 2001) (importing limitations into the claims is “one of the cardinal sins of patent law”). Patent Owner’s primary argument does not seriously challenge the strength of the Petition’s motivation to combine and the reasonable expectation of success from the combination of Thomas and Faucette with respect to the adoptive transfer claim limitations.

Patent Owner’s second argument (*i.e.*, Patent Owner’s Brief, Section IV(B)(2), pp. 54-56) is limited to only those claims (claims 34, 43-46, 48, 54 and 64) in Grounds VIII and X that combine NCT02952833 with Thomas and Faucette, for the express recitation in NCT02952833 of utilizing a 10 µg dose. The combinations utilizing the express recitation of the 10 µg dose in NCT02952833 are directed to non-adoptive transfer claim limitations of claims 34, 43-46, 48, 54 and 64 that are the same limitations also found in other claims (e.g., claims 5, 13, 16-18, 20, and 26) of the ‘802 patent, which Petitioner argued are obvious in view of Thomas and NCT02952833. *See e.g.*, Petition, pp. 58-59; Ex. 1002, ¶467 (“Claim 34 recites the same 10 µg dose administered one time as claim 5.”) *See also* Petition, pp. 57-59; Ex. 1002, ¶¶465-482, 522-528.

With respect to claim 5, Petitioner argued that claim 5 was obvious over Thomas and NCT02952833 based in part on the following facts:

- Thomas and Version 8 of NCT02952833 are in the same field of endeavor, i.e. making, testing, and using purified, inactivated whole Zika virus antigen vaccines for use in humans, including human trials of those vaccines;
- Thomas teaches that dosage amount is a result-effective variable and that one of its goals is to determine a “safe and effective dose and schedule for this ZIKV PIV, as needed for persons of any age and size.” Ex. 1004 4:24-28;
- Version 8 of NCT02952833 evaluates three dose levels of “5.0 mcg, 2.5 mcg and 10mcg of ZPIV” to assess their safety and reactogenicity. Ex. 1011, p. 6;
- One of ordinary skill would have only needed to employ routine skill and would have been motivated to modify the method of Thomas using a dose of 5 μ g to administer the Zika vaccine at a dose of 10.0 μ g because Thomas teaches to determine optimal doses of ZIKV antigen based on “dosing and schedule for other PIV flavivirus vaccines – such as Japanese encephalitis and tick-borne encephalitis – someone skilled in this art can determine a safe and effective dose and schedule for this ZIKV PIV, as needed for persons of any age and size.” Ex. 1004 4:24-28;

- Thomas further teaches exploring a range of antigen doses in an attempt to define the optimal dose of antigen as well as lower limits of antigen concentration required to effectively immunize a recipient. Ex. 1004 40:18-22; and
- One of skill would have had a reasonable expectation of successfully using a 10 µg dose from the human vaccination method of Version 8 of NCT02952833 to vaccinate against Zika virus infection in the human vaccination method of Thomas because Thomas demonstrated that a total of 10 µg was safe and provided significant immune response to provide protection against Zika virus.

Petition, pp. 40-43, citing in part Ex. 1002, ¶¶278-294. Rather than dispute the Petition's showing of invalidity of these claims, Patent Owner statutorily disclaimed claims 5, 13, 16-18, 20 and 26 (see Ex. 2005), implicitly conceding the accuracy of the cited basis for the obviousness of claims from the recited combination of Thomas and NCT02952833. Given Patent Owner's statutory disclaimer and implicit concession of invalidity, the only substantive argument that Patent Owner has not at least implicitly conceded regarding the obviousness of the adoptive transfer (claims 34, 43-46, 48, 54 and 64) based on Thomas in view Faucette and NCT02952833 (Grounds VIII and X) is not whether NCT02952833 includes pregnant woman (Patent Owner's Brief, pp. 54-55). Excluding pregnant women from a reference's

(i.e., NCT02952833's) experimental data set does not teach one of skill that 10 µg is unsuitable for a pregnant woman, as wrongly concluded by Patent Owner. Rather the correct analysis is whether Faucette expressly teaches away from using a 10 µg dose in pregnant woman. Teaching away requires that "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *Centripetal Networks, LLC v. Palo Alto Networks, Inc.*, No. 2023-1785, 2024 WL 4635578, at *7 (Fed. Cir. 2024), *quoting In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). Patent Owner does not even attempt to argue that Faucette discourages the use of a 10 µg dose.

Patent Owner's second argument regarding vaccine dose being a result-effective has been previously addressed. *See supra* Section VI(A)(3). Patent Owner's third argument (i.e., Patent Owner's Brief, Section IV(B)(3), pp. 56-59) is limited to only the two claims (claims 54 and 64) in Ground X that combine Barbero and NCT02952833 with Thomas and Faucette for utilizing 200 µg of an adjuvant. The combination's use of Thomas, Barbero and NCT02952833 for claims 54 and 64 is applied the same way and directed to the same claim limitation that is found in claim 26 of the '802 patent, which Petitioner argued was obvious in view of Thomas, Barbero, and NCT02952833:

“Following the analysis of claim 26 and applying that analysis to claim 54, a POSA would have understood that the amount of adjuvant is a result-effective variable affecting seroconversion as previously discussed. Barbero teaches to a POSA a vaccine dose including 500 µg of an aluminum hydroxide adjuvant. A POSA would have been motivated to modify the 500 µg amount of the aluminum hydroxide adjuvant of Barbero to 200 µg because Thomas teaches to use a suitable amount of an adjuvant. The amount of adjuvant is a routine design parameter for vaccines and is a result-effective variable affecting seroconversion. One of skill would have been able to modify the 500 µg to 200 µg as a matter of routine optimization using ordinary skill, simply by lowering the amount of adjuvant combined with the inactivated whole Zika virus antigen.”

Ex. 1002, ¶517; See also Petition, pp. 60-61; Ex. 1002, ¶521. Rather than dispute the Petition’s showing of invalidity of claim 26, Patent Owner statutorily disclaimed claim 26 (Ex. 2005), implicitly conceding the accuracy of the cited basis for the obviousness based on the recited combination of Thomas and Barbero and the strength of the argument that routine optimization using ordinary skill of a result-effective variable such as amount of the adjuvant was clearly obvious. Given Patent Owner’s concession, there is no substantive argument adversely affecting the strength of the argument that claims 54 and 64 are therefore also obvious in view of Thomas, Faucette, NCT02952833, and Barbero. Patent Owner does not even attempt to argue that either Faucette or NCT02952833 discourages the use of 200 µg of an adjuvant.

VII. THIS IPR IS APPROPRIATELY CONSIDERED BY THE OFFICE

Notwithstanding Patent Owner's above inaccurate attacks focusing on only a subset of the other considerations listed in the Acting Director's March 26, 2025 Memorandum on Interim Processes for PTAB Workload Management (hereinafter, "Memo")), a number of those considerations weigh against discretionary denial. First, there are no settled expectations. *See* Memo, p. 2. The '802 patent issued in August 2023, just over 18 months before this petition was filed. Patent Owner has thus "not developed strong settled expectations that favor discretionary denial." *Zhuhai CosMX Battery Co., Ltd. v. Ningde Ampere Tech. Ltd.*, IPR2025-00385, Paper 9, at *2 (PTAB July 2, 2025) (Director holding that patents issued in 2021, 2023, and 2024 "have not been in force for a significant period of time, and, accordingly, Patent Owner has not developed strong settled expectations that favor discretionary denial."). Here, "the early challenge" to the '802 patent "tip[s] the balance against discretionary denial." *Id.* at 2-3; *see also* *Ajinomoto Co., Inc. v. AbTis Co., Ltd.*, IPR2025-00283, Paper 13, at *2 (PTAB Jul. 2, 2025) ("Early challenges favor robust, predictable patent rights and weigh against discretionary denial."). Second, neither the PTAB nor another forum has previously adjudicated the validity of the issued of the '802 patent. *See* Memo at 2. This IPR is the first and only post-grant challenge to the '802 patent at the Patent Office and has already resulted in

Patent Owner statutorily disclaiming approximately 50% of the issued claims of the ‘802 patent.

VIII. CONCLUSION

For the reasons explained herein, discretionary denial of the current petition is inappropriate. The Board should therefore deny Patent Owner’s request for discretionary denial and grant such other further relief as the Board deems suitable.

Dated: July 18, 2025

By: /Robert F. Altherr, Jr./

Robert F. Altherr, Jr.
Reg. No. 31,810
Banner & Witcoff, Ltd.
1100 13th Street, NW
Suite 1200
Washington, DC 20005
(202) 824-3000
raltherr@bannerwitcoff.com

CERTIFICATION UNDER 37 C.F.R. §42.24(d)

Under the provisions of the Interim Processes for PTAB Workload Management dated March 26, 2025 and 37 C.F.R. §42.24, the undersigned hereby certifies that according to the word processing system used to prepare this document the word count for the foregoing Petitioner's Brief Against Discretionary Denial totals 13,476 words, which is less than the limit of 14,000 words.

Pursuant to 37 C.F.R. §42.24(a)(1), this count does not include the table of contents, the table of authorities, mandatory notices under §42.8, the certificate of service, this certification of word count, the claims listing appendix, or appendix of exhibits.

Dated: July 18, 2025

By: /Robert F. Altherr, Jr./

Robert F. Altherr, Jr.
Reg. No. 31,810
Banner & Witcoff, Ltd.
1100 13th Street, NW
Suite 1200
Washington, DC 20005
(202) 824-3000
raltherr@bannerwitcoff.com

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that I caused a true and correct copy of this **PETITIONER'S BRIEF AGAINST DISCRETIONARY DENIAL** in connection with IPR2025-00776 to be served via e-mail on July 18, 2025, in its entirety on the following counsel of record for Patent Owner:

EELLISON-PTAB@STERNKESSLER.COM
OPARTINGTON-PTAB@STERNEKESSLER.COM
CGALLO-PTAB@STERNEKESSLER.COM
PTAB@STERNEKESSLER.COM

Dated: July 18, 2025

By: /Carlos Goldie/

Carlos Goldie