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Paper 12
Date: October 16, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

VALNEVA AUSTRIA GMBH,
Petitioner,

v.

TAKEDA VACCINES, INC.,
Patent Owner.

IPR2025-00776
Patent 11,730,802 B2

Before JOHN G. NEW, RYAN H. FLAX, and TIMOTHY G. MAJORS, *Administrative Patent Judges.*

NEW, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

A. Background and Summary

Valneva Austria GMBH ("Petitioner") has filed a Petition (Paper 1, "Pet.") requesting *inter partes* review of claims 1–67 of U.S. Patent No. 11,730,802 B2 (Ex. 1001, "the '802 patent"). Subsequent to the filing of the Petition, Takeda Vaccines, Inc. ("Patent Owner") submitted a statutory disclaimer of claims 1–8, 10, 12–31, 59, and 63. Ex. 2005, 3. Patent Owner also filed a Preliminary Response (Paper 7, "Prelim. Resp.").

With our authorization, Patent Owner filed a Supplemental Preliminary Response (Paper 9, "Supp. Prelim. Resp."). Petitioner filed a Reply to Patent Owner's Supplemental Preliminary Response (Paper 10, "Reply to Supp.").

Patent Owner also filed a Request with the Acting Director of the USPTO seeking discretionary denial of institution of *inter partes* review (Paper 6, the "Request"). Petitioner subsequently filed a brief opposing Patent Owner's Request (Paper 8). On September 3, 2025, the Acting Director denied Patent Owner's Request for discretionary denial of institution of *inter partes* review and referred the case to the panel for an institution decision on the merits (Paper 11).

Institution of *inter partes* review is authorized by statute when "the information presented in the petition filed under [35 U.S.C. §] 311 and any response filed under [35 U.S.C. §] 313 shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a) (2018).

For the reasons set forth below, we determine that Petitioner has demonstrated that there is a reasonable likelihood that at least one of claims 9, 11, 32–58, 60–62, and 64–67 of the '802 patent is unpatentable, and we

institute *inter partes* review of claims 9, 11, 32–58, 60–62, and 64–67 based on the Grounds set forth in the Petition.

B. Real Parties-in-Interest

The parties identify themselves as the real parties-in-interest. Pet. xii; Paper 5, 1.

C. Related Matters

The parties do not identify any related litigation. *See* Pet. xii; Paper 5, 1. Patent Owner states that U.S. Patent No. 12,109,260 claims the priority benefit of the '802 patent. Paper 5, 1.

D. The '802 Patent

The '802 patent is entitled "Zika Vaccines and Immunogenic Compositions, and Methods of Using the Same" and issued on August 22, 2023. Ex. 1001, codes (45), (54). It issued from U.S. Application Ser. No. 16/761,329, with a PCT filing date of November 5, 2018, and claims the priority benefit of provisional applications filed on November 3, 2017, and November 30, 2017. *Id*. at codes (21), (22), (60).

The '802 patent "relates to Zika virus vaccines and immunogenic compositions having one or more antigens from a Zika virus (e.g., a Zika virus clonal isolate, a non-human cell adapted Zika virus, etc.) and methods of treatment and uses thereof." *Id.* at 1:29–33.

Zika virus is a flavivirus classified with other mosquito-borne viruses such as yellow fever, dengue, West Nile, and Japanese encephalitis viruses within the family Flaviviridae and, since the virus was introduced into the human population in Brazil in 2013, it has spread rapidly in a hemispheric-

wide epidemic. Ex. 1001, 1:41–45. In late 2015, it was noticed that there was a significant increase in fetal abnormalities (e.g., microcephaly) and Guillain-Barre syndrome in areas of widespread Zika virus infection, although the '802 patent states that the World Health Organization declared an end to a declared public health emergency. *Id.* at 2:9–17. Nevertheless, Zika continues to pose a particular threat for pregnant women and fetuses *in utero*. *See id.* at 2:17–19. The '802 patent explains that, as of at least the date of the application for the patent, there were no FDA-approved vaccine or treatments, and only preventative measures for controlling mosquito populations existed. *Id.* at 2:19–22.

The '802 patent is directed to a genetically-stable, non-human cell adapted Zika virus harboring an adaptation in the non-structural protein 1 (with a wild-type Envelope protein), allowing for the use of a single virus/viral system for vaccine production. Ex. 1001, 2:55–63. The '802 patent is also directed to a Zika virus clonal isolate that is genetically homogenous and has been purified away from adventitious agents. *Id.* The '802 patent states that the claimed invention is based, at least in part, on the finding that clonal, isolated Zika viruses expressing a mutation in protein NS1 grew well and predictably in Vero cells to a high titer and were surprisingly genetically stable/genetically homogeneous, without any detectable mutations in the viral envelope protein. *Id.* at 3:17–23.

The '802 patent acknowledges that such a mutation may have been known in a prior art reference, but that that reference failed to teach or suggest that a virus harboring the mutation may be used in the development of an effective vaccine against Zika virus that may be used at both low and high doses. Ex. 1001, 3:26–35.

The ’802 patent discloses vaccines and immunogenic compositions useful for treating and/or preventing Zika virus infections (e.g., in humans) that include one or more Zika virus antigens (e.g., one or more antigens from a whole, inactivated Zika virus). Ex. 1001, 2:63–3:3.

E. Illustrative Claims

Independent claim 9 is directed to a method of vaccinating a fetus or newborn against Zika, where the method comprises administering the vaccine to a pregnant human subject. Claim 9 recites:

> 9. 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, wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration.

Ex. 1001, 123:24–34. Independent claim 11 recites:

> 11. A method of vaccinating against Zika virus infection in a human subject in need thereof, the method comprising
>
> administering to the 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, wherein the vaccine or immunogenic composition is administered one or more times, wherein administration of the 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.

Id. at 123:40–52.

F. Prior Art and Asserted Grounds

The following table lists all Grounds asserted in the Petition. However, Petitioner may now only assert as unpatentable those claims not subsequently disclaimed by Patent Owner, i.e., claims 9, 11, 32–58, 60–62, and 64–67 of the '802 patent. Pet. 13–14; *see also* 37 C.F.R. § 42.107(e) (stating that "[n]o *inter partes* review will be instituted based on disclaimed claims").

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1–4, 6, 7, 10, 13, 19, 21, 23, 27–31, 59	102(a)(2)/103	Thomas[1]
11, 60, 61, 62	103	Thomas
8, 12, 14, 22, 24	103	Thomas and Barbero[2]
25	103	Thomas and Murata[3]
5, 15–18, 20	103	Thomas and NCT02952833[4]
26, 63	103	Thomas, NCT02952833, and Barbero

[1] Thomas et al., (WO 2017/210215, December 7, 2017) ("Thomas") (Ex. 1004).

[2] Barbero Calzado et al., (WO2017/109223, June 29, 2017) ("Barbero") (Ex. 1005).

[3] H. Murata et al., *Plaque Purification as a Method to Mitigate the Risk of Adventitious-Agent Contamination in Influenza Vaccine Virus Seeds*, 29 VACCINE 29 3155–61 (2011) ("Murata") (Ex. 1006).

[4] VERSION 8 OF CLINICAL TRIAL NCT02952833, available Nov. 3, 2017 ("NCT02952833") (Ex. 1011).

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
9, 32, 33, 35, 36, 38, 39, 41, 47, 49, 51, 55–58, 65–67	103	Thomas and Faucette[5]
34, 43–46, 48	103	Thomas, Faucette, and NCT02952833
37, 40, 42, 50, 52	103	Thomas, Faucette, and Barbero
54, 64	103	Thomas, Faucette, NCT02952833, and Barbero
53	103	Thomas, Faucette, and Murata

Petitioner also relies upon the Declaration of Farshad Guirakhoo, Ph.D. Ex. 1002. Patent Owner relies upon the Declaration of Dan H. Barouch, M.D., Ph.D. Ex. 2026.

II. ANALYSIS

A. Principles of Law

A "prior art reference—in order to anticipate under 35 U.S.C. § 102—must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements 'arranged as in the claim.'" *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008) (quoting *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983)). "A single prior art reference may anticipate without disclosing a feature of the claimed invention if such feature is necessarily present, or inherent, in that reference." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 958 (Fed. Cir. 2014).

[5] A.N. Faucette et al., *Immunization of Pregnant Women: Future of Early Infant Protection*, 11:11 HUMAN VACCINES & IMMUNOTHERAPEUTICS 2549–55 (2015) ("Faucette") (Ex. 1007).

"[A]nticipation by inherent disclosure is appropriate only when the [single prior art] reference discloses prior art that must *necessarily* include the unstated limitation." *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (citation omitted). "Inherency … may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Cont'l Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991) (internal quotation marks and citations omitted). Rather, "[t]he inherent result must inevitably result from the disclosed steps." *In re Montgomery*, 677 F.3d 1375, 1380 (Fed. Cir. 2012).

A patent claim is unpatentable under 35 U.S.C. § 103 if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. 35 U.S.C. § 103; *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). "[W]hen a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result." *KSR*, 550 U.S. at 416 (citing *United States v. Adams*, 383 U.S. 39, 50–51 (1966)). The question of obviousness is resolved based on underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of non-obviousness or obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In an *inter partes* review, a petition must identify "with particularity, each claim challenged, the Grounds on which the challenge to each claim is

based, and the evidence that supports the grounds for the challenge to each claim." 35 U.S.C. § 312(a)(3) (2018); *see also* 37 C.F.R. § 42.104(b) (2024) (requiring a petition for *inter partes* review to identify how the challenged claim is to be construed and where each element of the claim is found in the prior art patents or printed publications relied upon).

B. Level of Ordinary Skill in the Art

In determining the level of ordinary skill in the art, various factors may be considered, including the "type of problems encountered in the art; prior art solutions to those problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field." *In re GPAC, Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995) (quoting *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962, (Fed. Cir. 1986)). Furthermore, the prior art itself can reflect the appropriate level of ordinary skill in the art. *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

Petitioner asserts that a person of ordinary skill would have an M.D. or a Ph.D. degree in virology, immunology, and vaccinology, and at least 3 years of experience in one or more of the research, design, development, and testing of antiviral vaccines. Pet. 17. Petitioner asserts that a person of ordinary skill may be part of a multidisciplinary team having such experience. *Id.* (citing Ex. 1002 ¶ 81). Patent Owner does not dispute the level of skill asserted by Petitioner.

Petitioner's proposed definition of the level of ordinary skill in the art appears to be generally consistent with the level of skill presented in the cited prior art. *See generally, e.g.*, Exs. 1004–1007, 1011; *see also Okajima*

v. Bourdeau, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the prior art itself may reflect an appropriate level of skill in the art).

For the purposes of this Decision, we adopt Petitioner's proposed definition as defining a person of ordinary skill in the art as a person who would have had an M.D. or a Ph.D. degree in virology, immunology, or vaccinology, and at least 3 years of experience in one or more of the research, design, development, and testing of antiviral vaccines.

C. Claim Construction

We construe each claim "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." 37 C.F.R. § 42.100(b) (2024). Under this standard, claim terms are generally given their plain and ordinary meaning as would have been understood by a person of ordinary skill in the art at the time of the invention and in the context of the entire patent disclosure. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (*en banc*). In some cases, the patentee may serve as its own lexicographer. *Grace Instrument Indus., LLC v. Chandler Instruments Co. LLC*, 57 F.4th 1001, 1010 (Fed. Cir. 2023) (*quoting Phillips*, 415 F.3d at 1316).

Neither party requests construction of any claim terms. Petitioner asserts that all claim terms should be given their ordinary and customary meaning, and Patent Owner does not disagree. *See* Pet. 17. Accordingly, we find, for the purposes of this Decision, that no terms of the challenged claims requires construction beyond the ordinary and customary meaning of the terms, as understood by a person of ordinary skill in the art at the time of the invention. *Phillips*, 415 F.3d at 1312–13; *see also Vivid Techs., Inc. v.*

Am. Sci. & Eng'g, Inc., 200 F.3d 795, 803 (Fed. Cir. 1999) (tribunal construes claims only to the extent necessary to resolve a dispute).

D. Alleged Anticipation by, and/or Obviousness of, Claims 1–4, 6, 7, 10, 13, 19, 21, 23, 27–31, and 59 over Thomas

We need not analyze this asserted Ground because all of the challenged claims have been statutorily disclaimed and can no longer serve as a basis for institution. *See* 37 C.F.R. § 42.107(e); *see also Guinn v. Kopf*, 96 F.3d 1419, 1422 (Fed. Cir. 1996) (holding that "the patent is viewed as though the disclaimed claims had never existed in the patent."); *Micron Tech., Inc. v. Yangtze Memory Techs. Co., Ltd.*, IPR2025-00034, Paper 39 at 2 (Aug. 28, 2015) (vacating grant of institution where Petitioner failed to show reasonable likelihood that remaining non-disclaimed claim is unpatentable).

E. Alleged Obviousness of Claims 11, 60, 61, and 62 over Thomas

Petitioner contends that claims 11, 60, 61, and 62 would have been obvious over Thomas. Pet. 25–30. Patent Owner disagrees. *See* Prelim. Resp. 23–46.

1. Analysis of Independent Claim 11

We focus on the dispositive issue. Claim 11 recites, in relevant part: "wherein administration of the 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, 123:48–52.

Petitioner asserts that Thomas discloses a seroconversion rate of 92% for 55 humans 28 days after a boost administration, but acknowledges that Thomas does not expressly teach this rate after a single dose. Pet. 26 (citing Ex. 1002 ¶ 73).

Petitioner asserts that Thomas teaches that: (1) a single dose is effective to provide 100% complete protection (citing Ex. 1002 ¶ 170; Ex. 1004, 4:15–22); (2) there is a slight rise in antibody after a first (prime) dose (citing Ex. 1002 ¶ 174; Ex. 1004, 42:9–10); (3) that ideally only one dose is needed (citing Ex. 1002 ¶ 174; Ex. 1004, 7:30–32); and (4) that a booster dose is not required (citing Ex. 1002 ¶ 174; Ex. 1004, 4:15–22, 7:11). Pet. 26.

Petitioner argues that Thomas teaches that a person of ordinary skill in the art could determine, without undue experimentation, whether an initial dose is sufficient, because, e.g., Thomas discloses that someone skilled in this art can determine a safe and effective dose and schedule for its Zika virus ("ZIKV") purified-inactivated vaccine ("PIV") as needed, for persons of any age and size. *Id.* at 26–27 (citing Ex. 1002 ¶ 175–176; Ex. 1004, 4:24–28, 7:30–8:2). Petitioner argues that vaccine dose and adjuvant (type and amount) are result-effective variables. *See id.* at 27 (citing Ex. 1002 ¶¶ 171, 172, 177).

Petitioner argues, therefore, that a person of ordinary skill would have been motivated to modify/optimize the vaccine dose of Example 5 by varying either the amount of antigen and/or adjuvant or the type of adjuvant to induce a seroconversion rate of at least 60% in a population of at least 20 Zika virus seronegative subjects 14 and/or 28 days after administration, and contends that "the method would require no modification." *Id.* (citing Ex. 1002 ¶¶ 175–176; Ex. 1004:73–32). Petitioner asserts that a person of

ordinary skill would have been motivated to modify those variables because Thomas teaches that a single dose is effective, and also because a single dose administration provides more effective protection earlier and would decrease the need for booster administration. *Id.* at 28. Petitioner additionally argues that a person of ordinary skill in the art would have had a reasonable expectation of success because Thomas teaches that "a single immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against challenge with ZIKV." *Id.* (citing Ex. 1002 ¶ 178; Ex. 1004, 4:15–22, 8:17–20).

Patent Owner responds that there are deficiencies in the Petition and, to an extent, we agree (although we acknowledge below that Patent Owner admits there is evidence that supports Petitioner's arguments). First, as to Thomas's statement that "a single immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against a challenge with ZIKV," Patent Owner asserts that Thomas reports this result in mice rather than humans. Prelim. Resp. 31 (citing Ex. 1004, 12:14–33, 42:4–20, Fig. 7a; Ex. 2026 ¶¶ 82, 85). We agree. Dr. Barouch attests that Thomas achieved this result only in mice, and not in humans. Ex. 2026 ¶¶ 82 (citing Ex. 1004, 12:14−33, 13:1–21, 32:20–32, 33:1–4, Figs. 7a, 7b, 8), 85 (citing Ex. 1004, 13:1–21, 32:20–32, 33:1–4)). With respect to Figure 8, Thomas reports that "[w]ith the sham there is almost completely unrestricted viral replication in the mice while in the ZIKV PIV group viremia is 100% prevented in the [intramuscularly administered] recipients." Ex. 1004, 13:14–16.

As to humans, Patent Owner argues that Thomas observed a significant seroconversion in a population of human subjects only after the subjects received two doses of its vaccine, which were administered 28 days

apart. Prelim. Resp. 29 (citing Ex. 1004, 42:4–20; Ex. 2026 ¶¶ 72–79). We agree with Patent Owner. Dr. Barouch, analyzing the table from Example 5 of Thomas (Ex. 1004, 42:4–20), states that Thomas observes that none of the three groups (16-0033, 16-0062, and Z0001) of human subjects achieved mean titers ("GMT"; arrows) greater than 1:10 after a single dose, or prime administration, of Thomas's inactivated ZIKV vaccine. Ex. 2026 ¶ 72 (citing Ex. 1004, 42:4−20). The Table from Example 5 is reproduced below:

		5 mcg ZPIV				Placebo
Time Point[a]	Statistic	16-0033 (N=25)	16-0062 (N=20)	Z0001 (N=10)	All (N=55)	All (N=12)
Day 1	N*	25	20	10	55	12
	GMT	5.0	5.0	5.0	5.0	5.0
	95% CI	-	-	-	-	-
Day 15	N*	25	-	10	35	7
	GMT	5.0	-	8.6	5.8	5.0
	95% CI	-	-	2.5, 28.8	4.3, 8.0	-
Day 29	N*	25	20	10	55	12
	GMT	5.5	8.5	8.7	7.0	5.0
	95% CI	4.5, 6.8	4.7, 15.3	2.5, 30.4	5.2, 9.5	-
Day 43	N*	25	-	10	35	7
	GMT	316.9	-	983.3	437.9	5.0
	95% CI	152.9, 656.6	-	425.4, 2272.5	245.7, 780.6	-
Day 57	N*	25	17	9	51	12
	GMT	142.9	100.8	820.6	173.1	5.0
	95% CI	70.3, 290.4	39.7, 255.7	357.1, 1885.8	104.6, 286.5	-
Peak Titer	N*	25	20	10	55	12
	GMT	345.6	64.2	1061.7	229.8	5.0
	95% CI	166.4, 718.0	25.3, 163.2	452.8, 2489.2	132.6, 398.4	-

The table from Example 5 of Thomas provides antibody data representing site specific geometric mean titers based on the day of collection and the study site where the collection occurred

Dr. Barouch explains that Thomas determined the cutoff for determining seroconversion was a neutralizing antibody titer of 1:10 (citing Ex. 1004, 41:30–31), and that Thomas reported the neutralizing antibody titers as geometric mean titers (citing Ex. 1004, 42:4–20). Ex. 2026 ¶ 75.

On the record as developed at this stage of the proceeding, we determine that Dr. Barouch's analysis is supported by Example 5 of Thomas. Thomas states that "[t]he cutoff for determining a vaccine take (seroconversion) is a MN titer of 1:10." Ex. 1004, 41:30–31. Thomas further states that:

> Antibody kinetics based on MN50[6] titers indicat[ed] a slight rise in antibody after the first dose of vaccine with mean titers remaining below the 1:10 titer cutoff and then a robust and brisk rise in antibody titer for the Trial Group 2 and Trial Group 3 volunteers following dose two.

Id. at 42:9–11.

Petitioner's principal argument is that a person of ordinary skill would have been motivated to modify or optimize the vaccine dose of Example 5 by either the amount of antigen and/or adjuvant or the type of adjuvant, with a reasonable expectation of success. Pet. 27. Patent Owner responds that pre-clinical studies in mice used to investigate immunological responses are often not predictive of such results in humans. Prelim. Resp. 30 (citing Ex. 2021, 835–836; Ex. 2018, 5; Ex. 2026 ¶ 83). Patent Owner argues that the Balb/c mice used as subjects in Thomas are highly inbred and that inbreeding creates a wealth of homozygous recessive defects that can skew the regulation of the immune response. *Id.* at 31 (citing Ex. 2021, 835–836; Ex. 2026 ¶ 86).

Dr. Guirakhoo states that the amount of antigen and/or adjuvant are result-effective variables, and that Thomas demonstrates that vaccine dose affects seroconversion after a first (prime) dose, as well as after a second (boost) dose. Ex. 1002 ¶ 125. Assuming, for the purposes of this analysis,

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[6] Thomas explains that the MN50 represents the titer at which 50% of the control virus is neutralized. Ex. 1004, 41:29–30.

that the amount of antigen and/or adjuvant, or the type of adjuvant, are result-effective variables subject to optimization (a subject that is disputed), it is unclear on this preliminary record whether Petitioner has demonstrated a reasonable expectation of success of providing the proper dose to humans.

Dr. Barouch attests that the 1 μg dose Thomas discloses as administered to the mice is about a 560-fold to 640-fold higher dose, on a per weight basis, than the 5 μg dose Thomas administered to its human subjects. Ex. 2026 ¶ 88; *see* Prelim. Resp. 32. Dr. Barouch opines that Thomas would have had to administer a 2,800–3,200 μg dose to his human subjects for the dose to be equivalent to what was administered to the mice. Ex. 2026 ¶ 88; *see* Prelim. Resp. 32. Dr. Barouch states that such a single dose of a vaccine would not be feasible in terms of manufacturing or dosing, and that the maximum single dose tested in humans in Thomas was 5 μg, which is consistent with doses for other inactivated flavivirus vaccines. Ex. 2026 ¶ 88; *see* Prelim. Resp. 32–33. Ex. 1004 42:4−20; Ex. 2010, Table 3; Ex. 2015, Table 2; Ex. 2016, 20; Ex. 2017, 1471−72.

The evidence cited by Dr. Barouch supports his analysis. For example, Monath[7] is a study published in the New England Journal of Medicine concerning a vaccine against yellow fever, in which a "low-dose" vaccine was 0.48 μg and a "high-dose" vaccine was 4.8 μg. Ex. 2015, 1327–28. Martinez[8] is a study of vaccines against dengue virus employing dosages of 2.5 μg and 5 μg to determine vaccine immunogenicity.

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[7] T.P. Monath et al., *An Inactivated Cell-Culture Vaccine against Yellow Fever*, 364 N. ENGL. J. MED. 1326–33 (2011) ("Monath") (Ex. 2015).

[8] L.J. Martinez, *Safety and Immunogenicity of a Dengue Virus Serotype-1 Purified-Inactivated Vaccine: Results of a Phase 1 Clinical Trial*, 93(3) AM. J. TROP. MED. HYG. 454–60 (2015) ("Martinez") (Ex. 2010).

Ex. 1010, 5. Valneva[9] describes administering dosages of 0.25 ml and 0.5 ml of Japanese Encephalitis Vaccine, in which each 0.5 ml dose of vaccine contains approximately 6 mcg of purified, inactivated JEV proteins and 250 mcg of aluminum hydroxide. Ex. 2016, 16. And Schöndorf[10] describes a study of the immunogenicity of a vaccine against Tick-Born encephalitis using of 1.5 μg of formalin-inactivated virus strain K23 antigen in a 5 ml dose. Ex. 2017, 1471–72. The evidence cited by Dr. Barouch, therefore, supports his opinion that lower doses of vaccines (for a subject of a given weight) are generally administered to humans than are given to mice.

However, Patent Owner also acknowledges that Schuller, in a separate study ("Schuller 2"[11]), reported a point estimate of 65.8% seroconversion rate at Day 28 for a 1 x 12 μg dose group. Supp. Prelim. Resp. 4 (citing Ex. 1036, 2190, 2192–93). Patent Owner argues that Schuller 2 notes that this value was transient, however, and the mean seroconversion rate subsequently declined to 41.2% at Day 56. *Id.* As a consequence, Patent Owner contends, Schuller 2's study rejected its single-dose regimen in favor of two doses, the single-dose regimen having failed to meet the requisite endpoint of Schuller 2's clinical study. *Id.*

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[9] Valneva Austria GMBH, IXARO (Japanese Encephalitis Vaccine, Inactivated, Adsorbed), Suspension for Intramuscular Injection. ("Valneva") (Ex. 2016).

[10] I. Schöndorf et al., *Tick-borne Encephalitis (TBE) Vaccination: Applying the Most Suitable Vaccination Schedule*, 25 VACCINE 1470–75 ("Schöndorf") (2007) (Ex. 2017).

[11] E. 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*, 27 VACCINE 2188–93 (2009) ("Schuller 2") (Ex. 1036).

On its face, Schuller 2's single Day 28 data point satisfies claim 11's required "14 and/or 28 days after a single dose or prime administration[,] a seroconversion rate of at least 60%." However, in view Schuller 2's disclosure of the transient nature of this result, it is unclear whether the result is necessarily predictive of a reasonable likelihood of success of a higher dose formulation of the claimed Zika virus vaccine. *See* Ex. 1036, 3 (Table 2).[12, 13] We therefore decline to determine at this time whether a person of ordinary skill in the art would have had a reasonable expectation of success with respect to this limitation; rather, we conclude that this is an issue requiring fuller development at trial.

Nevertheless, as discuss below in Section II.G.1., we determine that Petitioner has shown a reasonable likelihood of proving that claim 9 is unpatentable under 35 U.S.C. § 103 over the combination of Thomas and Faucette. As a result, and as further explained below, institution of *inter partes* review is warranted as to all non-disclaimed, challenged claims on all Grounds asserted in the Petition, and the parties will have additional opportunities to address the patentability of claim 11 after institution.

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[12] Patent Owner also argues that Petitioner should not be allowed to belatedly rely on Schuller 2, which was not in its Petition. Supp. Prelim. Resp. 5. We do not reach this issue at this time.

[13] Patent Owner also argues that, as a theoretical matter, one dose of 10 μg is not the same as two doses of 5 μg, e.g., because an anamnestic response from a second exposure generally results in a significantly greater number of neutralizing antibodies than a primary response (from a first exposure). Prelim. Resp. 34–38. However, the fact that Schuller 2 reports that a single 12 μg dose of vaccine resulted in the claimed level of immune response, as discussed, contradicts this theoretical argument from Patent Owner.

2. Analysis of Dependent Claims 60–62

As we explain below in Section II.G.1., we determine that Petitioner has shown a reasonable likelihood of proving that claim 9 is unpatentable under 35 U.S.C. § 103 over Thomas and Faucette. As a result, institution of an *inter partes* review is warranted as to all non-disclaimed, challenged claims on all Grounds asserted in the Petition. *See* 37 C.F.R. § 42.108(a); *SAS Inst., Inc. v. Iancu*, 584 U.S. 357, 371 (2018); *PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (interpreting the statute to require "a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition"). The parties will have additional opportunities to address the patentability of the dependent claims at trial.

F. Alleged Obviousness of Claims 8, 12, 14, 22, and 24 over Thomas and Barbero;

Alleged Obviousness of Claim 25 over Thomas and Murata;

Alleged Obviousness of Claims 5, 15–18, and 20 over Thomas and NCT02952833; and

Alleged Obviousness of Claims 26 and 63 over Thomas, NCT02952833, and Barbero

We do not analyze these asserted Grounds because the claims challenged have all been statutorily disclaimed by Patent Owner. *See* 37 C.F.R. § 42.107(e); *Guinn*, 96 F.3d at 1422.

G. Alleged Obviousness of Claims 9, 32, 33, 35, 36, 38, 39, 41, 47, 49, 51, 55–58, and 65–67 Over Thomas and Faucette

Petitioner contends that claims 9, 32,33, 35, 36, 38, 39, 41, 47, 49, 51, 55–58, and 65–67 are unpatentable as obvious over the combination of

Thomas and Faucette. Pet. 45–57. Patent Owner disagrees. Prelim. Resp. 49–67.

1. Analysis of Independent Claim 9

a. [a] method of vaccinating against Zika virus disease in a fetus or newborn in need thereof, the method comprising

Petitioner asserts that Thomas discloses vaccinating a human subject that can be a fetus or a newborn. Pet. 48 (citing, e.g., Ex. 1002 ¶¶ 400–402; Ex. 1004, 2:13–24, 3:2–12, 4:2–7, 18:26–30).

On the record as developed at this stage of the proceeding, we determine that Petitioner has made a sufficient showing of a reasonable likelihood of success in prevailing with respect to the preamble of claim 9. In particular, Thomas discloses that the mechanism of action of a prophylactic vaccine "could include … protecting the fetus during material infection ([as] (infection during pregnancy occurs but vaccine induced immunity prevents fetal infection from taking hold)." Ex. 1004, 2:5–12. Thomas also discloses that a purified inactivated whole virus Zika vaccine is advantageous because of its potential for a superior safety profile in special populations like pregnant women. *Id.* at 18:26–30.

b. 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

Petitioner asserts that Thomas discloses administration to a pregnant subject, for the reasons set forth above for element 9(a). *See* Pet. 48 (citing, e.g., Ex. 1002 ¶ 404; Ex. 1004, 41:7–8. We address Patent Owner's arguments in Section II.G.1.e., below.

On the record at this stage of the proceeding, we determine that Petitioner has made a sufficient showing of a reasonable likelihood of success in prevailing on this limitation. In particular, Thomas suggests that its vaccine may be administered to pregnant women, as described above for element (a) of claim 9. Thomas also discloses administration of two doses of a Zika vaccine at 0 and 28 days, 5 μg per dose, and adjuvanted with alum to humans. Ex. 1004, 41:7–8.

c. wherein the antigen is an inactivated whole virus, and

d. wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration

Petitioner asserts that Thomas discloses these limitations for the reasons set forth above for limitation 9(a). *See* Pet. 49 (citing, e.g., Ex. 1002 ¶¶ 405–406, 421–22; Ex. 1004, 18:28–30); Pet. 19 (discussing identical element 1(c)) (citing Ex. 1002 ¶¶ 117–118; Ex. 1004, 4:20–22, 7:32–33, 18:28–30, 41:7–8). Briefly, Petitioner argues that Thomas teaches that the antigen is an inactivated whole virus. Pet. 19 (citing Ex. 1002 ¶ 117; Ex. 1004, 18:28–30). Petitioner also contends that Thomas teaches a first (prime) and a second (boost) administration. *Id.* (citing Ex. 1002 ¶ 118; Ex. 1004, 4:20–22, 7:32–33, 41:7–8 (disclosing that "[t]wo doses were administered at 0 and 28 days, 5 μg per dose, and adjuvanted with alum.").

We address Patent Owner's arguments in Section II.G.1.e., below.

On the record as developed at this stage of the proceeding, we determine that Petitioner has made an a sufficient showing of a reasonable likelihood of success in prevailing on limitations (c) and (d). In particular, as described in the preceding section for element (b) of claim 9, Thomas

discloses administration of two doses of a Zika vaccine at 0 and 28 days, 5 μg per dose, and adjuvanted with alum. Ex. 1004, 41:7–8. Further, as described for element (a) of claim 9, Thomas suggests that a Zika vaccine may consist of an inactivated whole virus. Ex. 1004, 18:28–30.

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

Petitioner asserts that Thomas does not expressly teach this limitation, but does teach that a mechanism of action of administering a vaccine to a pregnant women could include protecting a fetus, referring to induced immunity. Pet. 49 (citing Ex. 1004, 2:13–24, 3:2–12, 4:2–7, 18:26–30, 39:15–16; Ex. 1002 ¶¶ 408, 413, 415). Petitioner asserts that Thomas also discloses adoptive transfer studies in rhesus monkeys and mice. *Id.* at 49–50 (citing Ex. 1002 ¶ 409, Ex. 1004, 33:8–10, 33:21–25, 38:17–22, 38:24–26, 38:30–39:2). Petitioner argues that Thomas teaches that the adoptive transfer data in mice and rhesus monkeys, taken together, are reasonably predictive of how ZIKV vaccines will perform in humans. *Id.* at 50 (citing, e.g., Ex. 1004, 39:15–16, Ex. 1002 ¶¶ 410–411).

Petitioner also asserts that Faucette teaches that the benefits of immunizing pregnant women are to "generate maternal immune protection as well as elicit the production and transfer of antibodies cross the placenta … to provide early infant protection" (Ex. 1007, Abstr., 2549, 2550, 2552). Petitioner asserts that a person of ordinary skill would have been motivated to vaccinate a pregnant woman to adoptively transfer a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn, because Thomas teaches a need for a vaccine to protect both a pregnant

woman and a fetus. Pet. 51 (citing Ex. 1004, 2:13–24, 4:2–7, 18:26–30); Ex. 1002 ¶ 418). Petitioner also argues that Faucette discloses immunizing pregnant women to generate maternal protection, as well as to elicit the production and transfer of antibodies cross the placenta to provide early infant protection. *Id.* (citing Ex. 1007, Abstr., 2549).

Petitioner argues that a person of ordinary skill would have had a reasonable expectation of success in providing maternal to fetal vaccine protection because Thomas provides animal studies of adoptive transfer, and because Faucette acknowledges that inactivated virus vaccines have successfully been used to immunize pregnant women. *Id.* (citing Ex. 1004, 38:5–39:2; Ex. 1007, 2549; Ex. 1002 ¶ 419).

Patent Owner presents several arguments against the combination of Thomas and Faucette. *See* Prelim. Resp. 51–53, 59–67. We address each in turn.

Patent Owner argues that Petitioner fails to establish that a person of ordinary skill in the art would have sought to use Thomas's inactivated ZIKV vaccine to protect a fetus or newborn because Thomas's vaccine uses two doses spread 28 days apart, with insufficient titer after 28 days, and that this would not have been rapid enough to protect a fetus where there can be fatal consequences such as congenital defects. Prelim. Resp. 51–52 (citing, e.g., Ex. 2020, 1982; Ex. 2026 ¶¶ 57–59, 122). At this stage of the proceeding, we do not find this argument to be persuasive, because claim 9 does not require effectiveness after a single dose. Further, as explained above with respect to claim 11, there is evidence of record that there can be higher titers, at least transiently, after a single dose in a human subject. *See* Section II.E.1 *supra* (discussing Schuller 2).

Patent Owner also argues that Petitioner has failed to demonstrate a reasonable expectation of success because the animal studies in Thomas administered purified antibodies and are therefore not studies of human mother-to-fetus adoptive transfer of an effective amount of vaccine-induced, antigen-neutralizing antibodies. Prelim. Resp. 60 (citing, e.g., Ex. 2026 ¶¶ 141–150). Patent Owner also argues that Faucette does not adequately show that there would have been protection of a fetus from an *in utero* ZIKV infection. Prelim. Resp. 66 (citing Ex. 2026 ¶ 151; Ex. 1007, 2549).

On the record at this stage of the proceeding, we determine that Petitioner has made a sufficient showing of a reasonable likelihood of success in prevailing on this limitation. Claim 9 encompasses within its scope the transfer of antibodies to fetuses or neonates. *See* Ex. 1001, 123:30–32. Faucette discloses that transport of vaccine-induced material immunoglobulin G ("IgG") antibody across the placenta is mediated by neonatal Fc receptors expressed on trophoblasts that confers fetal and early infant immune protection. Ex. 1007, 2552. Faucette discloses that the amount of IgG transferred across the placenta correlates with the IgG concentration in maternal circulation, gestational age, maternal health, and with IgG subclass: IgG_1 and IgG_4 are preferentially transported over IgG_3 and IgG_2. *Id.*

Faucette explains that vaccines containing a protein antigen elicit greater production of IgG_1 and IgG_3, as opposed to polysaccharide vaccines, which mainly elicit the production of IgG_2.[14] Ex. 1007, 2552. Faucette also

[14] Petitioner does not make assertions as to whether the whole inactivated virus vaccine of Thomas presents proteins and/or polysaccharides as antigens. Nevertheless, Thomas states: "Inactivated ZIKV bulk may be

provides that additional passive immunity in the form of vaccine induced IgA, IgG, and IgM secreted in colostrum and breastmilk is transferred during breastfeeding. *Id.* We consequently determine that Petitioner has established a reasonable likelihood of prevailing on this limitation, including in showing a reasonable expectation of success.[15]

We note that the claim requires the transfer of neutralizing antibodies, but does not specifically require prevention of fetal or newborn infection, and that Thomas discloses titers of neutralizing antibodies, e.g., in the MN50 assay. *See, e.g.*, Ex. 1002 ¶¶ 84, 170 (citing Ex. 1004, 4:15–22).

In particular, Thomas discloses that a vaccine may be administered to a pregnant female, for the reasons described immediately above for element (a) of claim 9. *See* Section II.G.1.a., *supra*. Thomas additionally discloses administration of two 5 μg doses of Zika vaccine, adjuvanted with alum, to a human, one at 0 days and another at 28 days. Ex. 1004, 41:7–8.

For these reasons, we determine that Petitioner has shown a reasonable likelihood of proving that claim 9 is unpatentable under 35 U.S.C. § 103 over Thomas and Faucette. Furthermore, because we

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diluted to a protein concentration that is suitable for an immunizing dose in a subject (e.g., a mammal such as a human)." Ex. 1004, 26:5–6.

[15] Faucette states that: "[S]ignificant gaps exist in our knowledge of the efficacy and safety of many other vaccines with existing or novel formulations." Ex. 1007, 2549. Nevertheless, the test for obviousness is not the same as the test for safety and efficacy. *See, e.g., Janssen Pharmas., Inc. v. Teva Pharmas. USA, Inc.*, 97 F.4th 915, 928–29 (Fed. Cir. 2024) (holding that "[w]hatever role safety and efficacy data may play in assessing the strength of a motivation or a lack of motivation to combine, absence of such safety and efficacy data in the '548 Protocol cannot justify simply discarding that prior art particularly where, as here, the claims do not have any safety and efficacy requirement.") (internal citation omitted).

determine that Petitioner has demonstrated a reasonable likelihood of success in showing that at least one claim is unpatentable on at least one of the asserted Grounds, we institute *inter partes* review of all extant challenged claims of the '802 patent, based on each of the remaining asserted Grounds identified in the Petition. *See* 37 C.F.R. § 42.108(a); *SAS Inst., Inc. v. Iancu*, 584 U.S. 357, 371 (2018); *PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (interpreting the statute to require "a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition").

2. Analysis of Claims 32, 33, 35, 36, 38, 39, 41, 47, 49, 51, 55–58, and 65–67

As discussed above in Section II.G.1., we determine that Petitioner has shown a reasonable likelihood of proving that claim 9 is unpatentable under 35 U.S.C. § 103 over the combination of Thomas and Faucette. As a result, institution of an *inter partes* review is warranted as to all non-disclaimed, challenged claims on all remaining Grounds asserted in the Petition. The parties will have additional opportunities to address the remaining claims in this Ground after institution.

H. Alleged Obviousness of Claims 33, 43–46, and 48 over Thomas, Faucette, and NCT0295283

Petitioner contends that claims 33, 43–46, and 48 would have been obvious over the combination of Thomas, Faucette, and NCT0295283. Pet. 57–59. Patent Owner disagrees. Prelim. Resp. 54–56.

Petitioner relies upon NCT0295283, in combination with Thomas and Faucette, as teaching that it would have been obvious to those of ordinary

skill in the art to optimize a 10 μg dose for a pregnant woman. Pet. 58. Petitioner argues that the remaining limitations of these claims are substantially identical to the corresponding limitations of the other claims of the '802 patent challenged in the Petition. *See id.* at 57–59.

Patent Owner argues that pregnant women were specifically excluded from the NCT0295283 study. Prelim. Resp. 54–55 (citing, e.g., Ex. 1011, 13). Petitioner, however, relies instead on Faucette for the teaching that a vaccine may be administered to a pregnant woman. *See* Section II.G.1.e., *supra*. Nevertheless, the parties may address this issue at trial.

I. Alleged Obviousness of Claims 37, 40, 42, 50, and 52 over Thomas, Faucette, and Barbero

Petitioner contends that claims 37, 40, 42, 50, and 52 would have been obvious over the combination of Thomas, Faucette, and Barbero. Pet. 59–60. Patent Owner disagrees. Prelim. Resp. 56–59.

Petitioner relies on Barbero in combination with Thomas and Faucette as disclosing the claimed adjuvant amounts. *See* Pet. 46, 59 (citing Ex. 1002 ¶ 386; Ex. 1005, 112:1–4). Petitioner argues that the other limitations of these claims are substantially identical to those of other claims set forth in the Petition. *See id.* at 59–60 (citing Ex. 1002 ¶¶ 484–512). Furthermore, Dr. Guirakhoo asserts that "the amount of antigen and/or adjuvant or the type of adjuvant make the vaccine dose a result-effective variable, as Thomas demonstrates that vaccine dose affects seroconversion after a first (prime) dose, as well as after a second (boost) dose." Ex. 1002 ¶ 177; *see also id.* ¶¶ 243–244.

Patent Owner argues that Dr. Guirakhoo's opinion that aluminum hydroxide adjuvant is a result-effective variable is conclusory. *See* Prelim.

Resp. 57 (citing Ex. 2026 ¶¶ 91–107, 135–136). However, Petitioner argues that Thomas teaches that adjuvants are result-effective variables. Pet. 46 (citing Ex. 1004, 28:19–22; Ex. 1002 ¶¶ 385, 389). We agree with Petitioner that Thomas discloses that an adjuvant may enhance the antigen-specific immune response. *See* Ex. 1004, 28:19–22 ("An 'adjuvant' is a substance that serves to enhance, accelerate, or prolong the antigen-specific immune response of an antigen when used in combination with specific vaccine antigens but do[es] not stimulate an immune response when used alone"); *see also* Ex. 1002 ¶ 125. The parties may address at trial whether Dr. Guirakhoo's opinion is adequately supported by Thomas, or otherwise supported by evidence of record.

J. Alleged Obviousness of Claims 54 and 64 over Thomas, Faucette, NCT02952833, and Barbero;

Alleged Ground of Obviousness of Claim 53 Over Thomas, Faucette, and Murata

Patent Owner challenges Petitioner's reliance on NCT02952833 and Barbero. Patent Owner does not otherwise separately argue these Grounds from the above Grounds based on combining Thomas, Faucette, NCT02952833, and Barbero. The parties may address these Grounds at trial.

III. CONCLUSION

Because we determine that Petitioner has demonstrated a reasonable likelihood of success in showing that at least one claim is unpatentable on at least one of the asserted Grounds, we institute *inter partes* review of all extant challenged claims of the '802 patent, based on all of the remaining

Grounds asserted in the Petition. *See* 37 C.F.R. § 42.108(a); *SAS*, 584 U.S. at 371; *PGS Geophysical*, 891 F.3d at 1360.

At this stage of the proceeding, the Board has not made a final determination as to the patentability of any challenged claim or to the construction of any claim term. Therefore, our view with regard to any conclusion reached in the foregoing discussion may change upon consideration of Patent Owner's merits response and the completion of the record.

For the reasons we have explained, we institute *inter partes* review as set forth in the following Order.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 9, 11, 32–58, 60–62, and 64–67 of the '802 patent is instituted on all challenges to these non-disclaimed claims included in the Petition;

FURTHER ORDERED that, according to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial that commences on the entry date of this Decision.

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