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Paper 10
Date: September 28, 2022

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TRUTEK CORP.,
Petitioner,

v.

THE REGENTS OF THE UNIVERSITY OF MICHIGAN,
Patent Owner.

IPR2022-00674
Patent 10,138,279 B2

Before ULRIKE W. JENKS, TINA E. HULSE, and CYNTHIA M. HARDMAN, *Administrative Patent Judges.*

JENKS, *Administrative Patent Judge*.

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

I. INTRODUCTION

A. *Background*

Trutek Corp. ("Petitioner") filed a Petition for an *inter partes* review of claims 1–14 ("the challenged claims") of U.S. Patent No. 10,138,279 B2 (Ex. 1001, "the '279 patent"). Paper 1 ("Pet."). The Regents of the University of Michigan ("Patent Owner") have not filed a Patent Owner Preliminary Response to the Petition.

Under 35 U.S.C. § 314(a), an *inter partes* review may not be instituted unless the information presented in the petition "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." Having considered the evidence and arguments of record, Petitioner has not shown a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim. Accordingly, we deny the Petition and decline to institute an *inter partes* review.

B. *Real Parties-in-Interest*

Petitioner identifies itself, Trutek Corp., as the real party-in-interest. Pet. 2. Patent Owner identifies itself, The Regents of the University of Michigan, as the real party-in-interest. Paper 7, 1.

C. *Related Matters*

"Although presently unrelated" to this IPR proceeding, both parties identify the district court case, *Trutek Corp. v. BlueWillow Biologics, Inc.*, Case No. 2:21-cv-10312 (E.D. Mich. filed February 10, 2021), which alleges infringement of certain claims of Trutek's Patent No. 8,163,802 by BlueWillow's product, NanoBio Protect. Pet. 2; Paper 7, 1. Petitioner also states on "information and belief" that "by employing the technology of the

'279 Patent, Bluewillow is developing an anthrax vaccine that also reads on Trutek's patent." Pet. 3.

D. *Asserted Ground of Unpatentability*

Petitioner challenges the patentability of claims 1–14 of the '279 patent on the following grounds:

Claim(s) Challenged	35 U.S.C.[1,2,3] §	Reference(s)/Basis
1, 2, 4–7, 9–14	103(a)	Lowell[4], Yaghmur[5], Wright[6], Williamson[7], Baker Abstract[8]

[1] Although the Petition identifies eleven grounds (Pet. 5–6), there are only two distinct bases presented.

[2] Petitioner admits that Examiner was aware of '412 Baker and Baker Abstract, but contends that "Examiner incorrectly relied on the cited prior art references [Baker '412 and Baker Abstract], and he was unaware of the other non-cited prior art" such as Lowell, Wright, Yaghmur, and Williamson. Pet. 42. Because Patent Owner did not raise the issue in a Preliminary Response and because we deny on the merits, we need not address issues under 35 U.S.C. § 325(d).

[3] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. § 103, effective March 16, 2013. Because the application from which the '279 patent issued has an effective filing date prior to March 16, 2013, the pre-AIA version of § 103 applies.

[4] Lowell et al., U.S. Patent 5,961,970, published October 5, 1999 ("Lowell") (Ex. 1004).

[5] Yaghmur et al., *Phase behavior of microemulsions based on food-grade nonionic surfactants: effect of polyols and short-chain alcohols*, Colloids and Surfaces 209: 71–81 (2002) ("Yaghmur") (Ex. 1005).

[6] Wright, U.S. Patent 5,618,840, published April 8, 1997 ("Wright") (Ex. 1006).

[7] Williamson et al., *Immunogenicity of Recombinant Protective Antigen and Efficacy against Aerosol Challenge with Anthrax*, Infection and Immunity, 73(9): 5978–5987 (2005) ("Williamson") (Ex. 1007).

[8] Baker et al., *Enhanced Systemic and Mucosal Immune Responses in Mice Immunized With Recombinant Bacillus anthracis Protective Antigen (rPA)*

1, 3, 8–11, 14	103(a)	Baker '412[9], Williamson, Baker Abstract

In support of its patentability challenge, Petitioner relies on the Declarations of Dr. Edward Lemmo (Ex. 1002) and Dennis O'Donnell (Ex. 1003).

E. *The '279 Patent (Ex. 1001)*

The '279 patent is titled "Compositions and Methods for *Bacillus anthracis* Vaccination." Ex. 1001, (54). The '279 patent describes methods and compositions to induce an immune response to *Bacillus anthracis*. *Id.* at (57). The '279 patent issued on November 27, 2018 from U.S. Application No. 11/786,861, filed April 13, 2007. *Id.* at (21), (22).

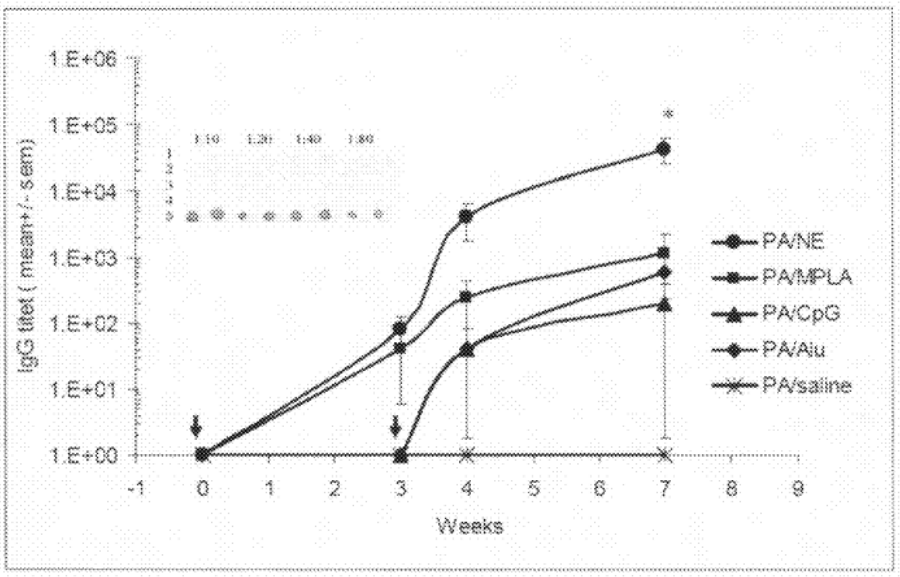
According to the Specification, the currently available vaccination for *B. anthracis* requires six immunizations over 18 months with annual boosters. *Id.* at 1:50–53. Additionally, the current vaccination is not effective against genetic variants to *B. anthracis*. *Id.* at 1:55–57. The Specification discloses an embodiment comprising providing a nanoemulsion and a *B. anthracis* immunogen. *Id.* at 2:27–31.

In one example, the Specification reports administering the composition to mice. *Id.* at 51:32–46. Specifically, mice were administered either one dose of the vaccine or two doses of the vaccine three weeks apart and were monitored for adverse reactions. *Id.* at 52:3–6. Antibody responses were measured at three to four weeks up to 12 weeks. *Id.* at 52:6–8. According to the Specification, mice that were administered a *B. anthracis*

Using a Novel Nanoemulsion Adjuvant, J Allergy Clin Immunol, S292, February 2004 ("Baker Abstract") (Ex. 1008).

[9] Baker et al., United States Patent Publication US 2003/0194412 A1, published October 16, 2003 ("Baker '412") (Ex. 1009).

immunogen in the nanoemulsion formula had a higher IgG titer than mice administered a *B. anthracis* immunogen in other formulations. *See id.* at 55:12–35 and Figure 3B. Figure 3B is reproduced below:



As shown above, the PA/NE line represents the protective antigen (PA) in a nanoemulsion (NE). *See id.* at 6:27–43 (describing Figure 3). Furthermore, according to the Specification, sera from immunized mice were effective in neutralizing the *B. anthracis* toxin. *Id.* at 56:2–5.

1. Illustrative Claims

Claims 1 and 14 of the '279 patent are reproduced below:

> 1. A method of inducing an immune response to *Bacillus anthracis* (*B. anthracis*) in a subject comprising intranasally administering an immunogenic composition comprising:
>
> A) a nanoemulsion, wherein the nanoemulsion comprises:
>
> 1. oil;
>
> 2. water;
>
> 3. ethanol;
>
> 4. a polysorbate surfactant selected from the group consisting of polyoxyethylene sorbitan monooleate and polyoxyethylene sorbitan monolaurate; and
>
> 5. cetylpyridinium chloride (CPC); and

> B) recombinant protective antigen (rPA) of *B. anthracis* to the subject, wherein the administering generates a *B. anthracis*-specific immune response comprising generation of a serum anthrax lethal toxin (LeTx)-specific neutralizing antibody titer that is at least 10 fold greater than the serum LeTx-specific neutralizing antibody titer generated in a control subject administered an equal amount of rPA suspended in saline.

Id. at 58:25–43.

> 14. A method of inducing an immune response to *Bacillus anthracis* (*B. anthracis*) in a subject comprising intranasally administering an immunogenic composition comprising:
>
> A) a nanoemulsion, wherein the nanoemulsion comprises:
>
> 1. oil;
> 2. water;
> 3. ethanol;
> 4. a polysorbate surfactant selected from the group consisting of polyoxyethylene sorbitan monooleate and polyoxyethylene sorbitan monolaurate; and
> 5. cetylpyridinium chloride (CPC); and
>
> B) recombinant protective antigen (rPA) of *B. anthracis* to the subject, wherein the administering generates a *B. anthracis*-specific immune response comprising generation of a serum anthrax lethal toxin (LeTx)-specific neutralizing antibody titer that permits said subject to survive a lethal *B. anthracis* challenge.

Id. at 60:1–17.

2. Relevant Prosecution History

Petitioner provides an overview of claim language changes made during prosecution. *See* Pet. 8–11. Petitioner acknowledges that the Examiner during prosecution relied on the Baker Abstract and U.S. Patent No. 7,314,624. *Id.* at 9. According to Petitioner, U.S. Patent No. 7,314,624 is technically not prior art "but the application upon which it is based was published as Baker '412 (Exhibit 1009) in 2002." *Id.* Petitioner, however,

does not provide a copy of the prosecution history as an exhibit when asserting that "Examiner failed to explain any rationale for allowance of claim 14." *Id.* at 11.

II. ANALYSIS

A. *Principles of Law*

A claim is unpatentable under 35 U.S.C. § 103(a) 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 of the invention to a person having ordinary skill in the art. 35 U.S.C. § 103(a) (2006); *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including "the scope and content of the prior art"; "differences between the prior art and the claims at issue"; and "the level of ordinary skill in the pertinent art." *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In analyzing the obviousness of a combination of prior art elements, it can be important to identify a reason that would have prompted one of skill in the art "to combine . . . known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418. A precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *Id.* Rather, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *In re*

Magnum Oil Tools Int'l, Ltd., 829 F.3d 1364, 1381 (Fed. Cir. 2016) (internal quotations and citations omitted).

B. *Level of Ordinary Skill in the Art*

In determining the level of skill in the art, we consider the type of problems encountered in the art, the prior art solutions to those problems, the rapidity with which innovations are made, the sophistication of the technology, and the educational level of active workers in the field. *Custom Accessories, Inc. v. Jeffrey-Allan Indus. Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986); *Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1011 (Fed. Cir. 1983).

Petitioner asserts that a person of ordinary skill in the art:

> would be familiar with the literature regarding the efficacy and safety of pharmaceutical products and biologics as well as recommended dosage ranges. Such a person should have an advanced degree in pharmaceutical chemistry and/or microbiology, and should have an understanding of vaccine technology.

Pet. 11 (citing Ex. 1002 ¶ 4(a)). Because Petitioner's proposed definition appears consistent with the Specification and art of record, we apply it for purposes of our analysis here.

C. *Claim Construction*

In an *inter partes* review, claim terms are interpreted "using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b), including construing the 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). "[C]laims are interpreted

with an eye toward giving effect to all terms in the claim." *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 950 (Fed. Cir. 2006). Claim terms also generally are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

Only those terms that are in controversy need be construed, and only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999); *see also Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (applying *Vivid Techs*. in the context of an AIA trial proceeding).

Petitioner proposes interpretations for the preamble, "nanoemulsion," and the efficacy requirement of the claims. *See* Pet. 12, 17–18. For purposes of this decision we only need to construe the efficacy requirement.[10]

> *Efficacy: at least 10 fold greater*
>
> Claim 1 recites:
>
> > wherein the administering generates a *B. anthracis*-specific immune response comprising generation of a serum anthrax lethal toxin (LeTx)-specific neutralizing antibody titer that is at least 10 fold greater than the serum LeTx-specific neutralizing antibody titer generated in a control subject administered an equal amount of rPA suspended in saline.

Ex. 1001, 58:37–43 (emphasis added).

[10] Only those terms that are in controversy need be construed, and only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999); *see also Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (applying *Vivid Techs*. in the context of an AIA trial proceeding).

Petitioner contends that the recitation of this wherein clause in claim 1 is a vague limitation. Pet. 13, 18; Ex. 1001, 58:37–43. Specifically, Petitioner contends that the computed antibody titer of the recombinant protective antigen (rPA) suspended in saline disclosed in the '297 patent specification would be zero, making the ratio of a 10 fold greater quantity meaningless because "division by zero is prohibited." Pet. 26, *see id.* at 23 ("If there was no seropositive response in animals immunized with rPA in saline, then $Titer_B = 0$. Division by zero is a prohibited operation."). Therefore, Petitioner contends that the condition following the "wherein" clause of the claim should be ignored. *Id.* at 26–27.

We are not persuaded by Petitioner's contention that we should simply ignore the 10-fold limitation as recited in the claim. *See Texas Instruments, Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1171 (Fed. Cir. 1993) ("[T]o construe the claims in the manner suggested by TI would read an express limitation out of the claims. This, we will not do . . . ."). We do not agree with Petitioner that the claims require division by zero in order to assess the required efficacy. The artisan is presumed to have ordinary skill. *In re Sovish*, 769 F.2d 738, 743 (Fed. Cir. 1985). The question is whether the "zero" denominator is a reasonable interpretation of the results presented in the '279 patent.

According to the '279 patent intranasal (IN) administration using the claimed nanoemulsion results in much greater IgG antibody production compared to other adjuvants and saline. Figure 3B of the '279 patent is reproduced below:

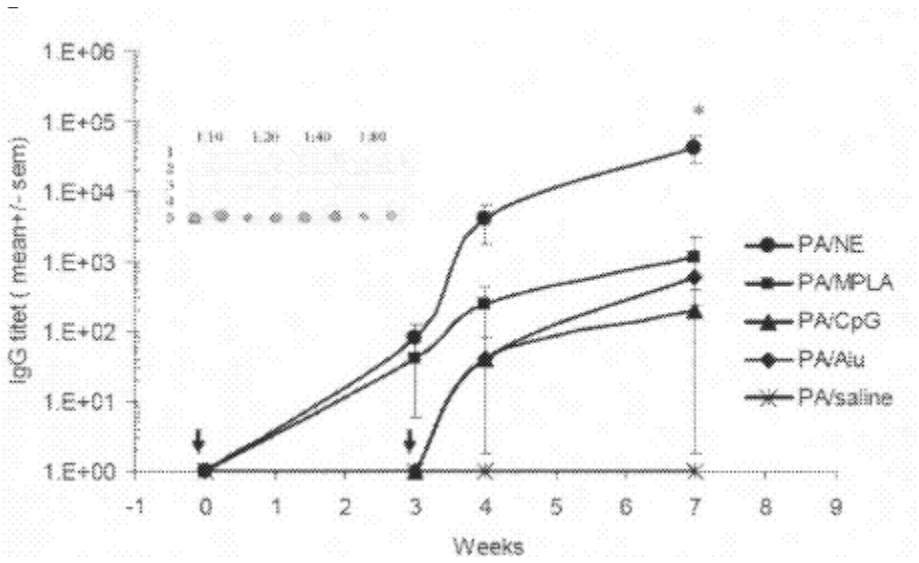


Figure 3B shows the IgG antibody titer results after IN immunization of rPA antigen using various adjuvants as well as a saline control.

> After two [IN] administrations of each formulation all mice immunized with rPA/NE were seropositive, with anti-PA IgG endpoint titers of at least 10^5. This was compared to titers ranging from 10^2 -10^3 in the rPA/MPL A, rPA/CpG and rPA/Alu immunization groups (See FIG. 3B). No anti-PA antibodies were detected in animals nasally immunized with rPA in saline.

Ex. 1001, 55:21–27.

Acknowledging that "[n]o anti-PA antibodies were detected in animals nasally immunized with rPA in saline," does not mean that the denominator is zero.

We note that the '279 patent does not provide the raw data for the results associated with either Figure 3A or 3B. Figures 3A and 3B[11] show the x-axes as 1 E+00 indicating that the value of the axis is 1. One of ordinary skill in the art at the time of the invention was made would have

[11] When an exponent is 0, the result of the exponentiation of any base will always be 1. *See* https://www.mathsisfun.com/exponent.html (last visited Sept 9, 2022).

been able to calculate an increase in titer over a background level response as there are many techniques for normalizing data. Accordingly, we are not persuaded by Petitioner's contention that the "at least 10 fold greater" limitation is vague and, therefore, should just be ignored.

Furthermore, we note that the '279 patent does disclose comparative data with other adjuvants that are also administered intranasally. The formula provided by Petitioner in the Petition is depicted below:

$$\frac{\text{Titer}_A}{\text{Titer}_B}$$

The formula is a fraction with Titer_A as the numerator and Titer_B as the denominator. *See* Pet. 23.

Applying this formula to the results provided in the '279 patent for rPA/NE (Titer A – 10^5) with the results for rPA/MPL A, rPA/CpG and rPA/Alu (Titer B – ranging 10^2–10^3) immunization groups shows that IgG titer with these comparative samples are 100–1000 fold less than compared to the nanoemulsion as the adjuvant. *See* Ex. 1001, 55:21–27. The rPA saline group in this example (shown above in Figure 3B) has an even lower IgG titer – no detectable IgG response – than the comparative adjuvants tested, indicating the fold increase of rPA/NE compared to rPA saline is even greater than the response observed with any of the other adjuvants. *See* Ex. 1001, 55:21–27. These disclosures indicating 100-1000 fold greater titers with the nanoemulsion as adjuvant appear consistent with the plain meaning of the phrase "at least 10 fold greater" as set forth above, and indicate that a skilled artisan would know how to calculate this efficacy requirement. *Cf. Accent Packaging, Inc. v. Leggett & Platt, Inc.*, 707 F.2d 1318, 1326 (Fed. Cir. 2013) (stating that the Court has "held that 'a claim interpretation that excludes a preferred embodiment from the scope of the

claim is rarely, if ever, correct'"). Based on the plain meaning of the phrase, and on these disclosures, we are not persuaded by Petitioner's contention that the "ratio is meaningless," rendering the claim vague. Pet. 23. Accordingly, we decline Petitioner's invitation to ignore this limitation.

On this record, we agree with Petitioner that the "at least 10 fold greater" limitation is reasonably interpreted to be a ratio of the antibody titers detected in the rPA adjuvant group compared to the rPA saline control group, but disagree that the ratio is "meaningless."

D. *Overview of Asserted References*

1. Lowell (Ex. 1004)

Lowell is titled "Submicron Emulsions as Vaccine Adjuvants" and discloses a "vaccine adjuvant composition of an oil-in-water submicron emulsion." Ex. 1004, (57). Specifically, Lowell teaches that the submicron emulsion is in a particle size range "between about 30 nm to about 500 nm to effect enhanced immunogenicity of antigens." *Id.* at 2:38–40. Lowell shows an increased IgG antibody titer when a submicron emulsion (SME) is used. *See id.* at 3:60–64 (describing Figures 2A and 2B). Figure 2A is reproduced below:

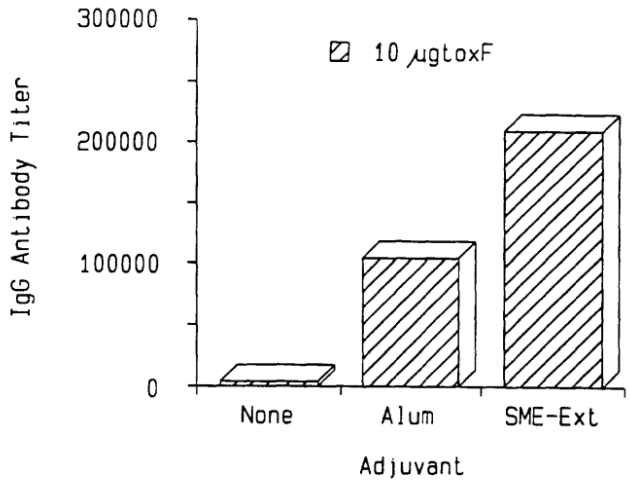


FIG. 2A

Figure 2A is a graph showing the immune response obtained after parenteral immunization of mice with *Staphylococcal* enterotoxin B toxoids alone or adjuvanted with aluminum or SME. *See id.* at 3:60–64, 15:38–55. The graph shows that the IgG antibody titers obtained with the SME-adjuvant were "several orders of magnitude higher than those obtained with the alum-adjuvanted formulation." *Id.* at 15:52–55.

Lowell provides examples of utilizing an HIV envelope protein, outer membrane protein from *Neisseria meningitidis*, *Staphylococcal* enterotoxin B toxoids, and the surface protein antigen of *Leishmania major* gp63. *See id. generally*.

2. Yaghmur (Ex. 1005)

Yaghmur is titled "Phase behavior of microemulsions based on food-grade nonionic surfactants: effect of polyols and short-chain alcohols" and describes the formation of microemulsions when adding short-chain alcohols together with polyols to the oil-water-surfactant system. Ex. 1005, 71. Yaghmur reviews the use of microemulsions in pharmaceuticals and states that "[m]icroemulsions based on Tweens have been described in the

literature as carriers of pharmaceuticals to achieve a controlled release of particular drug . . . [and that they] enhance significantly the solubilization of lipophilic drugs." *Id.* at 72. Specifically, Yaghmur investigates the physical properties of adding short chain alcohols and polyols to enhance the solubilization of water and oil in surfactants. *See id. generally* and *id.* at 80. Yaghmur concluded that microemulsions are easy to prepare when polyol and alcohol are added. *Id.* at 80.

3. Wright (Ex. 1006)

Wright is titled "Antibacterial Oil-in-Water Emulsions" and describes emulsions for inhibiting growth of *Helicobacter pylori*. Ex. 1006, (57). Wright discloses the use of a C_{12}–C_{16} chain. *Id.* at 2:23–36. Specifically, the C_{12}–C_{16} chain can be cetylpyridinium chloride (CPC). *Id.* Wright discloses that CPC can cause upper respiratory and mucous membrane damage and irritation but does not display any adverse effects when administered in an emulsion. *Id.* at 2:49–55. Wright shows that emulsions with CPC are effective at inactivating *H. pylori*. *Id.* at 9:33–40 (Table 6).

4. Williamson (Ex. 1007)

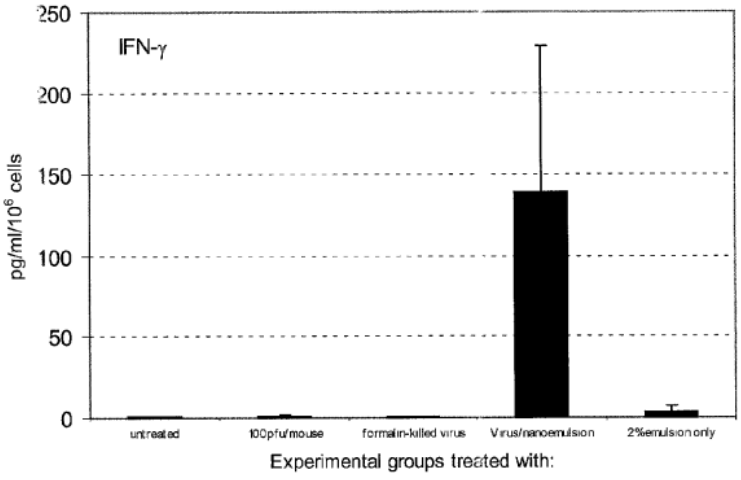
Williamson is titled "Immunogenicity of Recombinant Protective Antigen and Efficacy against Aerosol Challenge with Anthrax" and discusses immunization against *Bacillus anthracis* using a recombinant protective antigen. Ex. 1007, 1. Specifically, Williamson shows that the recombinant protective antigen has improved immunogenicity compared to the non-recombinant protective antigen. *Id.* at. 3.

5. Baker Abstract (Ex. 1008)

Baker Abstract is titled "Enhanced Systemic and Mucosal Immune Responses in Mice Immunized with Recombinant Bacillus anthracis Protective Antigen (rPA) Using a Novel Nanoemulsion Adjuvant" and is an abstract discussing recombinant protective antigen anthrax vaccines. Ex. 1008. The vaccines utilize a nanoemulsion adjuvant that resulted in higher titers of anti-PA IgG than immunizations without the nanoemulsion adjuvant. *Id.*

6. Baker '412 (Ex. 1009)

Baker '412 is titled "Nanoemulsion Vaccines" and discloses "methods and compositions for the stimulation of immune responses." Ex. 1009, (57). Specifically, Baker '412 describes methods of formulating emulsions. *See id.* at Example 1. Baker '412 tests *Bacillus cereus* as a model for *Bacillus anthracis*. *See id.* at Example 5. Baker '412 "demonstrates in vivo the adjuvanticity of nanoemulsion for influenza vaccine given intranasally." *Id.* ¶ 373. We reproduced Figure 15 below.



Id. Figure 15 shows cytokine response to influenza A formalin-killed virus mixed with a nanoemulsion. *Id.* ¶ 40.

E. *Grounds Based on Lowell, Yaghmur, Wright, Williamson, and Baker Abstract*

For the reasons discussed below, on this record Petitioner has not shown a reasonable likelihood of establishing that at least one of the challenged claims is unpatentable as obvious over Lowell, Yaghmur, Wright, Williamson, and Baker Abstract.

1. Analysis of Claim 1

Petitioner contends that claim 1 is unpatentable for obviousness over Lowell, Yaghmur, Wright, Williamson, and Baker Abstract. Pet. 21–24.

Petitioner contends that Lowell's adjuvant is a nanoemulsion, comprising oil, water, and a polysorbate surfactant such as TWEEN-80. Pet. 22. Petitioner acknowledges that Lowell does not use ethanol, a C2 alcohol, in the adjuvant but instead uses a C3–C6 alcohol. *Id.* In addition, Petitioner acknowledges that Lowell does not include cetylpyridinium chloride (CPC) in the adjuvant. *Id.* Petitioner relies on Yaghmur and Wright for teaching the use of ethanol and CPC in the adjuvant. *Id.* Petitioner contends that based on the combination of Lowell, Yaghmur, and Wright one of ordinary skill in the art would have arrived at the nanoemulsion as recited in claim 1.

Petitioner relies Williamson for teaching the use of recombinant protective antigen (rPA) of *B. anthracis*. Pet. 22. Baker Abstract similarly teaches using *B. anthracis* rPA dispersed in a nanoemulsion. *Id.* Petitioner contends that "it would be expected that a mere substitution of one known vaccine component for another should produce predictable results." *Id.*

Based upon our review of the arguments and evidence, Petitioner has not shown that the combination of Lowell, Yaghmur, Wright, Williamson, and Baker Abstract teaches or suggests the "nanoemulsion," as required by claim 1.

Petitioner directs us to references that in isolation contain each component as recited in claim 1. It is not enough to direct us to the individual components in the cited references; Petitioner needs to explain why one of ordinary skill in the art at the time the invention was made would have selected the various components in order to arrive at the claimed invention. *See KSR*, 550 U.S. at 418 (an obviousness determination requires "some articulated reasoning with some rational underpinning"). Petitioner asserts that it would have been obvious to substitute one vaccine component for another; however, Petitioner does not persuade us that the disclosure in Yaghmur would have prompted the ordinary artisan to have substituted ethanol – a C2 alcohol – for the C3–C6 alcohol used Lowell's nanoemulsion.

Yaghmur teaches that "the solubilization parameter (A_T) increased with the increase of chain length of alcohol and reached a maximum with the addition of butanol." Ex. 1005, 78. Yaghmur Figure 5 is reproduced below:

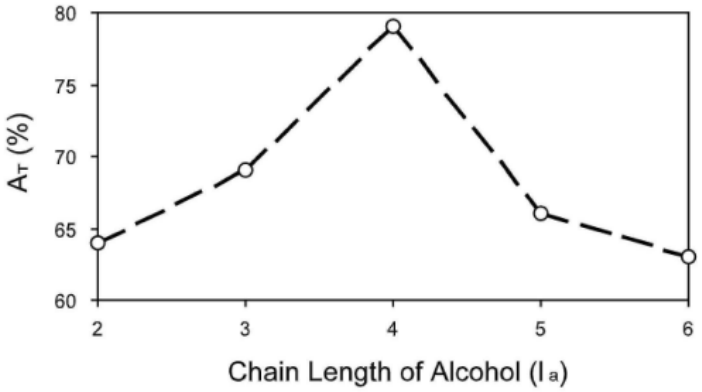


Figure 5 of Yaghmur, reproduced above, shows the effect of the chain length of alcohol at 25 °C on A_T (%) for systems based on Tween 60 with a R(+)-limonene / alcohol weight ratio (1/1). *Id.* "As the chain length of the alcohol is increased further (systems with pentanol and hexanol) the large attractive interaction among droplets plays the major role in the decrease of A_T by limiting the actual radius to smaller values than R^c." *Id.* Yaghmur suggests that C3 and C4 chain length alcohols provide better solubilization. Based on these teachings in Yaghmur, there would be no apparent reason to substitute the C3–C6 alcohols taught by Lowell with ethanol, a C2 alcohol. What is missing from the Petitioner's analysis is evidence that an artisan[12] would have had a reason to substitute a C3–C6 alcohol with a C2 alcohol to arrive at the claimed nanoemulsion. *See KSR*, 550 U.S. at 418; *see also Belden Inc. v. Berk-tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015) ("[O]bviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention.").

To the extent Petitioner asserts that a person of ordinary skill in the art would have been motivated to substitute a C3–C6 alcohol with a C2 alcohol given Yaghmur's teaching that its "nanoemulsion is suitable as a less toxic

[12] The Petition generally cites the declarations of Dr. Edward Lemmo (Ex. 1002) and Dennis M. O'Donnell (Ex. 1003) as supporting the challenges, but does not specifically cite the declarations in connection with Petitioner's unpatentability arguments. Pet. 5. Although we are not required to do so under the circumstances (*see, e.g.*, 35 U.S.C. § 312(a)(3), which requires a petition to identify with particularly the evidence that supports the grounds for the challenge to each claim), we have reviewed the declarations and find that neither declaration provides an explanation of why one of ordinary skill in the art would have substituted ethanol for the higher chain-length alcohols in Lowell's adjuvant.

adjuvant," we disagree. Pet. 22 (citing Ex. 1005, 72). This teaching in Yaghmur is not specific to ethanol.

The C2 alcohol, however, is not the only component missing from Lowell's nanoemulsion. Petitioner acknowledges that Lowell also does not include cetylpyridinium chloride (CPC) in the adjuvant. Pet. 22. Petitioner relies on the teachings of Wright as providing support for the inclusion of CPC with Lowell's adjuvant. *See* Pet. 22. Specifically, Petitioner directs us to a disclosure in Wright that suggests that CPC works as an anti-microbial. *See id.* ("Wright teaches an anti-microbial nanoemulsion adjuvant (at 4:23) comprising CPC (at 2:50)."); Ex. 1006, 4:22–24 ("to obtain an oil-in-water emulsion containing oil droplets which are approximately one micron in diameter").

Wright teaches the use of CPC containing emulsions as an antimicrobial for the inactivation of bacteria upon contact. *See* Ex. 1006, 9 (Table 6). Wright teaches that CPC "causes severe irritation and damage to tissues of the upper respiratory tract, mucous membranes and skin if administered alone. However, when administered in the form of an emulsion of the invention, no such adverse effects occur." *Id.* at 2:50–55. Wright teaches that the emulsion can be used for oropharyngeal application as a spray or a mouthwash (Ex. 1006, 4:56–58) as well as a cream or gel (*id.* at 66). Most importantly, however, Wright does not discuss using CPC as an adjuvant for eliciting an immune response in a subject.

The Petition does not provide a sufficiently articulated rationale that explains why one of ordinary skill in the art would have included CPC in Lowell's adjuvant. Although Petitioner does not specifically cite the testimony of its declarants, Dr. Lemmo and Mr. O'Donnell, in support of its arguments, we have nevertheless reviewed the testimony and find that it

does not support Petitioner's position that it would have been obvious to include CPC in the adjuvant based on the teachings of Wright. *See generally* Ex. 1002; Ex. 1003. Neither declarant explains why one of ordinary skill in the art would have included CPC, an antimicrobial composition that works by contact inhibition, in the nanoemulsion adjuvant of Lowell. Accordingly, Petitioner has not met the burden of providing a sufficiently articulated rationale for making the combination as proposed. *See KSR*, 550 U.S. at 418.

Because Petitioner has failed to show that the combination of Lowell, Yaghmur, and Wright teaches or suggests the "nanoemulsion" of claim 1, Petitioner has not shown a reasonable likelihood of prevailing on its assertion that claim 1 would have been rendered obvious by the cited art. Petitioner does not rely on Williamson or Baker Abstract to arrive at the "nanoemulsion" recited in claim 1. Thus, Petitioner has not shown a reasonable likelihood of prevailing on its assertion that independent claim 1 would have been rendered obvious by the combined teachings of Lowell, Yaghmur, Wright, Williamson, and Baker Abstract.

2. Analysis of Dependent Claims 2, 4–7, and 9–13

Claims 2, 4–7, and 9–13 depend from claim 1. *See* Pet. 27–28, 29–33, and 34–35. For at least the same reasons discussed above for claim 1, on this record, we also determine that Petitioner has not shown a reasonable likelihood of prevailing on its assertion that dependent claims 2, 4–7, and 9–13 would have been rendered obvious by the combination Lowell, Yaghmur, Wright, Williamson, and Baker Abstract.

3. Analysis of Claim 14

Petitioner contends that claim 14 is invalid for obviousness over Lowell, Yaghmur, Wright, Williamson, and Baker Abstract. Pet. 37–39.

Claim 14 is identical to claim 1, except for the "wherein" limitation, which in claim 14 reads: "wherein the administering generates a *B. anthracis*-specific immune response comprising generation of a serum anthrax lethal toxin (LeTx)-specific neutralizing antibody titer that permits said subject to survive a lethal *B. anthracis* challenge." Ex. 1001, 60:13–17. For the same reasons discussed above for claim 1, Petitioner has failed to show that the combination of Lowell, Yaghmur, and Wright teaches or suggests the "nanoemulsion" of claim 14. Petitioner therefore has not shown a reasonable likelihood of prevailing on its assertion that claim 14 would have been rendered obvious.

F. *Grounds Based on Baker '412, Williamson, and Baker Abstract*

For the reasons discussed below, on this record Petitioner has not shown a reasonable likelihood of establishing that at least one of the challenged claims is unpatentable as obvious over Baker '412, Williamson, and Baker Abstract.

1. Analysis of Claim 1

Petitioner contends that the claimed vaccine composition is made of a nanoemulsion and an immunogen. *See* Pet. 12–13. We agree with Petitioner that the components making up the vaccine include the nanoemulsion adjuvant comprising: (1) oil; (2) water; (3) ethanol; (4) a polysorbate surfactant; and (5) cetylpyridinium chloride (CPC) mixed with recombinant protective antigen (rPA) of *B. anthracis* immunogen.

Petitioner contends that claim 1 is invalid for obviousness over Baker '412, Williamson, and Baker Abstract. Pet. 24–27. Specifically, Petitioner contends that Baker '412 teaches an immunogen with a nanoemulsion comprising oil, water, and a polyoxyethylene (20) sorbitan

monolaurate such as for example TWEEN-20, and CPC. Pet. 25 (citing Ex. 1009 ¶¶ 12, 13, 140). Petitioner acknowledges that "Baker '412 is silent regarding using nanoemulsions for delivery of anthrax vaccines" but concludes that "that a substitution of one known vaccine component for another should produce predictable results." *Id.*

Claim 1 recites a method of inducing an immune response by the intranasal administration of the antigen combined with the nanoemulsion, where the administration of the composition by that specific route elicits a response that is 10-fold greater than compared to the antigen administered in saline alone.

Baker '412 teaches the use of a nanoemulsion as a mucosal adjuvant. Ex. 1009, (57). Baker '412 nanoemulsions contain oil, water, ethanol, surfactant, and CPC. Specifically, Baker '412's "formulations comprise from about 5 vol. % of TWEEN 20, from about 8 vol. % of ethanol, from about 1 vol. % of CPC, about 64 vol. % of oil (e.g., soybean oil), and about 22 vol.% of DiH_20." Ex. 1009 ¶ 145. Baker '412 teaches the use of TWEEN 20 (polyoxyethylene (20) sorbitan monolaurate) (s*ee* Ex. 1009, ¶¶ 8, 14, 21, 130 (Table 2), 145, 146, 161, 162, 169, *see also id.* at Figure 4) as well as TWEEN 80 (as polyoxyethylene sorbitan monooleate) (*see id.* ¶¶ 144, 157, 169 ("Examples of polysorbate detergents . . . include, but are not limited to, TWEEN 20, TWEEN 40, TWEEN 60, TWEEN 80, etc.")) as a surfactant in the adjuvant.

Williamson teaches that *B. anthracis* protective antigen (PA) is the most important antigen in natural and vaccine-induced immunity. Ex. 1007,

3.[13] Williamson explains that "[w]hen presented to the immune system in an appropriate adjuvant, rPA derived from either *B. subtilis* or *B. anthracis* has also been shown to protect rodents and nonhuman primates from an aerosol challenge with fully virulent *B. anthracis* spores." *Id.* (citation omitted). According to Williamson, IgG levels alone are not sufficient to extrapolate protection from lethal challenge:

> Some studies have shown that there is not a positive correlation between the amount of total circulating IgG to PA and protection against *B. anthracis* in the guinea pig or rhesus macaque, but a direct correlation has been found between the titer of neutralizing antibody and protection against challenge in the rabbit model. Other studies have used cytotoxicity assays to correlate protective immunity in guinea pigs with the levels of neutralizing antibodies present in serum samples.

Ex. 1007, 3–4 (citations omitted).

According to the Baker Abstract a "nanoemulsion was absolutely required for the development of immunity after IN [intranasal] administration since anti-PA specific IgA (in bronchial lavage) and IgG (in serum) were observed only in animals receiving [IN] rPA [recombinant *B. anthracis* protective antigen] with nanoemulsion." Ex. 1008. Baker Abstract also establishes that only IN administration using the nanoemulsion resulted in a mucosal immune response. *See* Ex. 1008 ("No animal immunized IM with rPA developed a mucosal antibody response."). Baker Abstract, however, does not discuss challenging the animals with *B. anthracis*. At best, Baker Abstract establishes that the use of the nanoemulsion results in higher serum IgG titers than the use of the antigen alone when administered

[13] We note that Williamson, Ex. 1007, is not paginated, therefore page numbers refer to the document as if it were consecutively paginated beginning on the first page of the exhibit.

via the IN route. *Id.* We note that Baker Abstract also does not disclose the components of the nanoemulsion.

"An obviousness determination requires finding both 'that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.'" *CRFD Research, Inc. v. Matal*, 876 F.3d 1330, 1340 (Fed. Cir. 2017) (quoting *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367–1368 (Fed. Cir. 2016)).

Here, we agree with Petitioner that based on the cited references it would have been obvious to substitute one antigen for another. *See* Pet. 25. "[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 Int'l Co. v. Teleflex Inc.,* 550 U.S. 398, 416 (2007) (citing *United States v. Adams*, 383 U.S. 39, 50–51 (1966)).

Subsumed within an obviousness analysis "is a subsidiary requirement" that when "all claim limitations are found in a number of prior art references, the burden falls on the challenger" to show that "a skilled artisan would have been motivated to combine the teachings of the prior art," and that a "skilled artisan would have had a reasonable expectation of success in doing so." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007); *see also Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015) ("The obviousness inquiry entails consideration of whether a person of ordinary skill in the art 'would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and . . . would have had a reasonable expectation of success in doing so.'")

(quoting *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009)).

We are, however, not persuaded by Petitioner's contention "that a substitution of one known vaccine component for another should produce predictable results." Pet. 25. Claim 1 requires establishing "a *B. anthracis*-specific immune response comprising generation of a serum anthrax lethal toxin (LeTx)-specific neutralizing antibody titer." Ex. 1001, 58:37–40. The art suggests that administering an antigen in conjunction with an adjuvant would elicit an immune response. However, not all antibodies "have neutralizing and opsonizing capabilities." Ex. 1001, 38:5–6. This observation is supported by Williamson, explaining "that there is not a positive correlation between the amount of total circulating IgG to PA and protection against *B. anthracis* in the guinea pig or rhesus macaque." Ex. 1007, 3; *see also id.* ("Protection by rPA in rodent and nonhuman primate models is likely to be T-cell dependent [] and also is mediated by the presence of neutralizing antibody []." (citation omitted)). That the substitution of one vaccine component for another *could* illicit an immune response does not provide any indication that the immune response created achieves "*neutralizing antibody titer*" that is at "*least 10-fold greater*" than the response with saline alone as recited in claim 1.

According to Baker Abstract, the use of the nanoemulsion adjuvant resulted in higher titers of anti-PA IgG than immunizations without the nanoemulsion adjuvant. Ex. 1008. Baker Abstract, however, says nothing about achieving 10-fold greater neutralizing antibody titer nor does Baker Abstract establish that the rPA response provides protection against lethal challenge. Establishing increased IgG antibody levels using the adjuvant does not provide information that the antibodies created are neutralizing

antibodies as required by the claim. *See* Ex. 1007, 3 (finding no correlation between IgG levels and protection against *B. anthracis*).

Neither the Petition, nor Petitioner's experts, explain why one of ordinary skill in the art would have had a reasonable expectation that the use of Baker '412 adjuvant would ellicit a neutralizing antibody titer to rPA antigen when administered intranasally as required by the claims. *See* Pet. 24–27. Dr. Lemmo's declaration[14] asserts that "[n]asal administration of vaccines and other pharmaceuticals was well known at the time of invention." Ex. 1002 ¶ 18. Asserting that something is well-known does not provide an explanation for why one of skill in the art at the time the invention was made would have expected the claimed result based on the combination of Baker '412, Williamson, and Baker Abstract. One's expertise, even when draped with a skilled-artisan veil, does not entitle a naked opinion to much weight in the absence of underlying factual support. *See Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985) ("Lack of factual support for expert opinion going to factual determinations" is sufficient to "render the testimony of little probative value in a validity determination.").

Based on our review of this record, Petitioner has not sufficiently shown a reasonable likelihood that the combination of Baker '412, Williamson, and Baker Abstract would have rendered claim 1 obvious.

[14] We reiterate that the Petition does not cite either Dr. Lemmo's declaration or Mr. O'Donnell's declaration in support of any arguments presented in the Petition, and only citing Dr. Lemmo's declaration in support of Petitioner's proposal regarding the level of ordinary skill in the art. *See generally* Pet.

2. Analysis of Dependent Claims 3 and 8–11

Claims 3 and 8–11 depend from claim 1. *See* Pet. 28–29, 33–34, 35–36. On this record, Petitioner has not sufficiently shown a reasonable likelihood that the combination of Baker '412, Williamson, and Baker Abstract would have rendered claim 1 obvious. Because Petitioner's challenge to claims 3 and 8–11 relies on the same analysis as that set out for claim 1, Petitioner also fails to show a reasonable likelihood that any of these dependent claims are unpatentable as obvious in light of Baker '412, Williamson, and Baker Abstract.

3. Analysis of Claim 14

Petitioner contends that claim 14 is unpatentable for obviousness over Baker '412, Williamson, and Baker Abstract. Pet. 39–42.

Claim 14 is identical to claim 1, except for the "wherein" limitation, which in claim 14 reads: "wherein the administering generates a *B. anthracis*-specific immune response comprising generation of a serum anthrax lethal toxin (LeTx)-specific neutralizing antibody titer that permits said subject to survive a lethal *B. anthracis* challenge." Ex. 1001, 60:13–17. Petitioner's challenge to claim 14 relies on the same analysis as that set out for claim 1. Williamson teaches that rPA derived from *B. anthracis* in the appropriate adjuvant can protect rodents and nonhuman primates from an aerosol challenge with fully virulent *B. anthracis* spores. Ex. 1007, 3. But Williamson warns that IgG level alone is not determinative of protection against challenge. *Id.* The Baker Abstract, at best, establishes that the undefined nanoemulsion is required in order to develop antibody response after IN administration. Ex. 1008. Establishing that the IN administration of rPA antigen produces an IgG response says nothing about whether that

response is sufficient to protect against lethal challenge as required by the claim. Petitioner has not articulated why one of ordinary skill in the art would have had a reasonable expectation of generating neutralizing antibody titers to lethal toxin (LeTx) in a subject sufficient to survive a lethal *B. anthracis* challenge when administered intranasally as required by claim 14.

Based on our review of this record, Petitioner has not sufficiently shown a reasonable likelihood that Baker '412, Williamson, and Baker Abstract would have rendered claim 14 obvious.

III. CONCLUSION

For the foregoing reasons, we deny the Petition and decline to institute the requested *inter partes* review.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner's request for an *inter partes* review of claims 1–14 of the '279 patent is *denied*.

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