

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LABORATORY CORPORATION OF AMERICA HOLDINGS,
Petitioner,

v.

QUEST DIAGNOSTICS INVESTMENTS LLC,
Patent Owner.

IPR2019-01517
Patent 7,972,867 B2

Before SUSAN L. C. MITCHELL, JENNIFER MEYER CHAGNON, and
Avelyn M. Ross, *Administrative Patent Judges*.

CHAGNON, *Administrative Patent Judge*.

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

I. INTRODUCTION

Laboratory Corporation of America Holdings (“Petitioner”) filed a Petition requesting *inter partes* review of claims 21–28 and 31 (“the challenged claims”) of U.S. Patent No. 7,972,867 B2 (Ex. 1001, “the ’867 patent”). Paper 1 (“Pet.”). Quest Diagnostics Investments LLC (“Patent Owner”)¹ filed a Preliminary Response. Paper 7 (“Prelim. Resp.”).

We have authority to determine whether to institute an *inter partes* review under 35 U.S.C. § 314, which provides that an *inter partes* review may be instituted only upon a showing 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). After considering the Petition, the Preliminary Response, and the evidence of record, we determine that Petitioner has not demonstrated a reasonable likelihood of prevailing with respect to at least one claim challenged in the Petition. Accordingly, we do not institute an *inter partes* review.

A. Related Proceedings

The parties identify *Quest Diagnostics Investments LLC v. Laboratory Corp. of America Holdings*, Case No. 1:18-CV-01436-UNA (D. Del. filed Sept. 17, 2018) as a related matter. Pet. 1; Paper 4, 1.

The parties also identify the following related *inter partes* review proceedings: IPR2019-00738 (related to U.S. Patent No. 8,409,862); IPR2019-01425 (related to U.S. Patent No. 8,101,427); and IPR2019-01618 (related to U.S. Patent No. 7,972,868). Paper 9, 1; Paper 10, 2.

¹ Patent Owner lists Quest Diagnostics, Inc. as an additional real party-in-interest for this proceeding. Paper 4, 1.

B. The '867 Patent

The '867 patent, titled “Methods for Detecting Vitamin D Metabolites by Mass Spectrometry,” was filed on March 21, 2006,² and issued on July 5, 2011. Ex. 1001, codes (22), (45), (54). The '867 patent relates to “methods of detecting the presence or amount of a Vitamin D metabolite in a sample using mass spectrometry,” where the methods generally include “ionizing a vitamin D metabolite in a sample and detecting the amount of the ion to determine the presence or amount of the Vitamin D metabolite in the sample.” *Id.* at (57).

The '867 patent discloses that “[m]easurement of vitamin D, the inactive vitamin D precursor, is rare in clinical settings and has little diagnostic value. Rather, serum levels of 25-hydroxyvitamin D₃ and 25-hydroxyvitamin D₂ . . . are a useful index of vitamin D nutritional status and the efficacy of certain vitamin D analogs.” *Id.* at 1:53–58. The '867 patent explains that mass spectrometry may be used to detect specific vitamin D metabolites, unlike immunologically-based assays that “do not separately resolve 25-hydroxyvitamin D₃ and 25-hydroxyvitamin D₂.” *Id.* at 2:13–22.

“Mass spectrometry is performed using a mass spectrometer which includes an ion source for ionizing the fractionated sample and creating charged molecules for further analysis.” *Id.* at 8:25–27. “After the sample has been ionized, the positively charged or negatively charged ions thereby

² The '867 patent claims priority as a continuation-in-part of application No. 11/101,166, filed on April 6, 2005. Ex. 1001, code (63). The specific priority date of the challenged claims currently is not at issue in this proceeding, and we need not make any determination in this regard.

created may be analyzed to determine a mass-to-charge ratio (i.e., m/z).” *Id.* at 8:39–41.

The ’867 patent further discloses that “tandem mass spectrometry” or “MS/MS” enhances resolution of the mass spectrometry (“MS”) technique. *Id.* at 8:59–60. “In this technique, a precursor ion . . . generated from a molecule of interest can be filtered in an MS instrument, and the precursor ion is subsequently fragmented to yield one or more fragment ions . . . that are then analyzed in a second MS procedure.” *Id.* at 8:60–66. A given set of ionization/fragmentation conditions reproducibly produces precursor and fragment ions thereby eliminating interfering substances in biological samples. *Id.* at 9:2–9. “Preferably, at least one fragment ion of the method is specific for the particular vitamin D metabolite of which detection is desired.” *Id.* at 10:17–19. “A specific fragment ion for a particular vitamin D metabolite is one that will not be formed in significant amounts by other molecules with similar molecular structures. In contrast a non-specific fragment ion is one that is formed by related molecules other than the desired analyte.” *Id.* at 10:19–27.

In one embodiment described in the ’867 patent, MS/MS is performed to select for precursor ions with a mass/charge ratio corresponding to protonated and dehydrated ions of vitamin D metabolites. *Id.* at 11:46–49. For example, the mass/charge ratio for the protonated and dehydrated precursor vitamin D metabolite ion is about 395.30 m/z for 25-hydroxyvitamin D₂. *Id.* at 11:50–53.

C. Illustrative Claim

Of the challenged claims, claim 21 is independent. Claims 22–28 and 31 depend directly or indirectly from claim 21. Independent claim 21 of the '867 patent is reproduced below, and is illustrative of the challenged claims.

21. A method for determining the presence or amount of 25-hydroxyvitamin D₂ in a sample by tandem mass spectrometry, comprising:

- (a) generating a protonated and dehydrated precursor ion of said 25-hydroxyvitamin D₂ with a mass to charge ratio (m/z) of 395.30±0.5;
- (b) generating one or more fragment ions of said precursor ion; and
- (c) detecting the presence or amount of one or more of said ions generated in step (a) or (b) or both and relating the detected ions to the presence or amount of said 25-hydroxyvitamin D₂ in said sample.

Ex. 1001, 22:21–32.

D. The Applied References and Other Evidence

Petitioner relies on the following references in the asserted grounds.
Pet. 6–7.

Reference	Publication Date	Exhibit
Voyksner, R. D. and Lee, H., <i>Improvements in LC/Electrospray Ion Trap Mass Spectrometry Performance Using an Off-Axis Nebulizer</i> , 71 Anal. Chem. 1441–47 (1999) (“Voyksner”)	Apr. 1, 1999	Ex. 1004

Reference	Publication Date	Exhibit
Watson, D. and Setchell, K. D. R., <i>Analysis of Vitamin D and Its Metabolites Using Thermospray Liquid Chromatography/Mass Spectrometry</i> , 5 Biomed. Chromatography 153–60 (1991) (“Watson”)	July 1991	Ex. 1007
Rainbow, S., et al., <i>The Analysis of Vitamin D Analogues by Atmospheric Pressure Ionization Coupled to Triple Quadrupole Mass Spectrometry</i> , Poster No. M-045, Proc. 51st ASMS Conference on Mass Spectrometry and Allied Topics, Montreal, Canada (June 8–12, 2003) (“Rainbow”)	June 12, 2003	Ex. 1008
Kamao, M., et al., <i>C-3 Epimerization of Vitamin D₃ Metabolites and Further Metabolism of C-3 Epimers</i> , Manuscript M311473200, JBC Papers in Press 1–31 (2004) (“Kamao”)	Feb. 2, 2004	Ex. 1006
Vogeser, M., <i>Liquid Chromatography-Tandem Mass Spectrometry – Application in the Clinical Laboratory</i> , 41 Clin. Chem. Lab. Med. 117–26 (2003) (“Vogeser”)	Feb. 2003	Ex. 1009

Petitioner also relies on the Declaration of Robert L. Fitzgerald, Ph.D. (Ex. 1002) to support its positions.

E. The Asserted Grounds

Petitioner sets forth its challenges to claims 21–28 and 31 as follows.
Pet. 7, 19–56.

Reference	35 U.S.C. § ³	Claim(s) Challenged
Voyksner, Watson, Rainbow	103	21–26, 31
Voyksner, Watson, Rainbow, Kamao	103	27
Voyksner, Watson, Rainbow, Vogeser	103	28

II. ANALYSIS

A. Legal Standards

“In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.” *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify “with particularity . . . the evidence that supports the grounds for the challenge to each claim”)). This burden of persuasion never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review).

A claim is unpatentable under 35 U.S.C. § 103(a) if “the differences between the subject matter sought to be patented 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

³ Because the application leading to the ’867 patent was filed before March 16, 2013, patentability is governed by the version of 35 U.S.C. §§ 102 and 103 preceding the Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112-29, 125 Stat. 284 (2011).

subject matter pertains.” *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: (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 nonobviousness.⁴ *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

To show obviousness, it is not enough to merely show that the prior art includes separate references covering each separate limitation in a challenged claim. *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011). “This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.” *KSR*, 550 U.S. at 418–419.

On the other hand, an obviousness analysis “need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.” *KSR*, 550 U.S. at 418; *accord In re Translogic Tech., Inc.*, 504 F.3d 1249, 1259 (Fed. Cir. 2007). However, Petitioner cannot satisfy its burden of proving obviousness by employing “mere conclusory statements.” *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016). Instead, Petitioner must articulate a reason why a person of ordinary skill in the art would have combined the prior art references. *In re NuVasive*, 842 F.3d 1376, 1382 (Fed. Cir. 2016); *see also Metalcraft of Mayville, Inc. v. The Toro Co.*, 848 F.3d 1358, 1366 (Fed. Cir.

⁴ The parties have not asserted or otherwise directed our attention to any objective evidence of non-obviousness.

2017) (“In determining whether there would have been a motivation to combine prior art references to arrive at the claimed invention, it is insufficient to simply conclude the combination would have been obvious without identifying any reason why a person of skill in the art would have made the combination.”); *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.”) (citing *InTouch Techs., Inc. v. VGO Commc’ns, Inc.*, 751 F.3d 1327, 1352 (Fed. Cir. 2014)).

We analyze the asserted grounds of unpatentability in accordance with these principles to determine whether Petitioner has met its burden to establish a reasonable likelihood of success at trial.

B. Level of Ordinary Skill in the Art

We review the grounds of unpatentability in view of the understanding of a person of ordinary skill in the art at the time of the invention. *Graham*, 383 U.S. at 17. Petitioner contends that a person of ordinary skill in the art “would have an advanced degree (e.g., M.S. or Ph.D.) in chemistry or a related discipline, such as pharmacology or biochemistry, and at least 2–3 years of experience in a clinical or research laboratory.” Pet. 18; *see* Ex. 1002 ¶ 12. Petitioner further contends that a person of ordinary skill in the art would typically have experience with MS and HPLC, and would have knowledge regarding the suitable parameters for optimizing MS and HPLC laboratory tests. *See* Pet. 18–19.

Patent Owner does not contest Petitioner’s proposed description at this stage of the proceeding. *See generally* Prelim. Resp. Based on the

current record, we determine that Petitioner’s proposed description of the person of ordinary skill in the art is consistent with the prior art of record, and apply it for purposes of this Decision. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required “where the prior art itself reflects an appropriate level and a need for testimony is not shown”) (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

C. Claim Construction

In this *inter partes* review proceeding claim terms shall be construed 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) (2019). Further, “[a]ny prior claim construction determination concerning a term of the claim in a civil action, or a proceeding before the International Trade Commission, that is timely made of record in the *inter partes* review proceeding will be considered.”⁵ *Id.*

Under the standard set forth in *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–19 (Fed. Cir. 2005) (en banc), claim terms are given their ordinary and customary meaning, as would have been understood by a person of ordinary skill in the art at the time of the invention, in light of the language of the claims, the specification, and the prosecution history of record. *See Thorner v. Sony Comput. Entm’t Am. LLC*, 669 F.3d 1362, 1365–66 (Fed. Cir. 2012).

⁵ No such prior claim construction determination has been made of record.

Petitioner does not propose any specific claim construction. *See generally* Pet. Patent Owner states that the “claim terms may be afforded their plain and ordinary meaning.” Prelim. Resp. 9. Patent Owner further notes, however, that “the term ‘precursor ion’ is interchangeable with ‘parent ion,’ which can then be fragmented to yield one or more ‘fragment ions,’ also known as ‘daughter ions’ or ‘product ions,’” indicating that this “distinction between ‘precursor/parent’ ions . . . and ‘fragment/daughter/product’ ions . . . is important to both a proper reading of the claims as well as the scope and content of the prior art.” *Id.* (citing Ex. 1001, 8:60–66).

After reviewing the parties’ arguments and evidence, we determine that it is not necessary to expressly construe any term or phrase in order to determine whether to institute *inter partes* review. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (citing *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (“[W]e need only construe terms ‘that are in controversy, and only to the extent necessary to resolve the controversy.’”)).

*D. Overview of the Asserted References*⁶

1. Voyksner (Ex. 1004)

Voyksner⁷ is titled “Improvements in LC/Electrospray Ion Trap Mass Spectrometry Performance Using an Off-Axis Nebulizer.” Ex. 1004, 5.

⁶ Petitioner also relies on Kamao and Vogeser in its challenges to dependent claims 27 and 28, respectively. We need not discuss those challenges in detail, and thus do not provide an overview of those references.

⁷ Petitioner contends Voyksner was published April 1, 1999 (Ex. 1004, 1), was publicly available at least as early as April 30, 1999 (*see* Ex. 1017), and is prior art under 35 U.S.C. § 102(b). *See* Pet. 11 and n.4.

Voyksner demonstrates the “advantages offered by an off-axis pneumatic nebulizer . . . compared to conventional on-axis nebulizers for the determination of dihydroxyvitamin D₃ in plasma.” *Id.* at 6. Voyksner compares the results of different mass spectrometry methods, including an off-axis nebulizer ion trap MS system and “the accepted and proven triple-quadrupole LC-MS/MS technique.” *Id.* at 10–11.

Both methods include the step of ionizing dihydroxyvitamin D₃ to generate protonated, dehydrated $[M + H - H_2O]^+$ vitamin D₃ ions having a m/z of 399. *Id.* at 6–7. The triple-quadrupole LC-MS/MS monitored “transitions of m/z 399 to 135 and 399 to 213” after collision with argon gas. *Id.* at 7–8, 11. The ion trap MS/MS monitored the transition of m/z 399 to 381. *Id.* at 7–8, 10.

As noted, Voyksner compares the “determination of dihydroxyvitamin D₃ in plasma for the off-axis nebulizer ion trap MS system” to the “determination of identical dihydroxyvitamin D₃ plasma extracts using a triple quadrupole with on-axis nebulization.” *Id.* at 11; *see id.* at Table 1, Fig. 8. Voyksner teaches that “[u]sing the off-axis nebulizer, dihydroxyvitamin D₃ could be measured from a plasma extract down to 1 ng/mL with relative standard deviation of less than 8%.” *Id.* at 11.

2. *Watson (Ex. 1007)*

Watson⁸ is titled “Analysis of Vitamin D and its Metabolites using Thermospray Liquid Chromatography/Mass Spectrometry.” Ex. 1007, 4. Watson describes “a new method for the analysis of vitamin D and its

⁸ Petitioner contends Watson was published in 1991 (Ex. 1007, 1), was publicly available at least as early as August 1, 1991 (*see* Ex. 1019), and is prior art under 35 U.S.C. § 102(b). *See* Pet. 13 and n.7.

metabolites,” and particularly “investigate[s] the TSP LC/MS behaviour of vitamin D and its most important metabolites and evaluate[s] the potential usefulness of the technique.” *Id.* at 6. “Positive ion TSP mass spectra were recorded for vitamin D₂, vitamin D₃, 25-hydroxyvitamin D₃ (25(OH)D₃), 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃) and 24,25-dihydroxyvitamin D₃ (24,25(OH)₂D₃). The spectra contained protonated molecular ions, ammonium adduct ions and fragment ions due to the loss of one or more molecules of water.” *Id.* at 4.

As described in Watson, “[i]ons specific for vitamin D₂, vitamin D₃ and the major metabolites of vitamin D₃ were monitored throughout the analysis and a mixture of authentic standards was chromatographed immediately afterward.” *Id.* at 6. Figure 1 of Watson is reproduced below.

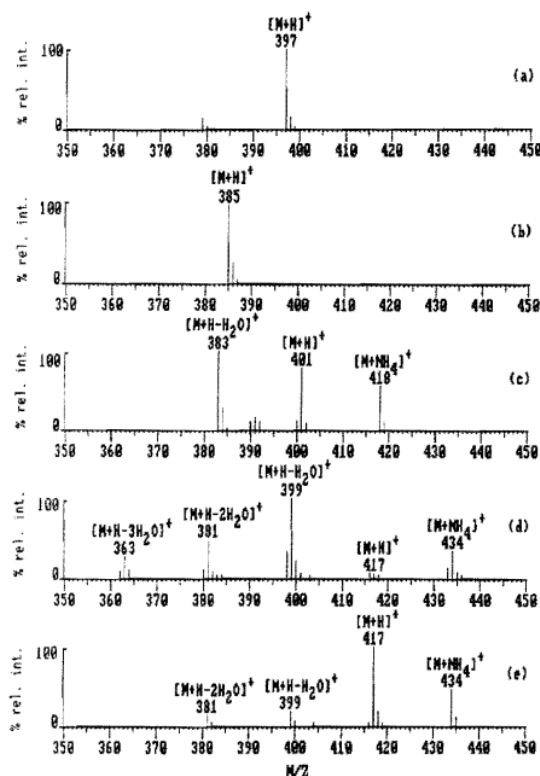


Figure 1, above, shows the TSP mass spectra of (a) vitamin D₂, (b) vitamin D₃, (c) 25(OH)D₃, (d) 1,25(OH)₂D₃, and (e) 24,25(OH)₂D₃. *Id.*

3. *Rainbow (Ex. 1008)*

Rainbow⁹ is titled “The Analysis of Vitamin D Analogues by Atmospheric Pressure Ionization Coupled to Triple Quadrupole Mass Spectrometry.” Ex. 1008. Rainbow describes “the ability of an LC-MS/MS method . . . to detect low levels of 25(OH) Vitamin D₂ & D₃.” *Id.* Rainbow teaches that the “LC-MS/MS Method described can be used to routinely assay and quantify plasma levels of vitamin D₂ & D₃ metabolites. Peak areas from each metabolite are automatically summed . . . to give a result for ‘total’ plasma Vitamin D products, exactly as is generated by traditional immunoassay methods.” *Id.* Additionally, “full metabolite profiling is also possible using this method.” *Id.*

E. Asserted Obviousness over Voyksner, Watson, and Rainbow

Petitioner asserts that claims 21–26 and 31 would have been obvious over the combination of Voyksner, Watson, and Rainbow. Pet. 19–48.

⁹ Petitioner contends that Rainbow was presented at the 51st ASMS Conference on Mass Spectrometry and Allied Topics in Montreal, Canada in June 2003 (*see* Ex. 1042; Ex. 1021), and was available online at least as early as April 22, 2003 (*see* Ex. 1020), thus making it prior art under 35 U.S.C. § 102(b). *See* Pet. 14–15 and n.9. In related IPR2019-01425, Patent Owner asserted that Rainbow is not prior art and the Institution Decision determined that the record did not “provide sufficient support for authentication of the Rainbow reference or sufficient evidence to show that it is prior art with respect to the [challenged] patent.” *See* IPR2019-01425, Paper 9 (Institution Decision) at 22–24. Patent Owner does not make a similar argument here, and Petitioner has presented additional evidence supporting the prior art status of Rainbow in this proceeding. *See generally* Prelim. Resp.; *see* Pet. 14–15 and n.9 (citing Ex. 1002 ¶ 46; Ex. 1020; Ex. 1021; Ex. 1043). Because we deny the Petition on the merits, as discussed below, however, we need not discuss further the sufficiency of Petitioner’s showing with respect to the prior art status of Rainbow.

Patent Owner opposes, arguing that the asserted combination does not teach or suggest all features of the claimed method (*see* Prelim Resp. 17–21) and that Petitioner has not articulated sufficient motivation to combine or reasonable expectation of success (*see id.* at 24–31).¹⁰

1. Independent Claim 21

Petitioner relies on Voyksner as disclosing most of the limitations recited in claim 21. Petitioner points to Voyksner’s disclosure of “detecting product ions from the $[M + H - H_2O]^+$ ion of dihydroxyvitamin D₃” using triple-quadrupole API-MS/MS and “monitoring the transitions of m/z 399 to 135 and 399 to 213.” Ex. 1004, 7–8 (cited at, e.g., Pet. 23, 26). As Dr. Fitzgerald testifies, the “notation $[M + H - H_2O]^+$ was and is commonly used by those of ordinary skill in the art to describe a protonated molecular ion that is dehydrated.” Ex. 1002 ¶ 41. Petitioner points to Table 1 and Figure 8 of Voyksner, which show that the detected ions are to determine the amount of dihydroxyvitamin D₃ present in plasma (at amounts of 3 ng/mL and 30 ng/mL). *See* Ex. 1004, 10–11; Pet. 32 (citing Ex. 1002 ¶ 64).

Petitioner acknowledges, however, that “Voyksner does not disclose measurement of 25-hydroxyvitamin D₂,” which is the specific metabolite recited in the claim. Pet. 24. Petitioner relies on Watson and Rainbow as

¹⁰ Patent Owner also argues that the asserted combination is “no different from what was in front of the Examiner during prosecution of the ’867 patent claims,” and specifically notes that Watson was expressly considered by the Examiner during prosecution of the parent application. *See* Prelim. Resp. 21–24; *see also id.* at 9–17 (discussing the prosecution history of the challenged patent and the parent application). Patent Owner’s arguments implicate our discretion under 35 U.S.C. § 325(d). We do not reach the question of exercising our discretion under § 325(d), however, because we deny the Petition on the merits, as discussed below.

support for its contention that a person of ordinary skill in the art would have modified Voyksner's method to instead detect 25-hydroxyvitamin D₂, as claimed. *See id.* at 24–25. According to Petitioner, “[a]s of the critical date for the ’867 Patent, others had shown that a single LC-MS method could be used for detection of multiple vitamin D metabolites,” including 25-hydroxyvitamin D₂. *Id.* (citing Ex. 1002 ¶¶ 54, 56, 65–67). Petitioner cites Rainbow and Watson to show using a single assay to detect multiple vitamin D metabolites. *See id.* at 25 (citing Ex. 1007, 4; Ex. 1008; Ex. 1002 ¶¶ 54, 56, 65–67). Petitioner relies on Rainbow as teaching a method for simultaneously measuring 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃ in a patient plasma sample by LC-MS/MS. *Id.* (citing Ex. 1008 (Results); Ex. 1002 ¶¶ 54, 65). Petitioner relies on Watson as teaching thermospray LC-MS for detecting Vitamin D₂, Vitamin D₃ and Vitamin D metabolites, e.g., 25-dihydroxyvitamin D₃ in a single assay. *Id.* (citing Ex. 1007, 4; Ex. 1002 ¶¶ 56, 58).

Petitioner asserts that one of ordinary skill would have been motivated to modify Voyksner's method to detect “25-hydroxyvitamin D₂, in view of Watson's disclosure showing that a single assay can be used to measure various vitamin D metabolites and Rainbow's showing of simultaneous detection of 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃ from the same patient sample.” *Id.* at 33 (citing Ex. 1007, 5–6; Ex. 1008; Ex. 1002 ¶¶ 66–67). Petitioner further asserts that there would have been a reasonable expectation of success because “a method suitable for measurement of dihydroxyvitamin D₃ or dihydroxyvitamin D₂ would also have been expected to be successful for their more abundant precursors,

[25-hydroxyvitamin D₃ or 25-hydroxyvitamin D₂], respectively.” *Id.* at 34 (citing Ex. 1002 ¶¶ 68–69).

Regarding the use of a protonated and dehydrated precursor, as claimed, Petitioner asserts that Watson (Figure 1) shows that “the protonated, dehydrated precursors of the dihydroxyvitamin D₃ metabolites (panels D and E) and 25-hydroxyvitamin D₃ metabolite (panel C) are the most abundant precursor ions formed, indicating that these ions should provide good sensitivity for the measurement of vitamin D metabolites.” *Id.* at 27–28 (citing Ex. 1007, 6; Ex. 1002 ¶ 58). Petitioner further asserts “the selection of precursor and fragment ions was often simply determined by the selected equipment, the conditions for ionization, and the relative abundance of the ions and the specificity of the ions for the analyte of interest.” *Id.* at 29–30 (citing Ex. 1005¹¹, 10; Ex. 1002 ¶¶ 59–61). Petitioner further argues that the recited *m/z* of 395.30±0.5 merely indicates the expected value for a protonated, dehydrated precursor of 25-hydroxyvitamin D₂ having a molecule weight of 412.7 g/mol. *Id.* at 27 (citing Ex. 1002 ¶ 57).

Patent Owner argues that none of Voyksner, Watson, and Rainbow discloses “determining the presence or amount of 25-hydroxyvitamin D₂ in a sample.” Prelim. Resp. 19–20; *see id.* at 18–19. We agree with Patent Owner to the extent that Voyksner and Watson do not disclose determining the presence or amount of 25-hydroxyvitamin D₂. Rainbow, on the other hand, at least mentions measuring amounts of 25-hydroxyvitamin D₂ in a sample. Ex. 1008; *see* Prelim. Resp. 19 (Patent Owner recognizing that

¹¹ Kissmeyer, A-M. and Sonne, K., *Sensitive Analysis of 1 α ,25-Dihydroxyvitamin D₃ in Biological Fluids by Liquid Chromatography-Tandem Mass Spectrometry*, 935 J. Chromatography A, 93–103 (2001) (Ex. 1005).

“Rainbow . . . mentions . . . 25-hydroxyvitamin D₂, but provides no legible or interpretable data.”).

Claim 21, however, requires more than merely determining the presence or amount of 25-hydroxyvitamin D₂ in a sample. The claimed method also requires the generation of a “protonated and dehydrated precursor ion of said 25-hydroxyvitamin D₂ with a mass to charge ratio (m/z) of 395.30±0.5.” Patent Owner argues that none of Voyksner, Watson, or Rainbow discloses this limitation of claim 21. Prelim. Resp. 19–20. We agree with Patent Owner that Petitioner does not explain sufficiently *why* a person of ordinary skill in the art would specifically choose the protonated, dehydrated 25-hydroxyvitamin D₂ as a precursor for the tandem mass spectrometry described in Voyksner, as required by claim 21. According to Patent Owner, “25-hydroxyvitamin D₂ can be converted to a variety of different precursor ions, only some of which may be useful in a mass spectrometric method.” Prelim. Resp. 22 (citing Ex. 1001, 10:60–11:1, 11:46–12:30). The ’867 patent confirms the importance of the specific precursor in the preferred embodiments. As described in the ’867 patent, “[g]enerally, the fragment ions that represent dehydrations or deaminations of the precursor ion are not specific fragment ions for a particular analyte. . . . Accordingly, in preferred embodiments of the invention, MS/MS is performed such that at least one fragment ion of a vitamin D metabolite is detected that does not represent only a loss of one or more water molecules and/or a loss of one or more ammonia molecules from the precursor ion.” Ex. 1001, 10:58–60, 11:2–6.

It is not in dispute that none of the cited references include the claimed protonated and dehydrated precursor ion of 25-hydroxyvitamin D₂

with a m/z ratio of 395.30 ± 0.5 . Petitioner asserts that “the selection of precursor and fragment ions was often simply determined by the selected equipment, the conditions for ionization, and the relative abundance of the ions and the specificity of the ions for the analyte of interest.” Pet. 29. (citing Ex. 1005, 10; Ex. 1002 ¶¶ 59–61). Petitioner, however, does not describe specifically *why* one of ordinary skill in the art would have selected the specific precursor ion as claimed. *See Magnum Oil*, 829 F.3d at 1380 (Petitioner cannot satisfy its burden of proving obviousness by employing “mere conclusory statements.”); *NuVasive*, 842 F.3d at 1382 (Petitioner must articulate a reason why a person of ordinary skill in the art would have modified the prior art references.); *see also Metalcraft*, 848 F.3d at 1366 (“In determining whether there would have been a motivation to combine prior art references to arrive at the claimed invention, it is insufficient to simply conclude the combination would have been obvious without identifying any reason why a person of skill in the art would have made the combination.”); *Belden*, 805 F.3d at 1073 (“[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.” (internal citations omitted)).

Without an explanation as to the reasons for selecting the specific claimed precursor ion, Petitioner appears to rely on nothing more than impermissible hindsight to arrive at the claimed invention. *See W.L. Gore & Assocs. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983) (“To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that

knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher.”).

For at least these reasons, we are not persuaded that Petitioner has demonstrated a reasonable likelihood of success in showing that claim 21 would have been obvious in view of Voyksner, Watson, and Rainbow.

2. Dependent Claims 22–26 and 31

Claims 22–26 and 31 each depend, directly or indirectly, from claim 21, therefore, include all of the limitations of claim 21. *See* Ex. 1001, 22:33–43, 57–59. In view of our determination that Petitioner fails to demonstrate a reasonable likelihood of success in showing that independent claim 21 would have been obvious in view of Voyksner, Watson, and Rainbow, we reach the same determination for dependent claims 22–26 and 31.

F. Asserted Obviousness over Voyksner, Watson, Rainbow, and Kamao and over Voyksner, Watson, Rainbow, and Vogeser

Petitioner asserts that claim 27 would have been obvious over Voyksner, Watson, Rainbow, and Kamao (Pet. 48–50) and that claim 28 would have been obvious over Voyksner, Watson, Rainbow, and Vogeser (*id.* at 50–56). Petitioner does not assert that either of Kamao or Vogeser addresses the deficiencies identified with respect to the proposed combination of Voyksner, Watson, and Rainbow as to independent claim 21. *See generally id.* at 48–56. Accordingly, for at least the same reasons discussed above, Petitioner also fails to demonstrate a reasonable likelihood of success in showing that claim 27 would have been obvious in view Voyksner, Watson, Rainbow, and Kamao, and in showing that claim 28

would have been obvious in view of Voyksner, Watson, Rainbow, and Vogeser.

III. CONCLUSION

After considering the evidence and arguments presented in the Petition and Preliminary Response, we determine that the record does not demonstrate a reasonable likelihood that Petitioner will prevail with respect to any claim challenged in the Petition. We, therefore, do not institute an *inter partes* review.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is *denied* as to all challenged claims, and no trial is instituted.

IPR2019-01517
Patent 7,972,867 B2

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