

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.

IPR2019-00738
Patent No. US 8,409,862 B2

Before ULRIKE W. JENKS, SUSAN L. C. MITCHELL, and
ROBERT A. POLLOCK, *Administrative Patent Judges*.

JENKS, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

Laboratory Corporation of America Holdings (“Petitioner”) filed a Petition requesting *inter partes* review of claims 1, 2, and 4–14 (“the challenged claims”) of U.S. Patent No. US 8,409,862 B2 (Ex. 1001, “the ’862 patent”). Paper 1 (“Pet.”). Quest Diagnostics Investments LLC (“Patent Owner”) filed a Patent Owner’s Preliminary Response. Paper 7 (“Prelim. Resp.”). With our authorization, Petitioner filed a Reply to the Preliminary Response (Paper 10), and Patent Owner filed a Sur-reply (Paper 12). On September 4, 2019, we instituted an *inter partes* review of claims 1, 2, and 4–14 of the ’862 patent. Paper 14 (“Dec. Inst.”), 31.

Patent Owner filed a Response to the Petition. Paper 20 (“PO Resp.”). Petitioner filed a Reply. Paper 27 (“Pet. Reply”). Patent Owner filed a Sur-reply (Paper 29, “PO Sur-reply”).

An oral hearing was held on June 3, 2020, a transcript of which has been entered in the record. Paper 35 (“Tr.”).

Pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73, we issue this Final Written Decision. Having considered the record before us, we determine that Petitioner has shown by a preponderance of the evidence that claims 1, 2, and 4–14 of the ’862 patent are unpatentable. See 35 U.S.C. § 316(e) (2018).

A. *Related Proceedings*

The parties identify the following matter in which the ’862 patent has been asserted: *Quest Diagnostics Investments LLC v. Laboratory Corp. of America Holdings*, No. 1:18-CV-01436-UNA (D. Del. Sept. 17, 2018). Pet. 1; Paper 5, 1.

B. The '862 Patent (Ex. 1001)

The '862 patent is titled “Determination of Testosterone by Mass Spectrometry.” Ex. 1001, code (54). The '862 patent issued from Application No. 12/946,785 (“the '785 application”), filed November 15, 2010, which ultimately claims the benefit of U.S. Provisional Application No. 60/501,255, filed Sept. 8, 2003. *Id.* at code (60).

The '862 patent explains that “[t]estosterone levels are much lower in females compared to males. . . . The clinical manifestations of excess testosterone in females include infertility, hirsutism, amenorrhea, and obesity.” *Id.* 1:49–56. The '862 patent explains that “[t]estosterone strongly binds to plasma proteins such as sex hormone-binding globulin (SHBG) or testosterone-estradiolbinding globulin (TEBG). Testosterone also binds with low affinity to CBG (cortisol-binding globulins) and albumin. Less than 2.5% of testosterone circulates unbound to plasma proteins.” *Id.* 1:60–65. The '862 patent exemplifies sample preparation from serum prior to detection of testosterone by ionization mass spectrometry. *Id.* 12:10–45 (Example 1), *see also* 16:15–21 (“Female samples were run on both RIA and HTLC/MS/MS Testosterone assays”). According to the Specification,

[t]he terms “mass spectrometry” or “MS” . . . refer to methods of filtering, detecting, and measuring ions based on their mass-to-charge ratio, or “m/z.” In general, one or more molecules of interest are ionized, and the ions are subsequently introduced into a mass spectrographic instrument where, due to a combination of magnetic and electric fields, the ions follow a path in space that is dependent upon mass (“m”) and charge (“z”).

Id. at 6:27–35.

The '862 patent describes that samples containing testosterone should be purified prior to ionization, citing numerous methods for purifying testosterone such as high performance liquid chromatography (HPLC), thin layer chromatography (TLC), and high turbulence liquid chromatography (HTLC) among others. *See id.* 3:7–44. “[P]urification refers to a procedure that enriches the amount of one or more analytes of interest [such as testosterone] relative to one or more other components of the sample.” *Id.* 3:50–54. Any of the known purification methods can be used alone or in combination. *Id.* 3:17–18. The '862 patent explains that liquid chromatography (LC) and high-performance liquid chromatography (HPLC) require a significant amount of sample preparation prior to the separation and subsequent analysis with a mass spectrometer (MS). *Id.* 6:8–14.

The '862 patent describes methods for determining the presence or amount of testosterone in a test sample by ionizing the testosterone present in a sample so it is detectable by a mass spectrometer. Ex. 1001, code (57). “[T]he testosterone ions detectable in a mass spectrometer include ions with a mass/charge ratio (m/z) of 289.1 ± 0.5 , 109.2 ± 0.5 , and/or 96.9 ± 0.5 , the latter two being fragments of the larger ion.” *Id.* 2:36–39. The preferred internal testosterone standard is 2,2,4,6,6- d_5 -testosterone having a mass/charge ratio (m/z) of 294.1 ± 0.5 , 113.2 ± 0.5 and/or 99.9 ± 0.5 . *Id.* 2:42–49. The '862 patent acknowledges that numerous ionization methods are known and available. *Id.* 3:59–67, 7:19–34.

The mass spectrometer typically provides the user with an ion scan; that is, the relative abundance of each m/z over a given range (e.g., 100 to 900). The results of an analyte assay, that is,

a mass spectrum, can be related to the amount of the analyte in the original sample by numerous methods known in the art.

Id. 4:19–24. The '862 patent explains that “one can quantitate the amount of testosterone in a sample by comparing the summed daughter ion signal of the unknown sample with a standard curve of summed daughter ion signals for known amounts of testosterone.” *Id.* 3:2–6.

C. Illustrative Claim

Claim 1, the sole independent claim under consideration in the present proceeding involving '862 patent is illustrative and reproduced below:

1. A method for determining the amount of testosterone in a sample when taken from a female human, comprising:
 - (a) purifying testosterone from a sample from a female human, wherein said purifying comprises extracting testosterone from said sample;
 - (b) ionizing said purified testosterone to produce one or more testosterone ions detectable by a mass spectrometer; and
 - (c) detecting the amount of one or more of the testosterone ion(s) by a mass spectrometer, wherein the amount of one or more of the testosterone ion(s) is related to the amount of testosterone in the sample;wherein said testosterone is not derivatized prior to mass spectrometry, and
wherein the method is capable of detecting testosterone at concentrations of less than 10 ng/dL in the sample.

Ex. 1001, 19:50–65.

D. Prior art

Petitioner relies upon the following prior art (Pet. 11, 19–63):

Reference	Patent / Publication	Exhibit No.
S.D. Clarke et al. (“Clarke”)	<i>Determination of Suppressed Testosterone Levels in Human Serum by LC-MS/MS</i> , Proceedings of the 49 th ASMS Conference on Mass Spectrometry and Allied Topics,	1003

Reference	Patent / Publication	Exhibit No.
	Chicago, Illinois, May 27–31, 2001	
R. Draisci et al. (“Draisci”)	<i>Quantitation of anabolic hormones and their metabolites in bovine serum and urine by liquid chromatography-tandem mass spectrometry</i> , 870 J. Chromatography A, 511–22 (2000)	1004
Robert L. Fitzgerald & David A. Herold (“Fitzgerald”)	<i>Serum total testosterone: immunoassay compared with negative chemical ionization gas chromatography-mass spectrometry</i> , 42 Clin. Chem. 749–55 (1996)	1005

Petitioner also relies upon the Declaration of Robert L. Fitzgerald, Ph.D. (Ex. 1002) to support its contentions. Patent Owner relies upon the Declaration of Dr. Patrick Sluss Ph.D. (Ex. 2013) to support its opposition to the Petition.

E. The Instituted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1, 2, and 4–14 of the ’865 patent on the following grounds (Pet. 19–63):

Claim(s) Challenged	Basis ¹	Reference(s)
1, 2, 5–7, 10–14	§ 102(b)	Clarke
8, 9	§ 103(a)	Clarke
4	§ 103(a)	Clarke and Fitzgerald
1, 2, 4–14	§ 103(a)	Draisci and Clarke

¹ We apply pre-AIA 35 U.S.C. § 103 because the effective filing date of the ’862 patent precedes the March 16, 2013, effective date for changes to 35 U.S.C. § 103. See MPEP § 2159 (Rev. 08.2017).

II. ANALYSIS

A. *Person of Ordinary Skill in the Art*

The level of skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)). 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).

Petitioner asserts that a person of ordinary skill in the art (POSITA) would have had at least a Masters or Ph.D degree in chemistry, or a related field with several years of experience with various extraction methods, mass spectrometry, and high performance liquid chromatography (HPLC), including the use of such methods for determining levels of analytes in biological samples. Pet. 18–19 (citing Ex. 1002 ¶ 12).

Patent Owner asserts that a person of ordinary skill in the art would have “a bachelor’s degree in chemistry, medicinal chemistry, biochemistry, pharmaceuticals, or a related discipline and at least three to four years of experience using chromatography to perform analytical assays to characterize organic and/or biological materials.” PO Resp. 14. Alternately, Patent Owner asserts that a person of ordinary skill in the art would have “an advanced degree in these same fields and a lesser amount of experience.” *Id.*

Based on the record as a whole, we find that Patent Owner’s description more appropriately encompasses the broad education that the person of ordinary skill in the relevant art may possess. Thus, we adopt that description of the POSITA. We note, however, that neither party asserts specifically that the ultimate conclusion of obviousness turns on the adoption of a particular level of ordinary skill. We further note that the prior art itself demonstrates the level of skill in the art at the time of the invention and supports the breadth of Patent Owner’s description of a POSITA. *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)).

B. Claim Construction

In an *inter partes* review based on a petition filed after November 13, 2018, such as the present Petition, the Board interprets a claim term by applying “the standard used in federal courts, in other words, the claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. [§] 282(b), which is articulated in Phillips.”² 83 Fed. Reg. 51,340, 51,343. Under that standard, the words of a claim “are generally given their ordinary and customary meaning,” which is “the

² See Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340, 51,340, 51,344 (Oct. 11, 2018) (amending 37 C.F.R. § 42.100(b) effective November 13, 2018) (now codified at 37 C.F.R. § 42.100(b) (2019)).

meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc) (citations omitted). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Neither party requests construction of any terms. *See generally* Pet.; PO Resp. 15. In a related litigation involving the ’862 patent, the district court addressed several terms in dispute in that litigation. *See* Ex. 1036, 2. We address one of the district court’s claim constructions below. In addition, we address construction of the term “from a human female.”

1. “*from a female human*”

Patent Owner emphasizes that the phrase “‘purifying testosterone from a sample from a female human,’ from claim 1(a), requires a sample ***from a female human.***” PO Resp. 15. Petitioner agrees that the claim requires a sample from a human female. *See* Tr. 6:10–11. We determine that the plain and ordinary reading of the limitation recited in claim 1(a) is that the sample to be purified is sourced from a human female.

2. “*less than 10 ng/dL*”

Claim 1 recites, “wherein the method is capable of detecting testosterone at concentrations of less than 10 ng/dL in the sample.”

Patent Owner asserts that the claimed method requires quantifying testosterone in a female human sample at the recited (below 10 ng/ ml) level. *see* PO Resp. 21 (asserting that “not a single female human sample [in Clarke] proves the purportedly anticipatory method” because the samples tested in Clarke were not quantified). Petitioner disagrees, contending that

“[t]he claims merely require the methods are capable of detecting testosterone at certain concentrations, without limiting sample or injection volumes or requiring high-throughput analysis.” Pet. Reply 3, 15 (“The claims merely require the methods are capable of detecting testosterone at certain concentrations, without limiting sample or injection volumes or requiring high-throughput analysis.”).

In the related district court litigation involving the ’862 patent, the court addressed the limitation “wherein the method is capable of detecting testosterone at concentrations of less than 10 ng/dL [, 5 ng/dL, or 1 ng/dL] in the sample,” of claims 1, 8, and 9, respectively, but did not address whether the sample derived “from a human female” needs to actually be measured below the detection level recited in the claim in order to meet the limitation. *See* Ex. 1036, 2 (alteration in original).

We agree with Petitioner, that the claim does not require measuring testosterone in a female sample below the recited detection limit, but need only be “capable” of such measurement.³ *See* Pet. Reply 3–4. As the district court also held, all that is required by the claim is that the method is *able* to detect testosterone below said limitation. *See* Ex. 1036, 2 (the limitation “shall be given its plain and ordinary meaning, which is ‘the method is able to detect testosterone at concentrations below 10 ng/dL [or 5 ng/dL or 1 ng/dL] in the sample’”); *see* Ex. 1035, 138:18–20 (testimony of Patent Owner’s expert, Dr. Sluss, that “the claims don’t indicate a limit of quantitation. They are talking about limit of detection.”); Tr. 31:9–11 (Patent

³ Normal serum testosterone levels in human females range from 0.15 to 0.7 ng/ml (i.e. 15 to 70 ng/dL). Ex. 1003, 1.

Owner's counsel, stating: "[T]he method has to be capable of detecting these levels of testosterone in a sample taken from a female human. There's no requirement that the measurement actually be done in a female human."). The '862 patent describes the construction of standard curves encompassing low concentrations of testosterone standards in the range of 0.25–2.5 ng/dL. See Ex. 1001, 4:24–35; 15:15–45. The '862 patent describes that the lower limit of quantification is "the point where measurements become quantitatively meaningful and concentration where CV of the replicates is less than 20%." *Id.* 15:18–20. In contrast the limit of detection is the '862 patent is described as the mean counts per second of the zero standard plus three standard deviations. *Id.* 14:63–65. In other words, limit of detection is the lowest counts measured that can be distinguished from the zero standard. Based on these disclosures, we determine that the record supports the position that the plain reading of the claim limitation "below 10 ng/dL" describes detecting testosterone above the zero standard but below the recited level.

Upon review of the record, we agree with and adopt the district court's claim construction and determine that the plain and ordinary reading of the limitation "the method *is capable* of detecting testosterone at concentrations of less than 10 ng/dL [, 5 ng/dL, or 1 ng/dL] in the sample" is that the method is *able* to detect testosterone below 10 ng/dL⁴ as recited in the claim.

⁴ We note that dependent claims 8 and 9 recite a method for detecting testosterone at a concentration of less than 5 ng/dL and 1 ng/dL respectively. We determine that these claims similarly require that the method need only be *able* to detect testosterone below 5 ng/dL and 1 ng/dL.

In view of our analysis, we determine that construction of other claim terms is not necessary for purpose of this Decision. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (only terms that are in controversy need to be construed, and only to the extent necessary to resolve the controversy).

C. *Principles of Law*

In an *inter partes* review, the burden of persuasion is on the petitioner to prove “unpatentability by a preponderance of the evidence,” 35 U.S.C. § 316(e), and that burden never shifts to the patentee. *Dynamic Drinkware, LLC v. National Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015).

To establish anticipation under 35 U.S.C. § 102(b), “all of the elements and limitations of the claim must be shown in a single prior reference, arranged as in the claim.” *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1383 (Fed. Cir. 2001). When evaluating a single prior art reference in the context of anticipation, the reference must be “considered together with the knowledge of one of ordinary skill in the pertinent art.” *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994) (quoting *In re Samour*, 571 F.2d 559, 562 (CCPA 1978)). “[T]he dispositive question regarding anticipation [i]s whether one skilled in the art would reasonably understand or infer from the [prior art reference’s] teaching’ that every claim element was disclosed in that single reference.” *Dayco Prods., Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1368 (Fed. Cir. 2003) (second and third alterations in original) (quoting *In re Baxter Travenol Labs.*, 952 F.2d 388, 390 (Fed. Cir. 1991)).

A patent 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 the invention was made to a person having ordinary skill in the art to which said 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 skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966).

“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR*, 550 U.S. at 418. “[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine elements in the way the claimed new invention does.” *Id.* Accordingly, a party who 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) (citations omitted).

We analyze the instituted grounds of unpatentability in accordance with the above-stated principles.

D. Ground 1: Anticipation based on Clarke

Petitioner asserts that claims 1, 2, 5–7, and 10–14 are unpatentable as anticipated by Clarke. Pet. 19–33. Patent Owner disagrees. PO Resp. 16–37.

1. Overview of Clarke

Clarke is titled “Determination of Suppressed Testosterone Levels in Human Serum by LC-MS/MS” and relates to an experimental protocol for determining testosterone levels in serum. Ex. 1003, 1. Clarke’s method allows for monitoring testosterone levels from a patient serum sample and shows “a lower limit of quantification of 50 pg/mL,” which is equivalent to 5 ng/dL.⁵ *Id.*; see also *id.* at 2 (“The lower limit of quantification (LLOQ), as defined by the lowest QC [(quality control)] at which accuracy was within 80-120% of nominal and precision was better than $\pm 20\%$, was 50 pg/mL”). Clarke discloses that the normal range for testosterone in serum in males is 3.5 to 10.8 ng/ml, while the normal range for females is 0.15 to 0.7 ng/ml. *Id.* at 1.⁶

Clarke’s experimental method contains three steps: (1) sample preparation step using solid phase extraction (SPE) cartridges (e.g. Isolute Array C18 100 mg/ 2 ml (96 well format)); (2) high pressure liquid chromatography (HPLC) step using a Genesis C18 column; and (3) mass spectrometry detection and quantification by monitoring ions at 289.2 $\rightarrow$ 97.1 (testosterone), and 292.2 $\rightarrow$ 97.1 (D3-testosterone). *Id.*

Clarke discloses that one of the issues with determining testosterone levels in serum “is obtaining suitable ‘blank’ serum” needed for testing and quantification. *Id.* Clarke describes three approaches for obtaining a “blank”

⁵ The formula for converting pg/ml $\rightarrow$ ng/dL is: pg/ml X (1 ng/1000 pg) X (100 mL/1 dL) = ng/dL. See Ex. 1002 ¶ 36 fn 2. Thus, 50 pg/ml is equal to 5 ng/dL. *Id.*

⁶ The formula for converting ng/ml $\rightarrow$ ng/dL is: ng/ml X (100 mL/1 dL). Accordingly, Clarke discloses that the normal ranges for testosterone in serum is 350 to 1,080 ng/dL in males and 15 to 70 ng/dL in females.

serum: (1) use of a surrogate matrix (i.e. equine (gelding) serum), (2) removal of testosterone from serum using a specific testosterone antibody, and (3) using charcoal stripped plasma. *Id.* Clarke’s experimental protocol opted to use equine (gelding) serum as a blank and relied on “stable isotopically labelled testosterone for preparation of calibration and quality control standards, quantifying the samples against the calibration line for the isotopically labelled testosterone.” *Id.* Clarke discloses using control human serum containing endogenous levels of testosterone as the “low QC level” control. *Id.* Clarke also discloses comparing calibration lines made with gelding serum, as well as human female serum. *Id.* at 2.

2. Analysis

We agree with Petitioner and find that Clarke teaches each of the elements of claims 1, 2, 5–7, and 10–14 for the reasons set forth in the Petition and the declaration of Dr. Fitzgerald. Pet. 19–33; Ex. 1002 ¶¶ 45–56. Patent Owner opposes. PO Resp. 16–37. Specifically, Patent Owner contends that Clarke (a) is not a printed publication (b) does not anticipate the claims (c) is not enabled, and (d) is not peer reviewed. PO Resp. 16–37. We address Patent Owner’s contention below.

(a) Printed publication

Each asserted ground of unpatentability relies on the Clarke reference. Pet. 11. Clarke is an abstract disclosed on a compact disk (CD) which is a compellation of the Proceedings of the 49th ASMS Conference on Mass Spectrometry and Allied Topics. Ex. 1003. Petitioner relies on declarations from Ms. Waters, a librarian at the University of Wisconsin-Madison library system, to establish the availability of the Clarke abstract. Pet. 13, n1 (citing Ex. 1017). Pet. Reply 5 (citing Ex. 1017 and Ex. 1030). In the initial

declaration Ms. Waters avers to the standard operating procedures for adding materials to the library system. Ex. 1017.⁷ In response to Patent Owner's Reply, Petitioner submitted the Supplemental Watters Declaration to clarify issues with the bar code numbering on the CD in the library system, and to the ability to search the CD. *See* Ex. 1030.⁸ Petitioner relies on these two Watters Declarations to establish that the Clarke abstract is a printed publication that was publically available more than one year before the earliest priority date of the '862 patent and, thus, available as prior art under §102(b). Pet. 13, n1 (citing Ex. 1017); *see* Pet. Reply 4–6 (citing Ex. 1030). In addition, Petitioner relies on the American Society for Mass Spectrometry (ASMS) website to show that the abstracts were searchable. Pet. Reply (citing Ex. 1029; Ex. 1032); Tr. 9:9–10 (“We’re relying on the catalogued CD. And we used the distribution to members as well as libraries to show that one with skill in the art would have been aware of the proceedings.”).

To qualify as a “printed publication,” a reference “must have been sufficiently accessible to the public interested in the art” before the critical date. *In re Cronyn*, 890 F.2d 1158, 1160 (Fed. Cir. 1989). Whether a reference is publicly accessible is determined on a case-by-case basis based on the “facts and circumstances surrounding the reference’s disclosure to members of the public.” *In re Lister*, 583 F.3d 1307, 1311 (Fed. Cir. 2009) (quoting *In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004)). “Because there are many ways in which a reference may be disseminated to

⁷ Declaration of Rachel J. Watters on authentication of publication, dated Dec. 14, 2018 (Ex. 1017 (“Watters Declaration”)).

⁸ Declaration of Rachel J. Watters, dated Sept. 30, 2019 (Ex. 1030 (“Supplemental Waters Declaration”)).

the interested public, ‘public accessibility’ has been called the touchstone in determining whether a reference constitutes a ‘printed publication’ bar under 35 U.S.C. § 102(b).” *In re Hall*, 781 F.2d 897, 898–99 (Fed. Cir. 1986); *see also SRI Int’l, Inc. v. Internet Sec. Sys.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008) (quoting *Hall*). “A reference will be considered publicly accessible if it was ‘disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it.’” *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1348 (Fed. Cir. 2016) (quoting *Kyocera Wireless Corp. v. ITC*, 545 F.3d 1340, 1350 (Fed. Cir. 2008)). Petitioner bears the burden of establishing public accessibility of the prior art references it relies upon for its patentability challenges. *See Blue Calypso*, 815 F.3d at 1350 (finding that petitioner in an AIA proceeding “failed to carry its burden of proving public accessibility”). As the cases make clear, a document may be a printed publication based on either (1) actual dissemination to people of ordinary skill in the art *or* (2) being made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it.

Petitioner relies the declarations from Ms. Waters, Dr. Fitzgerald, and Dr. Voyksner to establish that Clarke is a printed publication. Pet. 13, n.1; Pet. Reply 4–6. The first Waters Declaration describes the standard processing procedures for receiving and cataloging new library holdings into the Wisconsin-Madison library system. *See Ex. 1017, 1*. This Waters Declaration includes a copy of a CD from the 49th ASMS Conference on Mass Spectrometry and Allied Topics (Ex. 1017, 3), a copy of the CD sleeve with the barcode (*id.* at 4), and a copy of the public library catalog screen

(*id.* at 5). The Supplemental Waters Declaration clarifies the differences between the handwritten numbering on the CD and the two bar codes associated with the CD sleeve. Ex. 1030, 2–3. In addition, the Supplemental Waters Declaration also provides a copy of the information downloaded from the disk describing how the information can be viewed, searched, and retrieved, including a list of key words. *See* Ex. 1030, 2, 4–17.

The Fitzgerald Declaration details that Dr. Fitzgerald is a member of the ASMS but did not attend the 49th meeting held in Chicago, Illinois on May 2001. Ex. 1002 ¶ 34. Dr. Fitzgerald avers that proceedings from this meeting were distributed to all members of the ASMS. *Id.*

The Voyksner Declaration details that Dr. Voyksner is also a member of ASMS and avers that members are routinely provided with copies of the abstracts from the annual conference within a few months after the conference. Ex. 1029 ¶¶ 4, 6.

Patent Owner contends that the Declarations of Dr. Fitzgerald, Dr. Voyksner, and Ms. Watters are insufficient to support the position that the Clarke reference was actually disseminated to people of ordinary skill in the art. PO Resp. 32–37. Specifically, Patent Owner contends that “[t]he Watters Declaration [(Ex. 1017)] provides no evidence that Clarke was published, catalogued, indexed, or identified in any useful way by the University of Wisconsin-Madison library system prior to the critical date of the ’862 patent.” *Id.* at 37. In other words, Patent Owner contends that the Watters Declaration (Ex. 1017) does not speak to the ability of persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, to have located the Clarke reference. Patent Owner contends that a CD is very different from a textbook. *Id.* Even if a POSITA

would have located the CD, “finding Clarke would have required a POSITA to exhaustively sift through thousands of abstract pages at random without any guidance or idea concerning what might be found.” *Id.*; PO Sur-Reply 8. Because a CD “has no index or table of contents and its list of subject keywords would not have led a POSITA to Clarke.” PO Resp. 37; *see* PO Sur-Reply 10–11.

Petitioner responds that the two Watters Declarations and accompanying exhibits sufficiently explain how the ASMS conference proceeding, and therefore the Clarke reference, was available to the public. Pet. Reply 4–6 (citing Ex. 1017 and Ex. 1030). Petitioner explains that a search at the University of Wisconsin “library catalog could be done by title, author, and/or subject key words based on the Proceedings’ title and notes the CD itself was searchable.” *Id.* at 5 (citing Ex. 1017, 2). Thus, according to Petitioner, a person interested in mass spectrometry would be able to locate the CD of the ASMS conference proceedings at the library. Petitioner explains that:

The CD containing abstracts is similar to a book with chapters by different authors. A POSITA, exercising reasonable diligence, could have searched the catalog records (like searching for a book on MS) and then searched the CD (like reviewing chapter titles or index of a book) to access the Clarke abstract. Moreover, the content of the abstracts was searchable at the ASMS website.

Id. (citing Ex. 1029; Ex. 1032).

We determine that the record supports the position that the ASMS produced a compact disk from the 49th ASMS Conference on Mass Spectrometry and Allied Topics, and that abstracts from this conference

proceeding were available at the University of Wisconsin library in the form of a compact disk at least on July 16, 2002. Ex. 1017, 5; *see* Ex. 1030, 1–3.

[I]ndexing is not ‘a necessary condition for a reference to be publicly accessible’; it is but one among many factors that may bear on public accessibility. . . . Moreover, indexing is no more or less important in evaluating the public accessibility of online references than for those fixed in more traditional, tangible media.

Voter Verified, Inc. v. Premier Election Solutions, Inc., 698 F.3d 1374, 1380 (Fed. Cir. 2012) (citing *Lister*, 583 F.3d at 1312). Here, the University of Wisconsin library system is treating the compact disk from the ASMS Conference Proceeding as a “general (book),” i.e. tangible media. *See* Ex. 1017, 5; *see* Ex. 1030. Not all books are searchable by a computer search engine. Indeed retrieval of information from a book (i.e. tangible media) can require that the interested person physically open the book to access the information contained inside. Here, the evidence supports the position that “[a] POSITA, exercising reasonable diligence, could have searched the catalog records (like searching for a book on MS)” and retrieved the CD of the 49th ASMS conference proceeding. Pet. Reply 5.

In addition to being catalogued at the University of Wisconsin library, the record supports that in the normal course of these ASMS meetings the conference proceedings were regularly distributed to all 3500 ASMS members. Ex. 1002 ¶ 34;⁹ Ex. 1029 ¶ 6.¹⁰ The purpose of presenting an

⁹ We note that Dr. Fitzgerald does not attest to when he received the copy of the proceeding abstracts.

¹⁰ We note that Dr. Voyksner attested to attending the 49th ASMS Conference (Ex. 1029 ¶ 4), but does not mention any specific abstract in the declaration (Ex. 2008, 27:2–4).

abstract at a conference is public communication of the relevant information. This is true whether the abstract is physically displayed,¹¹ presented in a talk, or published as part of the proceeding – the purpose in any of these scenarios is to communicate the information to the relevant interested audience. Here, the evidence provided with the Petition supports the position that the Clarke Abstract was disseminated to the relevant audience, i.e. members of ASMS, as part of the information disclosed on the CD. *See* Ex. 1017, 3–5; Ex 1030, 8 (“A record number of 4,182 people attended the conference.”). Petitioner relies on the declarations of Dr. Fitzgerald and Dr. Voyksner, both ASMS members, to establish that as an ASMS member, one would receive meeting abstracts whether or not one attends the meeting, which supports the position that the meeting abstracts were publicly accessible by the relevant audience. *See* Pet. Reply 3 (citing Ex. 1002 ¶ 34), 4 (citing Ex. 1029 ¶ 6).

Based on these disclosures, we find that the evidence supports that a POSITA searching for information about mass spectrometry would have been able to locate the 49th ASMS conference proceeding. In addition, the evidence supports the position that the information was disseminated to ordinarily skilled artisans, in this case ASMS members at the time of the 49th ASMS conference. *See* Ex. 1002, ¶ 34; Ex. 1029, ¶ 6; Ex. 1030, 8.

Patent Owner contends that a CD differs from a book because it does not have an index and its list of subject keywords would not have led the POSITA to Clarke. PO Resp. 37 (citing 2009, 20:6–14); *see* PO Sur-Reply 8. Thus, Patent Owner’s position is that a POSITA could not have searched

¹¹ We note there is no evidence in the record that establishes that the Clarke Abstract was actually presented at the meeting.

the CD for “testosterone” in order to retrieve the Clarke abstract. *See* Tr. 34:18–19.

We determine that the record sufficiently supports the position that the CD of the 49th ASMS conference proceeding was searchable. The Voyksner Declaration includes two exhibits that show that at the time of the proceedings the abstracts of 49th ASMS conference proceeding were searchable by keyword, title of the abstract, title of the session, author, and author institution, similar to the index of a book. Ex. 1029 ¶ 5; Ex. 1030, 8–18. We agree with Patent Owner that “testosterone” is not among the keywords listed for the abstract entry on the CD. *See* PO Resp. 35; PO Sur-Reply 8; Ex. 1030, 8–10. The Clarke abstract is titled “Determination of Suppressed Testosterone Levels in Human Serum by LC-MS/MS.” Ex. 1003. A review of the keywords that are listed for the CD of the 49th ASMS conference proceeding shows the following keywords: LC-MS/MS (use instead MS/MS, Liquid Chromatography); MS/MS; MS/MS, Liquid Chromatography-(LC-MS/MS); Tandem Mass Spectrometry (use instead: MS/MS); and Plasma, human. Ex. 1030, 8–10. The key words LC-MS/MS and human are present in the Clarke abstract. Accordingly, a POSITA interested and LC-MS/MS would have been able to find the Clarke abstract based on the keyword search capabilities of the CD.¹² Thus, we are not persuaded by Patent Owner’s contention that Clarke was not available

¹² The CD has not been searched for human, LC-MS, or LC-MS/MS, but based on the list of keywords provided with the CD, it is reasonable to assume that the number of abstracts retrieved would have been reduced from the initial 1600. *See* Tr. 36:2–25.

because one could not have found Clarke among the more than 1600 abstracts presented at the meeting.

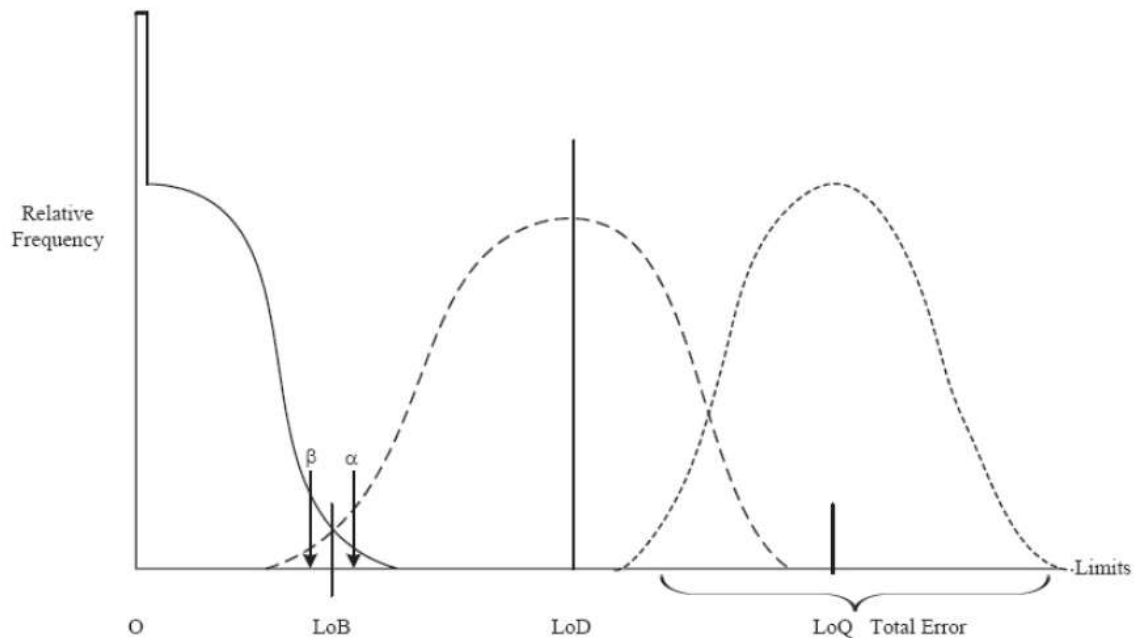
For the foregoing reasons, we determine that Petitioner has shown that Clarke is a printed publication based on the CD of the proceedings of the 49th ASMS Conference on Mass Spectrometry and Allied Topics as cataloged in the University of Wisconsin library system. See Ex. 1017, 3; Ex. 1030, 2.

(b) Anticipation

Petitioner contends that “Clarke describes methods for determining testosterone levels in [female] human serum by (a) purifying the testosterone, (b) ionizing the testosterone to produce mass spectrometer detectable ions, and (c) detecting the ions,” all without the need of derivatization at concentration levels of less than 10 ng/dL in the sample. Pet. 20.

Patent Owner contends that Clarke is not capable of detecting testosterone at concentrations of less than 10 ng/dL in female samples. PO Resp. 17. Patent Owner questions Clarke’s use of equine gelding serum as a control noting that this is not a standard reference serum. *Id.* at 18. Patent Owner contends that Clarke does not provide a sufficient description on how the serum samples were “spiked.” *Id.* at 19 (citing Ex. 2013 ¶ 53). Nor does Clarke describe how the endogenous levels of testosterone in equine gelding serum are accounted for in the reference. *Id.* at 20 (citing Ex. 1003, 2; Ex. 2013 ¶ 79 (“Equine gelding serum has been reported to contain trace amounts of endogenous testosterone. Ex. 2020 (Soma) at 1 (noting that serum testosterone levels have been reported as being 15.3 ± 4.9 pg/mL in geldings).”).

Much of the discussion in the briefing revolves around the difference between limit of detection (LOD or LoD) versus limit of quantitation (LOQ or LoQ). A figure is helpful to visualize these concepts. The figure below is from a review article and shows the relationship between limit of blank (LoB), limit of detection (LoD), and limit of quantification (LoQ).



The Figure, reproduced above, shows the distribution results for LoB, LoD, and LoQ. Ex. 1020, 3; *see* Ex. 2025, 34. “It can be expected that the LoD lies somewhere below an assay’s functional sensitivity. The LoQ may be equivalent to the LoD or it could be at a much higher concentration (Figure); it cannot be lower than the LoD.” Ex. 1020, 3; *see* Ex. 2025, 27. Put another way, the LoD is either the same or lower than LoQ.

Both Patent Owner’s and Petitioner’s experts agree that the limit of detection (LOD) is the lowest amount of testosterone that one can detect. *See* Ex. 1035, 135:1–3 (Patent Owner’s expert, Dr. Sluss testifies: “The limit of detection is exactly that, what is the smallest amount that you can detect.”),

138:19–20 (“[The claims] are talking about a limit of detection”); Ex. 2012, 150:3–6 (Petitioner’s expert, Dr. Fitzgerald testifies: “Q: So when you use the word “capable” or the phrase “capable of detecting” in your report here, are you referring to the limit of detection? A: Yes.”); Ex. 1002, ¶¶ 28, 29.

Based on our review of the arguments and the cited art, we determine that Petitioner has demonstrated that claim 1 is anticipated by Clarke. Clarke discloses that female serum is used as a quality control sample for measuring low testosterone levels. Ex. 1003, 1 (“Control human (female) serum containing an endogenous level of testosterone used as the low QC level”). Clarke also discloses the production of calibration lines using both gelding serum *and* female human serum. *Id.* at 2 (“A calibration line was prepared in each of six different human female sera and compared against a calibration line in equine gelding serum.”). Clarke discloses using labeled testosterone for the production of calibration and quality control standards. *Id.* at 1 (“stable isotopically labelled testosterone for preparation of calibration and quality control standards, quantifying the samples against the calibration line for the isotopically labelled testosterone.”). Clarke also measured the endogenous testosterone level (pg/ml) from human female 1–6. *Id.* at 2. Based on these disclosures, we agree with Petitioner that Clarke uses samples derived from a female human. Pet. 21 (citing Ex. 1003, 1 (Experimental) (“human (female) serum containing an endogenous level of testosterone used as the low QC level” (emphasis removed))). We are not persuaded by Patent Owner’s characterization that Clarke is missing any element of the claim.

Clarke explains that normal female serum testosterone levels range from 0.15 to 0.7 ng/ml, i.e., 17–70 ng/dL. Ex. 1003 at 1; footnote 6, *supra*.

Clarke discloses that the experimental range of endogenous testosterone level in the six female serum samples tested is 199 pg/ml–471 pg/ml, i.e., 19.9–47.1 ng/dL. Ex. 1003, 1–2; *see* footnote 5, *supra*. That all of Clarke’s female samples fall within the normal range expected for females is not surprising because Clarke uses these samples only as a way to validate low endogenous testosterone concentrations. *Id.* Claim 1 of the ’862 patent requires that the method be *able* to detected below 10 ng/dL, the claim does not require that the female sample tested needs to be at that level. *See supra* Section II.B. The fact that Clarke’s female serum samples are not below the level of detection recited in the claim does not detract from what the reference teaches – a protocol that can be used to detect testosterone from human female serum with an assay that has a lower limit of *quantification* at 50 pg/dL.¹³ Ex. 1003, 2. Because the limit of detection is either the same as the limit of quantification or lower, the disclosure in Clarke meets the claimed detection limit. *See* Ex. 1002 ¶¶ 28, 29, 57; Ex. 1020, 3; Ex. 2025, 27, 34.

Clarke exemplifies obtaining readings of a control sample at a concentration of 50 pg/ml (5 ng/dL). Ex. 1003, 2; Ex. 1002 ¶ 57 (“Clarke shows that, using the disclosed assay, a standard of 50 pg/mL had a mean reading of 46.8 pg/ml (4.68 ng/dL), a CV¹⁴ (precision) of 14.1%, and accuracy of 93.6%”). Based on this disclosure, we agree with Petitioner that Clarke is capable of detecting concentrations of less than 10 ng/dL in a

¹³ This is equivalent to 5 ng/dL. *See above* footnote 5.

¹⁴ “The CV, or coefficient of variation, is also referred to as the RSD, or relative standard deviation.” Ex. 1002 ¶ 29.

sample. Pet. 20 (citing Ex. 1002 ¶ 50 (“Clarke reports that their assay has an LOQ of 50 pg/ml (which equals 5 ng/dL)”)).

Patent Owner contends that Petitioner is treating samples sourced from different mammals as if they were interchangeable. PO Resp. 15 (citing Ex. 2013 ¶ 55). From the background section of the ’862 patent we know that “[t]estosterone strongly binds to plasma proteins such as sex hormone-binding globulin (SHBG) or testosterone-estradiol binding globulin (TEBG). Testosterone also binds with low affinity to CBG (cortisol-binding globulins) and albumin.” Ex. 1001, 1:60–63. In accord with Patent Owner’s argument, we agree that the degree of testosterone binding in native plasma or serum may be species specific.

Petitioner’s position, however, is that the detection of testosterone in the method occurs after a purification step that enriches the testosterone while removing other components. *See* Pet. 47. In other words, once testosterone is removed from its native matrix, such as blood, plasma, serum, or urine, testosterone is interchangeable in the analysis method because the testosterone molecule itself is the same molecule across species. Pet. 47 (citing Ex. 1002, ¶¶ 27 (“[T]he structure of testosterone is the same across vertebrate species”), 62 (“Testosterone is the same chemical entity in both bovine and human samples. . . . Once extracted, the testosterone from various mammalian species behaves similarly in chromatography and mass spectrometry steps.”); *see also* U.S. Patent No. 4,452,903, 5:12–15 (Ex. 1027) (describing testosterone standards prepared using human testosterone in a bovine serum base); Tr. 24:13–15 (counsel for Patent Owner stating “I’m not aware of any evidence of record that discuss species difference in testosterone at a molecular level.”). We, therefore, agree with

Petitioner that once purified from the native matrix, testosterone is not structurally different between species. *Compare* Ex. 1003, 1 (ions monitored 289.2→97.1 (testosterone) testing human and gelding samples) *with* Ex. 1004 (m/z 289→97 for both 17 α -testosterone and 17 β -testosterone testing bovine samples). Accordingly, based on our review of the arguments and the cited art, we agree with Petitioner that purified testosterone is the same molecule between species and therefore reasonably interchangeable across testosterone assays. Pet. 47 (citing Ex. 1002 ¶¶ 25, 62; Ex. 1027).

Patent Owner contends that Clarke does not disclose how the calibration lines are made and therefore it would be impossible to interpret or believe the results. PO Resp. 21–22 (citing Ex. 2013 ¶¶ 48 (Patent Owner’s expert, Dr. Sluss testifying: “Clarke does not provide sufficient experimental detail to allow replication of the disclosed information or even an objective evaluation of it by a POSITA.”), 83). Patent Owner contends that there is a linearity problem at low concentration levels. *Id.* at 23–24 (citing Ex. 2013 ¶ 82). According to Patent Owner, “a POSITA would not believe Clarke’s LLOQ disclosure of 50 pg/mL.” *Id.* at 25.

We determine that Petitioner has the better position in light of evidence that routine experimental protocols that a POSITA would use in the ordinary course of doing research, such as producing a calibration line, would not require detailed instructions. *See* Pet. Reply 2 (citing Ex. 1035, 99:14–16 (deproteination); 156:20–157:9 (dissolving testosterone to make standards); 165:6–15 (column selection); 214:19–215:2 (“[A]ny first year analytical chemist knows how to” create a calibration line); 230:22–231:2 (checking for matrix effects); 242:4–243:24 (determining injection volumes); 256:23–257:3 (adapting methods for animal testing to human

testing)). Clarke discloses that “[t]he method described has been fully validated to international standards for the rapid, specific and accurate quantitation of suppressed levels of testosterone in human serum.” Ex. 1003, 2. Given that POSITA would know something about making calibration lines, and given Clarke’s description that the method has been fully validated to international standards, we are not persuaded by Patent Owner’s position that Clarke’s method is so unsound that the results are unbelievable.

Patent Owner contends that Clarke does not describe how the endogenous levels of testosterone in equine gelding serum are accounted for in the reference. PO Resp. 20 (citing Ex. 1003, 2; Ex. 2013 ¶ 79 (Patent Owner’s expert, Dr. Sluss testifying: “Equine gelding serum has been reported to contain trace amounts of endogenous testosterone. Ex. 2020 (Soma) at 1 (noting that serum testosterone levels have been reported as being 15.3 ± 4.9 pg/mL in geldings).”).

We are not persuaded by Patent Owner’s contention. Even assuming that the gelding serum was not treated to remove endogenous testosterone, which is standard practice in this art,¹⁵ that would mean that 50 pg/ml sample disclosed in Clarke could contain an additional 15.3 ± 4.9 pg/mL (Ex. 2013 ¶ 51 (citing Ex. 2024 at 1)) bringing the sum total of testosterone in Clarke’s lower limit sample to 65.3 pg/ml, i.e. 6.5 ng/dL. This amount, however, would still meet less than 10 ng/dL detection limit as recited in

¹⁵ See e.g. Ex. 2025, 11 (“For endogenous compounds, blanks might be samples that are stripped of the component, e.g., by precipitation by an antibody, by enzymatic degradation, or by adsorption to charcoal, etc.”); Ex. 2021, 2 (“Steroid-free sera were charcoal stripped sera prepared in the laboratory.”).

claim 1 of the '862 patent. *See* Ex. 1002 ¶ 36 n.2 (conversion formula “pg/ml X (1 ng/1000 pg) X (100 mL/1 dL) = ng/dL”).

Patent Owner contends that Clarke’s results are “dubious considering that the coefficient of variation (CV%) is higher at 50 pg/mL in the ‘intra batch’ data than the ‘inter batch’ data,” when the expectation is that “[i]ntra batch numbers should have less variance (i.e., a lower CV%) than inter batch numbers.” PO Resp. 25–26 (citing Ex. 2013 ¶¶ 60–61); *see* Sur-Reply 15–16.

We are not persuaded by Patent Owner’s contention because the CV% values assayed for the other points in the table are indeed less for the intra batch variance than the inter batch variance. The lowest point measured is the 50 pg/ml which has an accuracy at 93% and is still within the $\pm 20\%$ precision limit set out by Clarke. A POSITA would understand that the limit of detection is either the same or, more likely, lower than the limit of quantification. *See* Ex. 1002 ¶¶ 28, 29, 57; Ex. 1020, S51; Ex. 2025, 27, 34. Having determined that Clarke measures serum samples derived from human females and is able to not only detect but quantify testosterone at a level of 50 pg/ml (i.e. 5 ng/dL), we find that Petitioner has shown by a preponderance of the evidence that claims 1, 2, 5–7 and 10–14 of the '862 patent are unpatentable as anticipated by Clarke.

(c) Enabling Disclosure

Patent Owner contends that Clarke does not adequately describe the method and thereby is not an enabling disclosure. PO Resp. 26–32.

To anticipate a claimed invention, a prior art reference must enable one of ordinary skill in the art to make the prior invention without undue experimentation. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d

1313, 1354 (Fed. Cir. 2003). The burden of proving non-enablement of a prior art reference rests on the Patent Owner. *Impax Labs., Inc. v. Aventis Pharms., Inc.*, 545 F.3d 1312, 1316 (Fed. Cir. 2008) (patentee may overcome the presumption of enablement by establishing with persuasive evidence that the prior art does not enable the claimed invention). See *Edmund Optics Inc. v. Semrock, Inc.*, IPR2014-00599, Paper 72, 26–28 (PTAB Sept. 16, 2015).

Anticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure. See *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1380 (Fed. Cir. 2003); citing *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985).

Some experimentation, even a considerable amount, is not “undue” if, e.g., it is merely routine, or if the disclosure provides a reasonable amount of guidance as to the direction in which the experimentation should proceed.

Factors to be considered in determining whether a disclosure would require undue experimentation . . . include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

(1). *Wands Factors #1 and #2: The quantity of experimentation and amount of direction or guidance presented*

Patent Owner contends that the 2-page Clarke abstract is sparse on detail and thereby it would require undue experimentation. PO Resp. 28

(citing Ex. 2013 ¶ 137; Ex. 2012, 119:11–120:9, 144:8–156:9). For example, Patent Owner notes that there is no description in how the samples were “spiked” or other “[v]ariables like pre-column sample preparation (such as a protein precipitation step), column preparation, flow rate, wash and extraction solvents, temperature, bead size, and pH are all absent from Clarke.” PO Resp. 27–29 (citing Ex. 2013 ¶¶ 76, 94, 137).

Clarke describes sample preparation using solid phase extraction (SPE) using Isolute Array C18 cartridge, component separation using a Genesis C18 chromatography column, and detection of the components using a mass spectrometry SCIEX API 3000 instrument. Ex. 1003, 1; Pet. Reply 12. Clarke also provides extraction details such as the starting sample volume and the final extraction volume for the initial sample preparation. Ex. 1003, 1. Clarke describes component separation by describing the specific column used, the mobile phase applied, the flow rate, and the injection volume as well as the runtime. *Id.* For the mass spectrometry component Clarke provides the instrument, the mode, and interface as well as the instructions for monitoring the particular ions 289.2 → 97.1 (testosterone) and 292.2 → 97.1 (D3-testosterone). Ex. 1003, 1.

Clarke discloses that “[a] calibration line was prepared in each of six different human female sera and compared against a calibration line in equine gelding serum.” Ex. 1003, 2. Clarke may not have provided details on how the sample was “spiked” or how the calibrations were made but a POSITA would have understood how to perform such assays and would not need to have every detail spelled out. *See* Pet. Reply 12; PO Resp. 22 (citing Ex. 21013 ¶ 48); *see* Ex. 1035, 157:1–6 (Patent Owner’s expert, Dr. Sluss

testifying: “You can’t put testosterone at reasonably high concentrations into water or in aqueous solution. It has to first go into an organic [solvent]. That is the nature of – that’s the non-polar nature of testosterone, and it would be well known.”), 232:1–3 (“In principle. The details [of a standards assay] are always a little different, but the basic concepts I would expect to be quite similar.”). Because testosterone is very hydrophobic Patent Owner contends that saying a sample was “spiked” is not enough to enable to procedure. PO Resp. 28 (citing Ex. 2013 ¶ 76). We are not persuaded by this argument because this presumes that the POSITA would have no knowledge about testosterone, how to dissolve testosterone, how to set up calibration curves, or how to run a standard LC-MS/MS assay. The POSITA is presumed to have ordinary creativity and intelligence. *KSR*, 550 U.S. at 421; *see also In re Sovish*, 769 F.2d 738, 743 (Fed. Cir. 1985).

Based on these disclosures, we agree with Petitioner that “a POSITA necessarily adapts the information disclosed in or missing from the reference to the particular parameters of the POSITA’s needs.” Pet. Reply 11 (citing Ex. 2012, 119:11–120:9; Ex. 1035, 165:6–15). Just because some variables need to be experimentally determined does not mean that the level of experimentation is undue. The creation of calibration standards are routine variables. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) (“[A] patent need not teach, and preferably omits, what is well known in the art.” (Citation omitted)).

Accordingly, we find that Wands factors #1 and #2 weigh in favor of enablement.

(2). *Wands Factor #3: The presence or absence of working examples*

Patent Owner contends that Clarke lacks working examples. PO Resp. 29 (citing Ex. 2013 ¶ 89). Patent Owner contends that Clarke is missing certain information requiring experimentation to replicate Clarke's work. *Id.* 29–30 (citing Ex. 2013 ¶ 89 (Patent Owner's expert, Dr. Sluss testifying: "Clarke lacks directions or working examples to guide a POSITA and those gaps could only have been filled with extensive experimentation.")).

The question here is how much information is required for POSITA to replicate Clarke's experiments. Clarke discloses preparing calibration lines for each of the six different human female samples tested as well as the gelding serum. Ex. 1003, 2. Clarke describes that each of these lines were then compared against the calibration line using equine gelding serum. *Id.* Clarke also determines the endogenous testosterone levels in at least six female samples. *Id.*; Pet. Reply 17 (citing Ex. 1003 1–2; Ex. 1002 ¶¶ 36, 50, 55). Clarke describes that the method was fully validated to international standards. Ex. 1003, 2. Creating a calibration line or standard is something a POSITA would know how to do. See Ex. 1035, 232:1–3 (Patent Owner's expert, Dr. Sluss testifying: "In principle. The details [of creating a standard] are always a little different, but the basic concepts I would expect to be quite similar.")). Based on these disclosures, in conjunction with what a POSITA would know about making calibration lines and standards, we agree with Petitioner that Clarke recites working examples for detecting testosterone in samples derived from human females. Clarke's human female sample may not have low enough testosterone levels to fall within the claim detection limit, but the levels are well within the normal range for human females. The

claim does not require that the females' samples have low testosterone levels. Ex. 1003, 1. All that is required by claim 1 of the '862 patent is that the assay is *able* to detect low levels testosterone. We determine that Clarke's lower limit of quantification (LLOQ) at 50 pg/ml (5 ng/dL) meets the claimed low detection level.

Accordingly, we find that Wands factor #3 weighs in favor of enablement.

(3). *Wands Factors #4, #5, #6, and #7: The nature of the invention; state of the prior art; relative skill of those in the art; and the predictability or unpredictability of the art*

Patent Owner contends that the '862 patent was a breakthrough in the field and that the level of skill is relatively high. PO Resp. 30 (citing Ex. 2013 ¶ 36). "It is undisputed that LC/MS-MS was a brand new technique for the detection of testosterone in the early 2000s," and thereby unpredictable. PO Resp. 31 (citing Ex. 2013 ¶ 14; Ex. 2012, 66:16–67:8).

We are not persuaded that detecting testosterone using LC-MS/MS method steps is unpredictable. As discussed above (*see II.A*), we find that the relative skill of the artisan is one having a degree in chemistry, medicinal chemistry, biochemistry, pharmaceuticals, or a related discipline and several years of experience using chromatography to perform analytical assays to characterize organic and/or biological materials; years of experience required is inverse to the degree held. With this skill level in mind we address the nature of the invention, state of the art, and unpredictability of the art.

We agree with Petitioner that LC/MS-MS is a known technique that has been used for years at least with respect to the purification of other

molecules. Pet. Reply 15 (citing Ex. 1026, Ex. 1023, 21–22); Ex. 1002 ¶¶ 20–25.

We note that Draisci published in 1999, describes quantification of testosterone using a combination of liquid chromatography (LC) with MS (mass spectrometry) and MS-MS (tandem mass spectrometry). Ex. 1004, 10. Specifically, Draisci describes that a serum “sample was purified by solid-phase extraction (SPE) using a C₁₈ cartridge (Baker C18, 500 mg, 3 ml cartridges).” *Id.* at 11. Draisci describes using mass spectrometry for quantification of the protonated molecule, [M + H]⁺ at *m/z* 275 for 17 α -19-nortestosterone and, *m/z* 289 for 17 α -testosterone and 17 β -testosterone, and *m/z* 291 for [²H₂]17 β -testosterone) as deuterated internal standard (I.S.) and two product ions for each anabolic hormone were identified for selected reaction monitoring (SRM) LC-MS-MS analyses. *Id.* Draisci describes that detection of the samples does not require the use of derivitization. *Id.* Based on at least these disclosures in Draisci in conjunction with the other references cited by Petitioner, we are not persuaded by Patent Owner’s contention that LC/MS-MS was a brand new technique for the detection of testosterone in the relevant time frame.

Accordingly, we find that Wands factors #4, #5, #6, and #7 weigh in favor of enablement.

(4). *Wands Factor #8: The breadth of the claims*

Patent Owner contends that Clarke’s disclosure “contains no test results from a female human sample that remotely approach the ’862 patent’s claimed detection limits.” PO Resp. 31. Patent Owner argues that just because “Clarke purports to ‘report’ results does not mean that a

POSITA could recreate the techniques used to obtain those results without undue experimentation.” *Id.* at 32.

Petitioner contends that Patent Owner narrows the state of the art and the breadth of the claims to LC-MS/MS methods as to only apply to testosterone, thereby “ignoring that each of the individual claimed method steps had been known and used for years and that characteristics of testosterone had been known for years as well.” Pet. Reply 15 (citing Ex. 1026; Ex. 1023, 21–22).

We agree with Petitioner that Patent Owner is narrowing the claims to require that a human female sample test below the detection limit set out in the claim. Claim 1 of the ’862 patent, does not require that the female sample tested actually has a low testosterone level; the claim only requires that the assay is *able* to detect testosterone at the recited low-level. Thus, Patent Owner’s contention that Clarke did not test serum samples from a human female in the range claimed by the ’862 patent is not persuasive. *See* Ex. 1003, 2.

Patent Owner contends that Clarke does not provide sufficient explanation on the methodologies used to arrive at the data disclosed and therefore the data is unbelievable at the lowest point measured. PO Sur-Reply 21–24 (citing Ex. 2013 ¶¶ 48, 80–83). Patent Owner contends “[a]chieving these results [as presently claimed] was extremely difficult—so much so that Dr. Fitzgerald needed to employ two different extraction steps and a derivatization¹⁶ step in a LC/MS-MS assay he and colleagues

¹⁶ It is our understanding that derivatization is a way to improve the ionization efficiency so that the molecule of interest is easier to detect by the mass spectrometer. Derivatization adds additional steps and is often not

developed more than three years after the ‘862 patent to even come close to these levels.” PO Resp. 31(citing Ex. 2013 ¶ 97; Ex. 2010, 6–9). We are not persuaded.

Clarke may not have disclosed how many samples were measured in creating the calibration lines, but that does not mean that the results are unbelievable. Ex. 1003, 2. Creating calibration lines and formulating stock testosterone solutions to use as control would be something that a first-year chemistry student is expected to perform and, thus, does not entail undue experimentation. *See* Ex. 1035, 214:19–215:2 (Patent Owner’s expert, Dr. Sluss testifying: “[A]ny first year analytical chemist knows how to” create a calibration line.). Accordingly, we are not persuaded by Patent Owner’s contention that the information disclosed in Clarke is insufficient. We agree with Petitioner that the claimed methods do not require a clinical laboratory application, thus, any arguments with respect to testing sufficiency or lack thereof to clinical standards is not persuasive. Pet. Reply 15.

Moreover, Clarke’s results are consistent with other prior art of record. Kushnir uses Strata X solid-phase extraction (SPE) columns, a 50 x 2.0 (i.d.) mm Phenomenex Luna C18 column with 5-µm particles, and an API 4000™ triple-quadrupole mass spectrometer. Ex. 2010, 2. These are different columns and instruments than those used by Clarke. Ex. 1003, 2. In addition, “the serum samples [in Kushnir] are limited to 100 µl, the [HPLC]

desirable because it adds time and expense to a given procedure. *See* Ex. 1002 ¶ 35 (“[O]ne of the advantages of the HPLC method [for detecting testosterone] was avoidance of the cost and time associated with a derivatization step.” (Citing Ex. 1004, 10)).

injection volume limited to 15 μ l” which is different from the 500 μ l sample size used in Clarke. Pet. Reply 15 (citing Ex. 2010 at 2–3); Ex. 2012, 157:16–18; Ex. 1003, 2. It was understood by the POSITA that increasing sample size is one way to get an improved signal of a low abundance analyte. See Ex. 2012, 157:20–23. Petitioner’s expert Dr. Fitzgerald, one of the authors of the Kushnir reference, explained that “this method [of Kushnir] was being developed to be a high-volume lab method. It doesn’t mean that we were optimizing it for -- to show that we could get down to an LOD of 10.” Ex. 2012, 175:8–11. It is not surprising that an assay that starts with less sample would show a reduced level of detection (LOD) because less sample would have fewer testosterone molecules. Therefore, we are not persuaded by Patent Owner’s contention that Clarke’s results are unbelievable.

Accordingly, we find that Wands factor #8 weighs in favor of enablement.

(5). *Summary*

A prior printed publication enjoys the same presumption of enablement as does a patent disclosure. See *In re Antor Media Corp.*, 689 F.3d 1282, 1288 (Fed. Cir. 2012). “[U]ndue experimentation experimentation is determined based on both the nature of the invention and the state of the art.” *Id.* at 1290 (citation omitted). Upon balancing the *Wands factors*, we determine that Patent Owner has not met its burden of production, *i.e.* sufficient arguments or evidence which overcome the presumption that Clarke is enabled as to detecting testosterone at less than 10 ng/dL in the sample as required by claim 1.

(d) Peer review

Patent Owner contends that “Clarke was not peer reviewed and there is no evidence that its methods were properly validated.” PO Resp. 16.

Petitioner responds that “Clarke is cited for the method it discloses.” Pet. Reply 10. “Neither length nor review status of a prior art reference is determinative of enablement.” Pet. Reply 7 (citing *Iovate Health Scis., Inc. v. Bio-Engineered Supplements & Nutrition, Inc.*, 586 F.3d 1376, 1380–83 (Fed. Cir. 2009)). Clarke does not need to “include details known to a POSITA.” Pet. Reply 8 (citing *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997)).

We find that Petitioner has the better position. “[A reference] must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole.” *In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986). As discussed above, even if Clarke does not provide every minutia of their experimental protocol the reference does provide the basic information necessary from which a POSITA could reconstruct the experimental design. The pertinent information includes the volume of sample loaded and extracted from the SPE column, the make and brand of the SPE column, the make and brand of the HPLC column, the flow rate, the mobile phase and the injection volume loaded onto the HPLC column, as well as information about the mass spectrometer used and the ions monitored. Ex. 1003, 1. Creating calibration lines and formulating stock testosterone solutions to use as control would be something that a first-year chemistry student is expected to perform. See Ex. 1035, 214:19–215:2 (Patent Owner’s expert, Dr Sluss testifying: “[A]ny first year analytical chemist knows how to” create a calibration line.). Additionally, we note that

Clarke discloses that “[t]he method described has been fully validated to international standards for the rapid, specific and accurate quantitation of suppressed levels of testosterone in human serum.” Ex. 1003, 2. We therefore, determine that Clarke provides sufficient detail from which to replicate the experiments and determine that the results disclosed are on its face believable.

3. Summary

Having determined that Clarke is a printed publication, and contains an enabling disclosure, we find that Petitioner has shown by a preponderance of the evidence that claims 1, 2, 5–7, and 10–14 are anticipated by Clarke.

E. Ground 2: Obviousness based on Clarke

In its Petition, Petitioner asserts that the limitations of claims 8 and 9 are rendered obvious by Clarke. Pet. 33–42. Claim 8 recites that the “method is capable of detecting testosterone at concentrations of less than 5 ng/dL in the sample.” Claim 9 recites that the “method is capable of detecting testosterone at concentrations of less than 1 ng/dL in the sample.” Petitioner also relies on the declaration of Dr. Fitzgerald. Ex. 1002, ¶¶ 24–26, 36, 57–59. Patent Owner opposes. PO Resp. 38–45.

Petitioner contends that one of ordinary skill in the art would have known that detecting extremely low levels of testosterone is clinically relevant. Pet. 37 (citing Ex. 1021, Ex. 1022, Ex. 1002 ¶¶ 24, 58). Petitioner acknowledges that Clarke did not expressly test testosterone concentrations below 5 ng/dL using their methods. *Id.* at 39. Based on the lowest level tested in Clarke, however, it would be reasonable to infer that Clarke’s protocol can achieve lower levels of detection. Specifically, Petitioner

contends that “the CV for both the intra-batch and inter-batch analysis [tested in Clarke] of a 50 pg/mL [(which is equivalent to 5 ng/dL)] standard are better than the required 20%, namely, 15.8% and 14.1%.” *Id.* According to Petitioner, Clarke’s lowest tested sample is well within accuracy and precision limits described in the protocol, and therefore, it would be reasonable to conclude that lower limits can be reached before the readings fall outside these parameters. *See id.* (citing Ex. 1002, ¶ 57 (“[N]oting the range and where the reported accuracy and precision data fell in Clarke, one of skill in the art that was in search of a lower LOQ would have been motivated to assess lower concentration standards to determine whether the assay would be useful at detecting lower levels of testosterone.”), *id.* ¶ 58 (“[A] skilled artisan would have known how to modify the method of Clarke. For example, instead of an injection volume of 50 µl, the person of skill in the art could have injected a larger volume.”)).

Patent Owner contends that neither the “less than 5 ng/dL” nor the “less than 1 ng/dL” detection “limits is disclosed in Clarke for any kind of sample (whether taken from a female human or any other source).” PO Resp. 38. Patent Owner contends that simply “optimizing” some random variable is “speculative guesswork comes with neither a reason to make specific changes nor a reasonable expectation of success.” *Id.* Patent Owner contends that the seven (or possibly eight) parameters that could potentially be modified would result in an excessively large number of combinations that would need to be tested. *Id.* at 42 (citing Ex. 2012 at 134:1–15, 155:12–159:18; Ex. 2013 ¶ 101).

Petitioner asserts that Clarke’s method would be capable of detecting levels slightly lower than the 5 ng/dL is expressly disclosed in Clarke. *See*

Pet. 39. Petitioner asserts that one of skill in the art in the field of chromatography would have understood the various ways Clarke's method could be manipulated to further lower the threshold of detectability Pet. 41 (citing Ex. 1002 ¶ 58 (Petitioner's expert, Dr. Fitzgerald testifying: "[A] skilled artisan would have known how to modify the method of Clarke. For example, instead of an injection volume of 50 µl, the person of skill in the art could have injected a larger volume.")). To reach a finding of obviousness, it is proper to "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, *see also id.* at 421 ("A person of ordinary skill is also a person of ordinary creativity, not an automaton."). "Obviousness does not require absolute predictability of success . . . *all that is required is a reasonable expectation of success.*" *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009).

Petitioner contends that the need to measure very low testosterone levels in certain clinical subjects was known, thereby providing a motivation to "optimize Clarke's method to detect testosterone at concentrations of less than 1 ng/dL." Pet. 41 (citing Ex. 1002 ¶ 59), 37 (citing Ex. 1021, 1–2 ("sera from children and women, in whom very low (0.17 nmol/L) and low (<1.7 nmol/L) testosterone concentrations are expected.")). The evidence supports Petitioner's position that measuring low testosterone levels are known to be clinically relevant, and therefore provides sufficient motivation to improve the detection limits of Clarke's testosterone assay.

Petitioner's expert Dr. Fitzgerald avers that one of ordinary skill in the relevant art would have recognized various ways to manipulate Clarke's method in order to further improve the limits of detection. Pet. 41 (citing Ex. 1002 ¶ 59). Parameters for modification of an LC-MS/MS assay include:

type of instrumentation used; type of extraction technique; resolution settings for the instrument; volume of the sample used for extraction; volume of the sample injected into the LC/MS system; column type; and type of liquid chromatography. *See* Pet. 41–42 (citing Ex. 1002 ¶¶ 25, 58, 59); PO Resp. 41–42 (citing Ex. 1002 ¶ 25).

We are not persuaded by Patent Owner’s contention that the parameters for modification are too numerous for one of ordinary skill in the art to improve upon the methods of Clarke with any reasonable expectation of success. *See* PO Resp. 41. When modifying an assay the POSITA would not make a wholesale change with all parameters at the same time. The POSITA would start with increasing sample volume used for extraction as well as the volume injected into the LC/MS system before making changes in the hardware (i.e. HPLC column, SPE column, mass spectrometer). *See* Ex. 1002 ¶ 25 (Petitioner’s expert, Dr. Fitzgerald testifying: “[A] larger injection volume would contain more testosterone than a smaller volume and one of skill in the art would have routinely identified the suitable volume to optimize sensitivity.”).

Patent Owner contends that optimizing Clarke’s method would have been anything but routine. *See* PO Resp. 41–45. Specifically, Patent Owner contends that increasing injection volume would not increase detection. *Id.* at 43. Patent Owner contends that Petitioner’s expert, Dr. Fitzgerald, acknowledges that the proposed specific suggestions such as injecting a larger volume or the use of a more concentrated sample “would have increased the signal but come at the cost of lower resolution and higher background noise.” PO Resp. 43 (citing Ex. 1002 ¶ 58). Patent Owner’s expert, Dr. Sluss, similarly suggests that increasing the volume “would come

at the cost of resolution and higher background noise,” and this could lead to peak overlap resulting in “inaccurate quantification of components.”

Ex. 2013 ¶ 129 (citing Ex. 2007 ¶ 26); PO Resp. 43 (citing 2007 ¶ 25).

Dr. Voyksner’s testimony also explains that increasing the injection volume may cause different components to overlap or not be completely resolved resulting in inaccurate quantification of the components. Ex. 2007 ¶¶ 25, 26; PO Resp. 43; Ex. 1012 ¶ 102. We are not persuaded.

Just because increased volume can result in a lower accuracy with respect to quantification does not mean that the component of interest – testosterone – is not reasonably detected with the application of a larger sample.

Here, both experts agree that the POSITA would have recognized that increasing the volume of the sample would increase the signal even if it comes at the peril that the signal may not be as clear. Ex. 2012, 157:16–23; Ex. 2013 ¶ 129. The claims, however, are not directed to quantifying testosterone where signal clarity and peak saturation may be an issue, the claims are directed to *detecting* testosterone levels in a sample. As Petitioner’s expert explains, the limit of quantification (LOQ) is generally higher than the limit of detection (LOD). Ex. 1002 ¶ 28 (citing Ex. 1020); Ex. 2025 at 27, 34. The evidence supports the position that one may detect the presence of a component with an assay before one can accurately quantify that component with the same assay. See Ex 1020 at 4; Ex. 2025 at 34; Ex. 1002 ¶ 28. Therefore, we are not persuaded by Patent Owner’s position that increasing the volume of injection would not result in more sensitive detection of testosterone. PO Resp. 43 (citing Ex. 2007 ¶ 25).

Another way of improving assay sensitivity is by modernizing the equipment. Petitioner's expert Dr. Fitzgerald explained that by using a newer more sensitive mass spectrometer they were able to develop a simplified LC-MS/MS analysis for testosterone, which further supports the position that improvements in instrumentation technology can improve assay sensitivity. Ex. 2012 at 180:17–181:1; *see* Ex. 1002 ¶ 25; Ex. 2010 at 4 (“Evaluation of the method performance on API 3000 and API 4000 tandem mass spectrometers (using conditions optimal for each instrument and the oxime derivative of Te) revealed that the assay performed on the API 4000 was ~8-fold more sensitive.¹⁷”).

Patent Owner contends that Petitioner's expert Dr. Fitzgerald also tried to solve the need for more sensitive and specific testosterone assays but could only reach the 1 ng/dL without the use of derivatization. PO Resp. 44 (citing Ex. 2010); Ex. 2013 ¶ 97. In other words, Patent Owner's position is that because others have tried and failed, therefore, the disclosure in Clarke is unbelievable and should not be given any weight.

We are not persuaded by Patent Owner's contention that failure by others in the field undermines Clarke's methods and results. In the paper by Dr. Fitzgerald and collaborators, cited by Patent Owner, the method steps include use of a different mass spectrometer, a different C18 column, and a different solid extraction column than those used in Clarke's reference. *Compare* Ex. 2010 at 2–3 *with* Ex. 1003 at 1. As Dr. Voyksner explains “[d]ifferent columns, even if they are same type of columns, such as C18

¹⁷ We would expect the same improvement in sensitivity if optimized for non-derivatized testosterone. We note that Clarke uses the SCIEX API 3000 mass spectrometer. Ex. 1003 at 1.

columns, have different surface chemistries, which will affect the retention time, elution order, peak separation and peak height and peak area.”

Ex. 2007 ¶ 20. Thus, comparing Clarke with other methods that use different instruments, different columns, and different sample preparation methods does not persuade us that Clarke’s methods and results are unreliable.

Having determined that there is sufficient motivation to direct the POSITA to improve on the testosterone detection limit disclosed in Clarke, we determine that there is also a reasonable expectation of success in lowering the detection to below the claimed limit by manipulating variables such as injection volume, sample size, or even by upgrading the instrumentation. We, therefore, find that Petitioner has shown by a preponderance of the evidence that claims 8 and 9 of the ’862 patent are unpatentable as obvious over Clarke.

F. Ground 3: Obviousness based on Clarke and Fitzgerald

Petitioner asserts that the combination of Clarke and Fitzgerald teaches all the limitations of claim 4 to render the claim obvious. Pet. 42–43. Petitioner relies on the declaration of Dr. Fitzgerald. Ex. 1002, ¶¶ 25, 35, 42–44, 60. Patent Owner opposes. PO Resp. 45–51.

1. Overview of Fitzgerald

Fitzgerald is titled “Serum total testosterone: immunoassay compared with negative chemical ionization gas chromatography-mass spectrometry.” Ex. 1005, 1. Fitzgerald teaches that there are no reported methods capable of accurately quantifying serum testosterone over the entire clinically important range of 0.69–69.3 nmol/L. *Id.* Fitzgerald teaches that “[p]revious GC-MS methods for the analysis of serum testosterone involved rigorous purification procedures combining liquid-liquid extraction, chromatography, and (or)

solid-phase extraction.” *Id.* Fitzgerald describes its sample preparation as follows:

Sample preparation for GC-MS. The internal standard (50 µL of 3.5 µ.mol/L testosterone-d₃) was added to 1 mL of plasma or serum and samples were briefly vortex-mixed. Ethyl acetate (3 mL) was added, followed by vortex-mixing for 1 min. Samples were centrifuged (1850g for 10 min), and the organic layer was pipetted into a 100 X 13 mm screw-cap test tube and evaporated to dryness at 40 °C under a gentle stream of nitrogen.

Id. at 2. Fitzgerald concludes that purification of testosterone before any assay procedure is important not only for analyzing infant samples but also when analyzing female samples. *Id.* at 7. Fitzgerald teaches that after liquid purification, the sample was derivatized before analysis in the gas chromatography-mass spectrometer analyzer. *Id.* at 2.

2. Analysis

Petitioner asserts that Clarke teaches all the limitations of claim 1. As discussed above (*see* II.D.2) we determine that Petitioner has presented a *prima facie* case that Clarke meets all limitations of claim 1. Claim 4 contains all the limitations of claim 1 and further recites purifying using a liquid extraction step. Petitioner acknowledges that Clarke does not disclose a liquid extraction step but relies on Fitzgerald for teaching that liquid extraction is a known method for purifying testosterone from a sample. Petition 42 (citing Ex. 1005, 1–2; Ex. 1002 ¶ 60). Petitioner asserts that one of skill in the art would have been motivated to modify Clarke with the liquid extraction step disclosed in Fitzgerald, based on the similarity of the methods. Pet. 43.

Patent Owner disagrees. PO Resp. 45–51. Patent Owner contends that one of ordinary skill in the art would have had no motivation to combine Clarke and Fitzgerald. *Id.* at 46. “The test for determining if there was a reason or motivation cannot rest on the mere fact that certain substitutions would have been feasible or appropriate.” *Id.* (citing *Ruiz v. AB Chance Co.*, 234 F.3d 654, 665 (Fed. Cir. 2000)). Patent Owner contends that Clarke and Fitzgerald confronted different problems and the solutions identified in each are not interchangeable. *Id.* at 46–47. Patent Owner contends that the mixing and matching of extraction techniques as proposed by Petitioner is impermissible hindsight. *Id.* at 47. “Petitioner’s contention that the methods disclosed in Clarke (solid phase extraction) and Fitzgerald (liquid phase extraction) were “similar” or “routine,” . . . is insufficient to establish a motivation to combine.” *Id.* at 40.

The parties dispute whether a POSITA would have had a reason to use the liquid extraction step taught in Fitzgerald in place of the SPE (“solid phase extraction”) taught in Clarke. Here, both Clarke and Fitzgerald are directed to detection of testosterone in serum samples indicating they are from the same field of endeavor. Ex. 1003; Ex. 1005. Both Clarke and Fitzgerald are interested in detecting low levels of testosterone in serum samples. For example, Clarke discloses that in order to measure suppressed levels of testosterone in castrated patients a lower limit of quantification of 50 pg/ml was required. Ex. 1003 at 1. Fitzgerald discloses that the relevant clinical range for testosterone to detection is 0.69-69.3 nmol/L. Ex. 1005. Based on these disclosures we find that both references are interested in measuring low levels of testosterone.

“[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). It is obvious to those skilled in the art to substitute one known equivalent for another, be those equivalents method steps or apparatus components. *See In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1374 (Fed. Cir. 2007); *see In re Fout*, 675 F.2d 297, 301, (CCPA 1982) (“Express suggestion to substitute one equivalent for another need not be present to render such substitution obvious.”).

Petitioner’s expert, Dr. Fitzgerald avers that a POSITA would have had a reasonable expectation of success in combining the teachings of Clarke and Fitzgerald. Ex. 1002 ¶ 60 (“One of skill in the art seeking an alternative to solid phase extraction (SPE) would readily adopt the well-accepted and tested method of liquid extraction from the limited options available.”). We agree with Petitioner’s position that given the knowledge that testosterone needs to be purified before applying the sample to an LC–MS/MS detection system a POSITA trying to improve the method of Clarke would be motivated to consider other well-known testosterone extraction methods such as the liquid extraction step taught in Fitzgerald. Pet. Reply 22 (citing Ex. 2012, 155:12–16).

Additionally, we note that the claims of the ’862 patent are sufficiently broad that they are not limited to a single extraction technique. Fitzgerald teaches that regardless of the detection method when analyzing infant or female samples better results are obtained when the samples are first purified for testosterone before analysis. Ex. 1005, 7. Fitzgerald

additionally teaches that there are numerous purification procedures available to obtain serum testosterone and that these procedures can be used either separately or in combination. *Id.* at 1. Thus, there is a reasonable expectation that the combination of SPE and liquid extraction can be applied to purifying testosterone before the application of LC-MS/MS for detection.

We find that under the *KSR* standard of obviousness the combined teachings of Clarke and Fitzgerald would have rendered claim 4 obvious. In particular, we note that the POSITA is also a person of ordinary creativity. Such a person would be familiar with testosterone purification and quantification, and based on the record before us, such a person would have known to substitute known purification procedures such as liquid-liquid extraction purification taught in Fitzgerald for the equivalent solid-phase purification taught in Clarke because such a combination is merely a “predictable use of prior art elements according to their established functions.” *KSR*, 550 U.S. at 417.

3. Summary

Having determined that there is sufficient motivation to direct the POSITA to improve on the testosterone detection limit disclosed in Clarke, we determine that there is also a reasonable expectation of success in substituting the liquid extraction procedure of Fitzgerald for the SPE procedure described in Clarke because such substitution would potentially improve the testosterone detection in Clarke. We, therefore, find that Petitioner has shown by a preponderance of the evidence that claim 4 of the ’862 patent is unpatentable as obvious over Clarke and Fitzgerald.

G. Ground 4: Obviousness over Draisci and Clarke

In its Petition, Petitioner asserts that the limitations of claims 1, 2, and 4–14 are rendered obvious over Draisci and Clarke. Pet. 44–63. Petitioner also relies on the declaration of Dr. Fitzgerald. Ex. 1002, ¶¶ 24–27, 36, 39, 45, 46, 57–59, 61–71, 74, 75. Patent Owner opposes. PO Resp. 51–61.

1. Overview of Draisci

Draisci is titled “Quantitation of anabolic hormones and their metabolites in bovine serum and urine by liquid chromatography-tandem mass spectrometry.” Ex. 1004, 9. The hormones quantified include: 17 α -19-nortestosterone, 17 β -testosterone, and progesterone and their major metabolites (17 α -19-nortestosterone and 17 α -testosterone). *Id.*

Draisci describes purification of the samples using a combination of liquid chromatography (LC) with mass spectrometry (MS) and tandem mass spectrometry (MS-MS). *Id.* at 10. Draisci describes that a serum “sample was purified by solid-phase extraction (SPE) using a C₁₈ cartridge (Baker C₁₈, 500 mg, 3 ml cartridges).” *Id.* at 11.

Draisci describes using mass spectrometry for quantification of the protonated molecule, [M + H]⁺ at *m/z* 275 for 17 α -19-nortestosterone and, *m/z* 289 for 17 α -testosterone and 17 β -testosterone, and *m/z* 291 for [²H₂]17 β -testosterone as deuterated internal standard (I.S.) and two product ions for each anabolic hormone were identified for selected reaction monitoring (SRM) LC-MS-MS analyses. *Id.* at 11. Draisci describes producing standard curves for quantification ranging from “2-600 ng/ml [(200-60000 ng/dL)] by plotting peak area ratios of the analyte to I.S. versus hormone concentrations using a least-squares linear regression model. Calibration curves were prepared daily by spiking serum and urine control

samples with mixtures of the anabolic compounds to obtain concentration in the range 0.1-30 ng/ml [(10-3000 ng/dL)].” *Id.* at 11–12.

Draisci describes that detection of the samples does not require the use of derivatization. “The combination of liquid chromatography (LC) with MS and MS-MS offers a rapid, simplified, specific and sensitive alternative to GC-MS methods involving simple extraction procedures and removing the need for derivatization reactions.” *Id.* at 10.

2. Analysis

We agree with Petitioner and find that the combination of Draisci and Clarke teaches each of the elements of claims 1, 2, and 10–14 for the reasons set forth in the Petition and the declaration of Dr. Fitzgerald. Pet. 44–64; Ex. 1002 ¶¶ 61–74. We address Patent Owner’s contentions that the evidence is insufficient below.

We are not persuaded by Patent Owner’s contention that there is no reason to combine Draisci and Clarke because they are directed to equine and bovine samples and are not directed to “female human sample” as recited in the claims. PO Resp. 52.

The POSITA would have known that detecting extremely low levels of testosterone is clinically relevant in humans. Pet. 37 (citing Ex. 1021, Ex. 1022, Ex. 1002 ¶¶ 24, 58). Both Draisci and Clarke are directed at detecting low levels of testosterone in serum samples extracted from female mammals. *See* Ex. 1004, 11 (bovine female sample); Ex. 1003, 1–2 (human female sample). Draisci and Clarke are analogous art with respect to testosterone detection and are therefore reasonably combined. *See In re Clay*, 966 F.2d 656, 658–9 (Fed. Cir. 1992). Both references purify testosterone from serum samples before detecting the presence of testosterone with a mass

spectrometer. *See* Ex. 1004, 11; Ex. 1003, 1–2. The purifying step is understood to enrich the amount of testosterone relative to one or more other components of the sample. Ex. 1036, 2. Thus, the POSITA would have understood the process of purification to remove testosterone from the native matrix before proceeding to the testosterone detection step.

Testosterone is the same chemical entity between species. *See* Pet. 47 (citing Ex. 1002 ¶¶ 25, 62; Ex. 1027); Tr. 24:13–15 (“I’m not aware of any evidence of record that discuss species difference in testosterone at a molecular level.”); *compare* Ex. 1003, 1 (ions monitored 289.2→97.1 (testosterone) testing human and gelding samples) *with* Ex. 1004 (m/z 289→97 for both 17 α -testosterone and 17 β -testosterone testing bovine samples). Dr. Fitzgerald avers that testosterone is the same chemical entity in bovine, equine, and human samples, and therefore, it is reasonable to conclude that an assay disclosed in one vertebrate species is transferable to another vertebrate species with a reasonable expectation of success. Ex. 1002 ¶¶ 27 (“[T]estosterone is the same across vertebrate species”), 62 (“Testosterone is the same chemical entity in both bovine and human samples. . . . Once extracted, the testosterone from various mammalian species behaves similarly in chromatography and mass spectrometry steps.”). Because testosterone is the same chemical entity between different species we agree with Petitioner that it is reasonable to consider testosterone assays as being interchangeable. Accordingly, we are not persuaded by Patent Owner’s contention that there is no reason to combine Draisci and Clarke.

Patent Owner contends that Petitioner does not provide support for the position that sensitivity of the assay may be improved by manipulating

variables. PO Resp. 56 (Dr. Fitzgerald “provides no citing references or other evidence to demonstrate that the two variables he does identify (injection volume and orifice potential voltage) were important to Clarke’s sensitivity and would have similarly improved the sensitivity reported in Draisci.”); *see* PO Sur-Reply 23.

Here, both Petitioner’s and Patent Owner’s experts agree that there are at least eight variables that can be manipulated in an attempt to improve an assay, but acknowledge that each variable would have to be empirically determined to assess the level of success. *See* PO Sur-Reply 22–23 (citing 2013 ¶ 101; Ex. 2012, 134:1–15, 155:12–159:18, 160:22–161:9, 161:19–25); PO Resp. 41–43; Ex. 1002 ¶¶ 25, 67, 68. Thus, the contention lies with the predictability of manipulating these variables to make changes that would result in improved signal for the detection of testosterone.

One approach for improving the sensitivity of an assay is to use “a larger injection volume [that] would contain more testosterone than a smaller volume and one of skill in the art would have routinely identified the suitable volume to optimize sensitivity.” Ex. 1002 ¶ 25 (citing Ex. 1023). Petitioner points out that Clarke already uses a larger injection volume than the method disclosed in Draisci. Pet. 53 (citing Ex. 1003, 1; Ex. 1004, 11; Ex. 1002 ¶ 67). The larger injection volume may explain why Clarke established a limit of quantitation at 5 ng/dL versus 10 ng/dL disclosed in Draisci. *Compare* Ex. 1003, 1, *with* Ex. 1004, 11.

Another way of improving the assay sensitivity is by modernizing the equipment. Petitioner’s expert Dr. Fitzgerald explained that by using a newer more sensitive mass spectrometer they were able to develop a simplified LC-MS/MS analysis for testosterone. Ex. 2012, 180:17–181:1;

see Ex. 1002 ¶ 25; Ex. 2010, 4 (“Evaluation of the method performance on API 3000 and API 4000 tandem mass spectrometers (using conditions optimal for each instrument and the oxime derivative of Te) revealed that the assay performed on the API 4000 was ~8-fold more sensitive.¹⁸”). Improved instrumentation sensitivity reasonably supports the position that improvements in technology can improve component detection.

Patent Owner contends that the modifications Dr. Fitzgerald suggests make no sense, because increasing sample volume could drastically affect HPLC readings. PO Resp. 57 (citing Ex. 2007 ¶ 25 (“Sample injection volumes can also impact the results since larger injection volumes can lead to peak saturation and peak broadening and to measurements in the non-linear range of the detector’s operation.”)).

Both experts agree that one of skill in the art would have recognized that increasing the volume of a sample would increase the signal even if it comes at the peril that the signal may not be as clear. Ex. 2012, 157:16–23; Ex. 2013 ¶ 129. The claims, however, are not directed to quantification of testosterone where signal clarity and peak saturation may be an issue; the claims are directed to *detecting* testosterone levels in a sample. As Petitioner’s expert explains, the limit of quantification (LOQ) is generally higher than the limit of detection (LOD). Ex. 1002 ¶ 28 (citing Ex. 1020); Ex. 2025 at 27, 34. We find that the evidence in the record supports Petitioner’s position that increasing sample volume to increase the amount

¹⁸ We would expect to see the same level of improved sensitivity for non-derivatized testosterone, because the spectrometer technology provides the improved sensitivity. We further note that Clarke uses the less sensitive API 3000 mass spectrometer. Ex. 1003, 1.

of testosterone loaded into the detection system and thereby would reasonably improve the limit of detection as required by the claims.

Patent Owner contends that there is lack of evidence that optimizing the orifice potential voltage would have resulted in improved detection of testosterone. PO Resp. 58.

Draisci explains that the ions were monitored at m/z 275, 289, 291 and 315. “The effect of varying orifice potential voltage [OR] was investigated between the range 60-100 V. An OR of 90 V was adopted for all the hormones as the best compromise in terms of signal-to-noise ratio.”

Ex. 1004, 12. Draisci recognizes that the orifice potential used in their assay is a compromise setting, suggesting that each hormone has its own optimized setting. We find that this disclosure provides sufficient support for position that adjusting the orifice potential voltage could be optimized for the individual hormone including testosterone. Petitioner’s expert Dr. Fitzgerald avers that “[o]ne of skill in the art would recognize that optimizing the orifice potential voltage to be the best value for testosterone could have improved the LOD and LOQ.” Ex. 1002 ¶ 40, ¶ 68 (“In an assay specific for testosterone, however, one of skill in the art, based on the teachings of Draisci, would select an orifice potential voltage that gives the best signal to noise ratio for testosterone, without regard for other analytes.”), ¶ 71. Even if the recited 90V in Draisci is later determined to be the optimum setting for testosterone, we find that the record never the less supports the position that optimizing the potential is one way to increase limit of detection of a sample.

For the reasons set out above, we determine that there is sufficient reason to combine the references, and we determine that there is also a

reasonable expectation of success in lowering the limit of detection by manipulating variables such as increasing the injection volume or modernizing the instrumentation. This optimization would reasonably be expected to achieve the claimed detection limit. Ex. 2012, 154: 3–5 (Petitioner’s expert, Dr. Fitzgerald testifying: “I mean if you have a more modern instrument, you have a much better chance of being more sensitive.”); Ex. 1002, ¶ 25 (Dr. Fitzgerald testifying: “[A] a larger injection volume would contain more testosterone than a smaller volume and one of skill in the art would have routinely identified the suitable volume to optimize sensitivity.”). We, therefore, find that Petitioner has shown by a preponderance of the evidence that claims 1, 2, 4–7, and 10–14 of the ’862 patent are unpatentable as obvious over Draisci and Clarke.

Claims 8 and 9

Patent Owner contends that Petitioner fails to explain why the combination of Draisci and Clarke would provide a reasonable expectation to arrive at the lower limit of detection of “less than 5 ng/dL” or “less than 1 ng/dL” as recited in claims 8 and 9. PO Resp. 58–61. Patent Owner contends that Dr. Fitzgerald’s inability to detect “testosterone in human females at levels less than 10 ng/dL” in his own work published even after the filing of the ’862 patent disclosure is evidence that the optimization argument is unreasonable. *Id.* at 59–60; see PO Sur-Reply 23.

We are not persuaded by Patent Owner’s contention that failure by others in the field undermines Petitioner’s position. We find that the prior art and expert testimony cited by Petitioner provides a reasonable expectation of success for improving testosterone detection by optimizing the method. See *Kubin*, 561 F.3d at 1360 (“[o]bviousness does not require absolute

predictability of success . . . *all that is required is a reasonable expectation of success.*”); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) (“[T]he expectation of success need only be reasonable, not absolute.”).

Patent Owner provides a table comparing the instrumentation between Draisci and Clarke. The comparison highlights that there are differences in the SPE extraction columns and HPLC columns used between Draisci and Clarke’s methods. See PO Resp. 54–55. Patent Owner also cites Dr. Fitzgerald’s post-patent method as allegedly showing failure by others to detect testosterone at the levels claimed – less than 5 ng/dL and 1 ng/dL. *Id.* at 59–60 (citing Ex. 2010, 6–7). Fitzgerald’s method uses yet a different mass spectrometer, a different C₁₈ column, and a different solid extraction column from those used in Draisci and Clarke. Ex. 2010. Comparing Draisci, Clarke, and Fitzgerald’s methods we note that each use different instruments, different columns, and different sample preparation methods. Compare Ex. 1003, 1, with either Ex. 1004, 11, or Ex. 2010, 2–3. It is known that SPE and HPLC columns even if they are the same type can behave differently. Ex. 2007 ¶ 20 (“Different columns, even if they are same type of columns, such as C18 columns, have different surface chemistries, which will affect the retention time, elution order, peak separation and peak height and peak area.”). Because Clarke uses different matrixes in the SPE and HPLC columns from those disclosed in Draisci and Fitzgerald, the detection limits in Draisci and Fitzgerald cannot be imputed to Clarke. We, therefore, are not persuaded by Patent Owner’s contention that just because others could not detect testosterone below 10 ng/dL that Clarke’s methods of quantification at a level of 5 ng/dL is unbelievable. See PO Resp. 60, see *id.*

at 16; Ex. 2013 ¶ 56. Accordingly, we are not persuaded by Patent Owner's failure by others argument.

We are also not persuaded that the detection limit could not be further improved by the routine optimization and manipulations as suggested by Petitioner's expert. For example, such as by increasing the sample volume or using a newer instrument as suggested by Petitioner's expert would reasonably improve the level of detection of testosterone. Pet. 58 (citing Ex. 1002, ¶¶ 24–26, 57–59, 71–73); *see* Ex. 2010, 4 (“Evaluation of the method performance on API 3000 and API 4000 tandem mass spectrometers (using conditions optimal for each instrument and the oxime derivative of Te) revealed that the assay performed on the API 4000 was ~8-fold more sensitive.”); Ex. 2012, 154: 3–5 (Petitioner's expert, Dr. Fitzgerald testifying: “I mean if you have a more modern instrument, you have a much better chance of being more sensitive.”). Improved instrumentation sensitivity reasonably supports the position that improvements in technology can improve component detection.

On this record, we find that Petitioner has shown by a preponderance of the evidence that claims 8 and 9 of the '862 patent are unpatentable as obvious over Draisci and Clarke.

3. Summary

Having determined that there is sufficient reason to combine the references, we determine that there is also a reasonable expectation of success in lowering the detection limit by manipulating variables such as increasing the injection volume, sample size, or even upgrading the instrumentation. We, therefore, find that Petitioner has shown by a

preponderance of the evidence that claim 1, 2, and 4–14 of the '862 patent is unpatentable as obvious over Draisci and Clarke.

III. CONCLUSION

We conclude that Petitioner has demonstrated that claims 1, 2, and 4–14 of the '862 are unpatentable under 35 U.S.C. § 102(b) and § 103(a).

IV. ORDER

In consideration of the foregoing, it is hereby

ORDERED that on the record before us, Petitioner has shown by a preponderance of the evidence that claims 1, 2, and 4–14 of the '862 patent are unpatentable;

FURTHER ORDERED that this is a Final Written Decision. Parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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