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PUBLIC VERSION

Paper 108
Date: May 3, 2023

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SPECTRUM SOLUTIONS LLC
Petitioner,

v.

LONGHORN VACCINES & DIAGNOSTICS, LLC
Patent Owner.

IPR2021-00860
Patent 9,683,256 B2

Before ZHENYU YANG, WESLEY B. DERRICK, and
ROBERT A. POLLOCK, *Administrative Patent Judges.*

POLLOCK, *Administrative Patent Judge*.

JUDGMENT

Adverse Judgment
Ordering All Challenged Claims Cancelled Based on Adverse Judgment

FINAL WRITTEN DECISION
35 U.S.C. §§ 318(a)

Determining Some Challenged Claims Unpatentable
Denying Patent Owner's Revised Contingent Motion to Amend

Denying-in-Part and Dismissing-in-Part Patent Owner's Motion to Exclude
37 C.F.R. § 42.64(c)

Denying Patent Owner's Motion to Seal
37 C.F.R. §§ 42.54, 42.55

Executive Summary:

In our concurrently-filed Sanctions Order (Paper 107), we determine that Patent Owner failed to meet its duty of candor and fair dealing in its actions before the Board. As detailed in that Order, Patent Owner conducted, and relied on, biological testing in an attempt to distinguish the asserted Birnboim reference in this and related IPRs, but selectively and improperly withheld material results that were inconsistent with its arguments. For the reasons set forth in our Sanctions Order, we determine, as adverse judgment, that all challenged claims of the '256 patent are unpatentable.

For the sake of completeness, and to add further context to our Sanctions Order, we also address the merits of the Petition. In so doing, we further determine that Petitioner has demonstrated by a preponderance of the evidence that claims 1–13, and 15–20 of the '256 patent are unpatentable under 35 U.S.C. § 103 based on the grounds set forth in the Petition. As a further sanction, we deny Patent Owner's revised motion to amend.

I. INTRODUCTION

A. Procedural Background

Spectrum Solutions LLC ("Petitioner" or "Spectrum") filed a Petition for an *inter partes* review of claims 1–20 of U.S. Patent No. 9,683,256 B2 ("the '256 patent," Ex. 1001). Paper 1 ("Pet."). Longhorn Vaccines & Diagnostics, LLC ("Patent Owner" or "Longhorn") timely filed a Preliminary Response. Paper 6 ("Prelim. Resp."). With our authorization (*see* Paper 3001), Petitioner filed a Reply to the Preliminary Response (Paper 7) and Patent Owner filed a corresponding Sur-reply to the Preliminary Response (Paper 10, "Prelim. Sur-reply").

In view of the then-available, preliminary record, we concluded that Petitioner satisfied the burden, under 35 U.S.C. § 314(a), to show that there was a reasonable likelihood that Petitioner would prevail with respect to at least one of the challenged claims. Accordingly, on behalf of the Director (37 C.F.R. § 42.4(a) (2018)), and in accordance with *SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1353 (2018) and the Office's Guidance on the Impact of *SAS* on AIA Trial Proceedings (Apr. 26, 2018) ("Guidance"),[1] we instituted an *inter partes* review of claims 1–20 on all the asserted grounds. Paper 12 ("Inst. Dec." or "DI"), 37–38.

After institution, Patent Owner filed a Patent Owner Response to the Petition. Paper 21 ("Original POR."). Petitioner filed a Reply to Patent Owner's Response (Paper 38, "Reply") and Patent Owner filed a respective (corrected)[2] Sur-reply (Paper 102, "Sur-reply").

Pursuant to our authorization, Patent Owner submitted an Amended (and subsequently corrected)[3] Patent Owner Response along with an Amended Supplemental Expert Report of its technical expert. Paper 101, "AmPOR"; Ex. 2033 (Amended Supplemental Expert Report of Dr. Louis DeFilippi); Paper 60 (authorizing amendments to Patent Owner Response and Supplemental DiFilippi Declaration); *see also*, Paper 51, Appx. A and B (red-lined documents showing authorized amendments)). Unless otherwise

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[1] https://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board/trials/guidance-impact-sas-aia-trial.

[2] Patent Owner's Sur-reply was originally filed as Paper 53. We cite herein to the corrected version, Paper 102.

[3] The Amended Patent Owner Response was originally filed as Paper 64. We cite herein to the corrected version, Paper 101.

specified, we cite herein to the Amended Patent Owner Response ("AmPO Resp.") and the Amended Supplemental DeFilippi Declaration ("Ex. 2033").

Patent Owner filed a Contingent Motion to Amend (Paper 20, "MTA"); Petitioner opposed the Motion (Paper 39, "Opp. MTA"); and we provided Preliminary Guidance (Paper 48, "Prelim. Guide"). Patent Owner subsequently filed a Revised Contingent Motion to Amend. Paper 54, "RMTA" Petitioner opposed the revised motion (Paper 66, "Opp. RMTA"); Patent Owner filed a Reply in support (Paper 76, (Reply. RMTA"); and Petitioner responded with a Sur-reply (Paper 93, "Sur-reply RMTA").

Patent Owner filed a motion to exclude evidence (Paper 81, "MTE") Petitioner opposed the motion (Paper 87, "Opp. MTE"); and Patent Owner filed a reply in support of its motion (Paper 95, "Reply MTE"). Patent Owner also filed a motion to seal (Paper 41, ("Mot. Seal"); Petitioner opposed the motion (Paper 49, "Opp. Seal"); and Patent Owner filed a Reply in support of its motion (Paper 61, "Reply Seal").

Petitioner filed a Motion for Sanctions (Paper 55); Patent Owner opposed (Paper 74); and Petitioner filed a Reply in support of its motion (Paper 83). On August 16, 2022, the panel entertained argument on the sanctions motion. Paper 100 ("Mot. Tr."). Because Petitioner's motion involves conduct common to similar motions filed in IPR2021-00847, -00850, -00851, -00854, and -00857, we address the substance of those motions under separate cover. *See* Paper 107, issued concurrently.

On August 19, 2022, the parties presented arguments at oral hearing, the transcript of which is of record. Paper 104 ("Tr.").

B. Real Parties-in-Interest

Petitioner identifies itself, Spectrum Solutions LLC as a real party-in-interest. Pet. 1. Petitioner further identifies two companies having a financial interest in, or potentially substantially affected by the outcome of, this proceeding: its parent company, Spectrum Holdco LLC, and Spectrum Intermediate LLC. *Id.* Petitioner does not expressly identify those companies as real parties-in-interest.

Patent Owner identifies only itself, Longhorn Vaccines & Diagnostics, LLC, as the real party-in-interest in this proceeding. Paper 3, 1.

C. Related Matters

Petitioner concurrently challenges claims of related U.S. Patents Nos. 8,084,443 ("the '443 patent"); 8,293,467; 8,415,330 ("the '330 patent"); 8,669,240; and 9,212,399 ("the '399 patent"), in IPR2021-00847, -00850, -00851, -00854, and -00857, respectively. According to the parties, the same patents are at issue in *Longhorn Vaccines & Diagnostics, LLC v. Spectrum Solutions LLC*, C.A. No. 2:20-cv-00827 (D. Utah). Pet. 1; Paper 3, 1; Ex. 1007 ¶¶ 9–15.

D. Parallel Motion for Sanctions and Adverse Judgment

As noted above, Petitioner moved for sanctions (Paper 55), Patent Owner opposed (Paper 74), and Petitioner replied (Paper 83). Also, as noted above, the panel heard argument on the sanctions motion. Mot. Tr.

The sanctions sought by Petitioner include: (1) judgment against Patent Owner; (2) a holding that a particular reference meets particular claim limitations and precluding Patent Owner from contesting otherwise; and (3) compensatory expenses in favor of Petitioner, including attorney fees. Paper 55, 1–2. Having considered the issues, as set forth under separate

cover and filed concurrently, we determine Patent Owner has failed to meet its duty of candor and fair dealing in its actions before the Board under 37 C.F.R. § 1.56, § 11.106(c), § 11.303, § 42.11(a), and § 42.51(b)(1)(iii). *See* Paper 107. In the Sanctions Order, we further determine the proper Sanctions to include Adverse Judgment against Patent Owner as to all challenged claims (claims 1–20) and Denial of Patent Owner's Revised Contingent Motion to Amend.[4] *Id.* at 59–60.

Based on the Sanctions Order and determinations made therein, we enter Adverse Judgment against Patent Owner, cancel claims 1-20 of the '256 patent, and Deny Patent Owner's Revised Contingent Motion to Amend. For the sake of completeness, and to add further context to our Sanction's Order, we address herein the merits of the Petition.

E. Asserted Challenges to Patentability

Petitioner challenges the patentability of claims 1–20 on the following basis: (Pet. 11):

Ground	Claims Challenged	35 U.S.C. §	Reference(s)/Basis
1	1–10, 13, 15–19	§ 103(a)	Birnboim,[5] Mori,[6] Farrell[7]

[4] Lead Administrative Judge Braden, paneled on related cases involving the same facts, concurred in the determination of sanctions, except to disagree with the majority declining to provide Petitioner with compensatory expenses, including attorney fees.

[5] Birnboim, US 2004/0038269 A1, published Feb. 26, 2004. Ex. 1003.

[6] Mori, WO 2005/111210 Al, published Nov. 24, 2005. Ex. 1011.

[7] Robert E. Farrell, Jr., Ph.D., "RNA Methodologies: A Laboratory Guide for Isolation and Characterization," (3rd Ed., 2005). Ex. 1026.

Ground	Claims Challenged	35 U.S.C. §	Reference(s)/Basis
2	11	§ 103(a)	Birnboim, Mori, Farrell, Das[8]
3	12, 20	§ 103(a)	Birnboim, Mori, Farrell, Helftenbein[9]
4	14	§ 103(a)	Birnboim, Mori, Farrell, Heineman[10]

In support of its patentability challenge, Petitioner relies on, inter alia, the Declaration of Richard F. Taylor, Ph.D. Ex. 1002. Patent Owner relies on, inter alia, the Declaration of Louis DeFilippi Ph.D (Ex. 2001), and on Dr. DeFilippi's Amended Supplemental Expert Report (Ex. 2033).

In support of its Revised Motion to Amend, Patent Owner further relies on the Supplemental Declaration of Dr. DeFilippi. Ex. 2033. Correspondingly, Petitioner relies on Dr. Taylor's Supplemental Declaration (Ex. 1082), and on the Declaration of Christopher M. Beausoleil (Ex. 1077).

F. The '256 Patent and Related Background

The '256 patent, titled Biological Specimen Collection and Transport System, issued to Fischer et al., from U.S. Application 14/969,339 ("the '339 application, Exhibit 2025), filed April 10, 2019, via a series of continuation and continuation-in-part applications first filed on October 1, 2008, and further claims benefit of priority to US provisional Application No. 60/976,728 ("the 728 provisional application"), filed on October 1, 2007. Ex. 1001, code (21), (22), (54), (60), and (63). In addressing the art of record, the parties presume the earliest possible priority

[8] Das et al., US 2005/0123928 Al, published June 9, 2005. Ex. 1008.

[9] Helftenbein, US 6,776,959 B1, Aug. 17, 2004. Ex. 1019.

[10] Heineman et al., US 2005/0079484 A1. April 14, 2005. Ex. 1033.

date (October 1, 2007). *See, e.g.*, Pet. 4; Ex. 1002 ¶ 1; PO Resp. 4. Patent Owner does not dispute the prior art status of the asserted references.

1) Background and Specification

The ’256 patent is directed to “aqueous compositions for collection, transport, and storage of a biological specimen containing a population of nucleic acids in a single reaction vessel, which can then be purified and/or analyzed using conventional molecular biology methods.” Ex. 1001, 1:21–25, 2:34–53 (reviewing known analytic methods). According to the Specification, “[e]xemplary formulations of the invention include a one-step collection solution that lyses, stabilizes, and preserves the integrity of nucleic acids prepared from a biological sample for subsequent RNA and/or DNA analysis.” *Id.* at 6:28–31.

The Specification asserts that prior art methods could result in the degradation of nucleic acids, even when stored under freezing temperatures, and had the potential for exposure to infectious agents during collection, transfer, and testing. Ex. 1001, 1:42–2:22. Moreover, the Specification asserts, “clinical laboratory methods for pathogen detection were labor-intensive, expensive processes that required highly knowledgeable and expert scientists with specific experience.” *Id.* 2:23–26.

Against this background, the ’256 patent, purports to disclose

> new and useful compositions . . . that may advantageously improve conventional collection, lysis, transport and storage methods for the preparation of nucleic acids from one or more biological sources. . . . such that the integrity of the nucleic acids is at least substantially maintained, and preferably entirely maintained, so that a portion of the nucleic acids are readily available for molecular diagnostic analysis.

Id. 3:9–13; *see also id.* 8:18:23 (disclosing that samples may be, e.g., clinical, veterinary, environmental, or ecological and contain nucleic acids "of viral, microbial, animal or plant origin"). In particular, the '256 patent discloses a one-step, aqueous stock solution that:

> a) inactivates viruses or microbes in the sample, b) lyses the biological cells or tissues to free the nucleic acids from cellular debris and extraneous biomolecules, c) protects the nucleic acids from degradation by endonuclease activity, and d) preserves the nucleic acids for subsequent isolation, detection, amplification, and/or molecular analysis.

Id. 1:20–39; *see id.* 6:32–40. The Specification further discloses exemplary stock solutions comprising a buffered solution of nuclease-free water containing:

> a chaotrope, e.g., guanidine thiocyanate, guanidine hydrochloride, or guanidine isocyanate;
>
> a detergent, e.g., sodium dodecyl sulfate (SDS), lithium dodecyl sulfate (LDS), sodium taurodeoxycholate (NaTDC), sodium taurocholate (NaTC), sodium glycocholate (NaGC), sodium deoxycholate (NaDC), sodium cholate, sodium alkybenzene sulfonate (NaABS), or N-lauroyl sarcosine (NLS);
>
> a reducing agent, e.g., β-mercaptoethanol (β-ME), dithiothreitol (DTT), dimethylsulfoxide (DMSO), formamide, or phosphine (TCEP);
>
> a chelator, e.g., EGTA, HEDTA, DTPA, NTA, EDTA, citrate anhydrous, sodium citrate, calcium citrate, ammonium citrate, ammonium bicitrate, citric acid, diammonium citrate, ferric ammonium citrate, or lithium citrate);
>
> a surfactant/defoaming agent, e.g., a silicone polymer such as Antifoam A®, or a polysorbate such as Tween®; and
>
> a short chain alkanol, e.g., methanol, ethanol, propanol, butanol, pentanol, hexanol.

Id. 4:19–7:36, 7:49–67; *see also* Ex. 2001 ¶ 2 ("The disclosure of the '256 Patent provides multiple examples including of a PrimeStore™ solution that improves significantly on the collection and transport systems disclosed in the references of record and asserted in the Petition.").

According to the Specification:

> In certain embodiments, the composition containing the sample suspected of containing nucleic acids will stabilize the nucleic acids to the extent that they either remain at least substantially non-degraded (i.e., at least substantially stable) even upon prolonged storage of the composition at ambient, refrigerator, or sub-zero temperatures. It will be desirable that this stability provides that at least about 70%, at least about 85%, more preferably at least about 90%, more preferably at least about 95%, or even more preferably, at least about 98% of the polynucleotides contained within the stored sample will not be degraded upon prolonged storage of the sample. In certain embodiments, substantially all of the polynucleotides contained within the sample will be stabilized such that the original integrity of the polynucleotides is preserved during the collection, lysis, storage, and transport of the processed sample.

Id. at 9:57–10:5; *see also id.* 10:34–50 (asserting that "no more than about 1 or 2% of the sample will be degraded even when the composition is stored at a temperature from 0° C. to about 40° C. for periods of several days to several weeks").

2) Challenged Claims

The Petition challenges claims 1–20 of the '256 patent. Claim 1, the only independent claim, is representative of the challenged claims and reproduced below.

> 1. A stock solution comprising components with concentrations as follows:
>
> [a] a chaotrope present in an amount from 0.5 M to 6M;

[b] a detergent present in an amount from 0.1% to 1% (wt./vol.);

[c] a reducing agent in an amount from 0.5 mM to 0.3 M;

[d] a chelator present in an amount from 0.01 mM to 50 mM;

[e] a surfactant present in an amount from 0.0001% to 0.3% (wt./vol.);

[f] a short-chain alkanol present in an amount from 1 to 25% (vol./vol.);

[g] a buffer present in an amount from 1 mM to 1 M;

[h] an acid or base present in an amount that provides a pH from 5 to 7 to the stock solution; and

[i] nuclease-free water,

[j] wherein the stock solution, when combined with a biological sample suspected of containing a pathogen, denatures proteins, inactivates nucleases, and kills pathogens all without degrading nucleic acids of the sample.

Ex. 1001, 31:57–32:46 (bracketing added as per pages 16–17 of the Petition). Independent claims 15 and 17, respectively, recite a method for detecting a nucleic acid and a diagnostic kit, each of which recite the stock solution of claim 1. *Id.* 34:9–18, 23–24.

Depending from claim 1, claims 2, 4, and 5 are particularly relevant to our analysis. Claim 2 requires that "the chaotrope comprises guanidine thiocyanate, guanidine isocyanate, guanidine hydrochloride or a combination thereof." Claim 4 defines the reducing agent as "β-ME, DTT, DMSO or formamide present in an amount from 0.05 M to 0.3 M, or wherein the reducing agent is TCEP present in an amount from 0.5 mM to 30 mM." Claim 5 recites that the "chelator comprises ethylene glycol tetra acetic acid, hydroxyethylethylenediaminetriacetic acid, diethylene triamine pentaacetic

acid, N,N-bis(carboxymethyl)glycine, ethylenediaminetetraacetic, citrate anhydrous sodium citrate calcium citrate, ammonium citrate, ammonium bicitrate, citric acid diammonium citrate, ferric ammonium citrate, lithium citrate or a combination thereof."

II. ANALYSIS

A. Legal Standards

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

Petitioner contends that each claim of the '256 patent is invalid as obvious under § 103(a). The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), reaffirmed the framework for determining obviousness set forth in *Graham v. John Deere Co*., 383 U.S. 1 (1966). The *KSR* Court summarized the four factual inquiries set forth in *Graham* (383 U.S. at 17–18) that are applied in determining whether a claim is unpatentable as obvious under 35 U.S.C. § 103 as follows: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of

ordinary skill in the art; and (4) considering objective evidence indicating obviousness or non-obviousness, if present.[11] *KSR*, 550 U.S. at 406.

"[W]hen a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious." *Id.* 417 (quoting *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 282 (1976)). But in analyzing the obviousness of a combination of prior art elements, it can also be important to identify a reason that would have prompted one of skill in the art "to combine . . . known elements in the fashion claimed by the patent at issue." *Id.* 418. Combining teachings in a single prior art reference, however, "does not require a leap of inventiveness." *Bos. Sci. Scimed, Inc. v. Cordis Corp.*, 554 F.3d 982, 991 (Fed. Cir. 2009). This is especially true when the claimed composition is used for the identical purpose taught by the prior art. *Id.*

"[I]n considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom." *In re Preda*, 401 F.2d 825, 826 (CCPA 1968). Moreover, a precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *KSR,* 550 U.S. at 418. Rather, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* 420. Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show that

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[11] Patent Owner does not identify evidence of objective indicia of non-obviousness.

"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 International, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (quotations and citations omitted).

B. Level of Ordinary Skill in the Art

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

In our Institution Decision, we applied Petitioner's then-unopposed definition of one of ordinary skill in that art as:

> A person of ordinary skill in the art ("POSA") would have had (1) a Ph.D. in microbiology, molecular biology, biochemistry, or related discipline; (2) at least two years of post-graduate experience in the area of nucleic acid extraction and analysis; and (3) experience with the development or use of nucleic acid extraction formulations, and the literature concerning nucleic acid extraction and analysis.

Inst. Dec. 11 (citing Pet. 10; Ex. 1002, ¶¶34–35).

Patent Owner now argues that the above definition is flawed for two reasons.[12] First, because "a POSA would not have experience with

[12] At oral hearing, Counsel for both parties acknowledged that neither aspect of the dispute over the skill level affects the patentability analysis. *See* Tr. 84:18–85:5, 107:11–108:10.

'development' of nucleic acid extraction formulations." AmPO Resp. 3 (citing Ex. 2020, 104:1–9).[13] Patent Owner's argument is not persuasive. Patent Owner's sole support for this proposition derives from Dr. Taylor's statement that his research at the Arthur D. Little consulting company did not require the development of new methods for extracting DNA. Ex. 2020, 103:12–104:15; Ex. 2033 ¶¶ 56–57. That Dr. Taylor personally may not have been involved with this type of assay or formulation development hardly speaks to the breadth of knowledge of one of ordinary skill in the art. Moreover, that the art of record is largely directed to the development of formulations and methods for extracting nucleic acids is directly contrary to Patent Owner's position. *See, e.g.*, Exs. 1003, 1011, 1026; *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) ("the prior art itself [may] reflect[] an appropriate level" as evidence of the ordinary level of skill in the art) (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

Patent Owner further takes issue with the requirement that one of ordinary skill in the art have "*experience* with . . . the literature concerning nucleic acid extraction and analysis," as allegedly ambiguous. AmPOR 3 (citing Ex. 2033 ¶¶ 56–57) (italics added). One of ordinary skill in the art is a "hypothetical person who is presumed to be aware of all the pertinent prior art." *Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985). To the extent the above definition may be misconstrued, we

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[13] At oral argument, counsel for Patent Owner attempted to distinguish "developing compositions for nucleic acid extraction as opposed to simply using them," but could not identify any issue that turned on the precise wording of one of ordinary skill in the art. *See* Tr. 82:18–85:5; *see also id.* at 107:11–108:10 (Petitioner's comments regarding the relevance of "know[ing] how to put these compositions together").

substitute "presumed awareness" for "experience." As such, we define one of ordinary skill in the relevant art as having had:

> (1) a Ph.D. in microbiology, molecular biology, biochemistry, or related discipline; (2) at least two years of post-graduate experience in the area of nucleic acid extraction and analysis; and (3) experience with the development or use of nucleic acid extraction formulations; and (4) presumed awareness of the literature concerning nucleic acid extraction and analysis.

C. Claim Construction

We interpret a claim "using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b)." 37 C.F.R. § 42.100(b) (2020). Under this standard, we construe the claim "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." *Id.*

1) "stock solution"

The independent claims before us are directed to stock solutions and methods and kits employing the same. *See* Ex. 1001, claims 1, 15, 17. Petitioner contends that we should apply the plain and ordinary meaning of "stock solution" as meaning "a formulated supply of solution for future use," which, in the context of the instant claims, refers to "the aqueous composition before it is mixed with a sample." Pet. 8 (citing Ex. 1029; Ex. 1002 ¶ 38). Patent Owner does not contest this construction. AmPOR 3. For the sake of clarity, we apply the plain and ordinary meaning of this term as Petitioner proposes.

2) "kills pathogens"

Independent claim 1 is directed to a stock solution which, "when combined with a biological sample suspected of containing a pathogen,

denatures proteins, inactivates nucleases, and kills pathogens all without degrading nucleic acids of the sample." The Specification does not expressly define "kills pathogens" and the parties did not formally address the meaning of this language prior to institution. In its Preliminary Response, however, Patent Owner appeared to equate this term with complete sterilization of a sample "to prevent 'dissemination of live infections pathogens." DI 23–24 (citing Prelim. Resp. 16).

On the limited record before us, we concluded that plain language of "the claims do[es] not require killing every potential pathogen in a sample," and made clear that we did not otherwise "read the challenged claims as suggesting that *every* pathogenic agent including, for example, prions and bacterial spores, must be so susceptible." DI 24 (citations omitted). Applying the plain and ordinary meaning, we provisionally determined that "kill pathogens" merely requires that at least some potential pathogens are killed in the extraction process, and invited further briefing. *Id.* 24, 30. For the reasons discussed below, we further refine our initial construction.

We first address what pathogens are contained within the scope of "kills pathogens." At oral argument, Patent Owner's counsel clarified that "kills pathogens" only applies to those classes of pathogen disclosed in the Specification. Tr. 104:8–106:13, 134:11–15. Patent Owner's counsel initially argued that the disclosed classes were "viruses, bacteria, and spores." *Id.* at 122:8–135:15.

By way of explanation, some bacteria have the capacity to form spores (endospores) under adverse environmental conditions. *See* Ex. 1046, 50:6–23; Ex. 1064, 63:6–64:1. This spore stage is generally more resistant to inactivation than the corresponding vegetative-stage bacteria. *See, e.g.*,

Ex. 1096, 1005:4–1008:1 (Dr. DeFilippi explaining spore resilience); Ex. 2003, 9–10, 34, 102 (CDC Guidance discussing difficulty of eliminating bacterial spores and prions as opposed to, for example, lipid encapsulated viruses and vegetative bacteria); Ex. 1008 ¶ 38 (characterizing spores as among "the toughest cells"); Tr. 141:8–11; Ex. 1069; 68:13–70:9 (Dr. Birkebak at Assured Bio Labs ("ABL")[14] testifying that spores are more resistant to desiccation and disinfection).

Contrary to the initial assertion of Patent Owner's counsel that the Specification disclosed spores, we do not identify any disclosure of bacterial spores in the '256 patent. Consistent with our understanding of the '256 Specification, Patent Owner's declarant, Dr. DeFilippi testified that he "do[es] not believe spores were addressed in the specifications." Ex. 1064, 185:1–186:5. Patent Owner's counsel also was unable to point to such evidence at oral argument and conceded that, to the extent the Specification does not disclose spores, the claims do not encompass killing or inactivating spores. *See* Tr. 123:19–125:5. Also pertinent to our understanding of "kills pathogens," Dr. DeFilippi testified that "[a] spore in the form of a spore is not pathogenic" but a "pre-pathogen." Ex. 1064, 186:19–187:10.

The Specification, largely focused on killing bacteria and inactivating viruses, states that "it may also be desirable to include one or more additional anti-microbial, anti-viral, or anti-fungal agents to the compositions to render them substantially non-pathogenic." Ex. 1001, 9:35–38; *see also Id.* 18: 37–57 (listing various microorganisms that may be present in a biological sample); '256 patent, claim 16 ("wherein the

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[14] Patent Owner engaged ABL to conduct biological testing in support of Patent Owner Response and its original MTA.

pathogen comprises bacteria, virus, or a fungus”); ’330 patent, claim 33 (“wherein the pathogen is an infectious pathogen, a virus, a bacterium, a parasite, a yeast, a fungal cell, a eukaryotic cell, a prokaryotic cell, a bioterrorism agent, a vector, or a microorganism”). In light of the above, we understand “kills pathogens” to encompass the killing or inactivation[15] of at least fungi, viruses, and vegetative bacteria capable of causing disease—but excluding bacterial spores, which are neither “pathogens” (according to Dr. DeFilippi), nor disclosed in the ’256 Specification.

Having address the scope of “pathogens” encompassed by independent claim 1, we turn to Patent Owner’s contention that “kills pathogens” further means “rendering the sample substantially non-pathogenic[16] so that the regulations for transporting “Infectious Substances’ would not apply–i.e., so that pathogens could not cause disease if exposure to the sample occurs.” AmPOR 11 (citing Ex. 2033 ¶¶ 8–11); *see also id.* at 25, n.1 (alternatively defining the term “as rendering the sample (that may contain pathogens safe for shipment and handling ‘non-pathogenic’”);

[15] Petitioner distinguishes killing bacteria from inactivating viruses on the basis that “[v]iruses are never alive to begin with.” Tr. 12:11–13:4. For the purpose of this Decision, however, we consider killing synonymous with inactivation as the critical point is that the pathogen is has a reduced ability to replicate or cause disease. *See e.g.*, Ex. 1001, 8:1–17 (disclosing embodiment “effective to . . . substantially kill or inactivate potentially-infectious pathogens in a sample”).

[16] Although the ’256 patent defines “substantially non-pathogenic” as “leaving less than about 10 percent, less than about 5 percent, etc., of the pathogenic activity,” it is unclear how much remaining pathogenic activity is allowed. Ex. 1001, 20:10–15. Thus, we agree with Petitioner’s analysis that, read in the context of the Specification, “[*s*]*ubstantially* non-pathogenic” would render the claims indefinite. *See* Reply 1, n.1 (citing Ex. 1001, 20:10–15) (emphasis added).

Tr. 134:19–135:14 (Patent Owner explaining that "substantially nonpathogenic . . . doesn't mean entirely").

In support of its construction(s), Patent Owner points to U.S. regulatory standards and exceptions for transport of Division 6.2 infectious substances, and an Emergency Use Authorization (EUA) Memorandum for SDNA-1000 Saliva Collection Device indicating that USDOT packaging requirement UN3373 "was in place at the time of the invention." AmPOR 9–11 (citing 49 C.F.R. §§173.124(a)(1)(iii), and 173.124(b)(4), (5); Ex. 2016, 7). As neither 49 C.F.R. §173 nor the USDOT packaging requirement is referenced in the '256 Specification, they are of limited value here.

Patent Owner further contends that "rendering samples potentially containing dangerous pathogens safe for unsecured shipment to laboratory facilities" is a "fundamental purpose" of the '256 patent. Sur-Reply 13–14 (citing AmPOR 9–11; Ex. 2033 ¶¶ 8–10); AmPOR 9–11 (further citing Ex. 1001, 2:8–23, 2:63–3:5, 6:32–37, 9:25–39, 14:57–15:2, 15:61–16:9, 25:66–26:8, code (54), (57)). As such, Patent Owner attempts to draw a parallel with the Federal Circuit's holding in *Praxair, Inc. v ATMI, Inc.*, 543 F.3d 1306 (Fed. Cir. 2008). AmPOR 6–8; Sur-reply 13–14.

In addressing the claim term "flow restrictor," the *Praxair* Court found that "the specification teaches that the flow restriction must be sufficient to achieve the overall object of the invention—that is, to prevent a hazardous release of gas." 543 F.3d at 1324. The court, therefore, construed "flow restrictor" as "a structure that serves to restrict the rate of flow sufficiently to prevent a hazardous situation," because "[t]he fundamental object of the invention disclosed by the . . . specification is to prevent a

hazardous situation from the uncontrolled discharge of gas." *Id.* Notably, however, the court rejected a construction requiring a "severe restriction of gas flow" because the specification made clear that "severe restriction" pertained only to specific, albeit the most common, embodiments rather than the full scope of the invention. *Id.* at 1323.

Considering the court's reasoning in *Praxair*, we do not find Patent Owner's argument availing for at least the reasons set forth in Petitioner's Reply. *See* Reply 1–3 (arguing, *inter alia*, that "safe handling and transport" is merely a preferred or desirable goal of the invention). We further note that the '256 patent describes compositions and methods "that may advantageously improve conventional collection, lysis, transport and storage methods for the preparation of nucleic acids from one or more biological sources." Ex. 1001, 3:9–13. The Specification states, for example, that the

> invention advantageously can provide a collection and preservation formulation to inactivate and lyse a biological specimen containing nucleic acids, and preserve nucleic acids (RNA/DNA) within the biological specimen, preferably all in a single reaction vessel, such that the integrity of the nucleic acids is at least substantially maintained, and preferably entirely maintained, so that a portion of the nucleic acids are readily available for molecular diagnostic analysis.

Id. 3:14–22. As such, and considering the Specification as a whole, the fundamental goal of the invention—to the extent one can be assigned—is the extraction and preservation of nucleic acids for molecular diagnostic analysis. And while the Specification also discusses the desirability of killing or inactivating pathogens "to facilitate safe handling of the sample," we agree with Petitioner that such language points to preferred embodiments, as opposed to some fundamental object of the invention. *See* Reply 1–2 (citing Ex. 1001, 9:25–31, 15:61–16:9); Tr. 24:4–25:21.

Illustrative of this point, the Specification discloses an embodiment having three distinct and alternative goals, no one of which is presented as mandatory:

> A clinical or veterinary specimen or a forensic or environmental sample collection system . . . for efficiently:
>
> 1) obtaining a high yield of suitable specimen beyond what is currently available in the art;
>
> 2) inactivating potentially infectious biological pathogens so that they are no longer viable and can be handled; shipped, or transported with minimal fear of pathogen release or contamination; ***or***
>
> 3) effectively stabilizing and preserving lysed 'naked' RNA/ DNA polymers from hydrolysis or nuclease degradation for prolonged periods at ambient temperatures until samples can be processed at a diagnostic laboratory, and
>
> ***preferably for achieving two or more, or all three, of these goals***.

Ex. 1001, 14:57–15:2 (paragraphing and emphasis added); *see also* 15:61–16:9 (similar); 15:5–22 ("Exemplary benefits include, without limitation, ***one or more*** of the following," including "[i]nactivation, killing, and/or lysis of microbes, viruses, or pathogens.") (emphasis added).

In sum, having determined that the "pathogens" at issue are limited to fungi, viruses and vegetative bacteria (excluding spores), we find to no reason to otherwise depart from the plain and ordinary meaning of "kills pathogens." Accordingly, we define the term as meaning that "at least some viral or vegetative bacterial pathogens in a sample are killed or inactivated."

3) "inactivates nucleases"

Patent Owner contends that "inactivates nucleases" should be construed to mean that substantially all DNases and RNases in a sample

should be inactivated. AmPOR 15–17; Sur-reply 9–10.[17] In support of its position, Patent Owner relies on the intrinsic record, the opinion of its technical expert, Dr. DeFilippi, and the deposition testimony of Petitioner's expert, Dr. Taylor, that he understands "that both DNA and RNA nucleases are involved" because "[n]ucleases is plural." AmPOR 15–17 (citing Ex. 1001, 6:32–40; 14:57–15:1, 25:66–26:8; Ex. 2033 ¶¶ 13–17, 19–21; Ex. 2020, 314:17–316:16). Considering the totality of the evidence, however, we agree with Petitioner that "inactivates nucleases" more broadly encompasses inactivating DNases or RNases (or both) in a sample. *See* Reply 4–5.

The present controversy arises from the claim term's use of the plural "nucleases" which, Patent Owner asserts, "requires inactivation of both RNA and DNA nucleases." Tr. 102:8–18. But it is undisputed that there are entire families of both RNases and DNases such that "inactivates nucleases" can also apply to the inactivation of multiple RNases or multiple DNases. *See* Tr. 102:19–103:6, 30:17–31:6; Reply 4 (citing Ex. 1064, 144:4–21, 145:16–146:16); Ex. 1011, 62 (RNase H); Ex. 1026, 48 ("RNases are a family of enzymes present in virtually all living cells."); Ex. 1015, 5294 (RNase A); Ex. 1009, 3:65–4:3 (RNases A, T1, and S1)).

As noted by Patent Owner, the Specification refers to the stabilization of "DNA/RNA." *See* AmPOR 15–16 (citing Ex. 1001, 6:32–40, 14:57–15:1, 25:66–26:8). Patent Owner initially argued that we should interpret this convention as meaning "DNAses *and* RNases," as opposed to "DNases *and/or* RNases" *See id.* at 16 (citing Ex. 2015 ¶¶ 19–21). When questioned

[17] The prior art, the '256 Patent, and the parties' briefs inconsistently capitalize these enzymes as "RNAse"/"RNase" and "DNAse"/"DNase." We consider the two conventions interchangeable.

at trial, however, Patent Owner's counsel conceded that the use of "DNA/RNA" in the Specification was not necessarily conjunctive. Tr. 95:8–21. Indeed, an understanding of the "DNA/RNA" convention as referring to the inactivation of either DNases or RNases, is consistent with the Specification's disclosure that:

> The compositions of the present invention will typically at least substantially inactivate, and preferably entirely inactivate, any endogenous or exogenous RNAses or DNAses present in the sample such that the nucleic acids of the sample are substantially free of any degradation, and preferably do not degrade, or lose integrity, during the collection, lysis, storage, and transport of the sample for subsequent in vitro or in vivo analyses.

Ex. 1001, 6:20–27. First, by including the word "typically" the Specification indicates, at best, that "substantial[] inactiv[ation]" of RNases or DNases present in the sample is a preferred, but not absolute requirement. Second, we understand the above-quoted passage's reference to inactivation of "RNAses *or* DNAses" to reflect the underlying purpose of the invention in providing samples for molecular analysis of RNA (e.g., RT-PCR analysis) or DNA (e.g., PCR analysis). *See* Reply 4; Ex. 1001, 6:20–27 (emphasis added), 2:34–50 (discussing molecular analysis techniques).

Petitioner also contends that, "Claim 1 of the related '443 patent recites "inactivate nucleases." Dependent claim 13 of the '443 patent adds "free of RNase ***or*** DNase activity." "The term 'inactivate nucleases' cannot be construed to require inactivating DNase ***and*** RNase, rendering the dependent claim broader than the independent cla[i]m." Sur-reply 4 (citing 35 U.S.C. § 112(d); *Baxalta Inc. v. Genentech, Inc.*, 972 F.3d 1341, 1346 (Fed. Cir. 2020)). Patent Owner responds that Petitioner's claim differentiation argument fails because claim 13 of the '443 patent requires

the *composition* rather than the resulting sample to be free of RNase and DNase activity. *See* Sur-reply 4.

Although Patent Owner is correct that claim 13 is directed to the composition prior to the addition of a biological sample, Petitioner's argument is, nevertheless, consistent with its construction of "inactivate nucleases." The "free of RNase or DNase" language of claim 13 implicitly permits the composition to contain, for example, RNase activity. Adding such a composition to a biological sample, therefore, would be expected to degrade RNA in the sample. Accordingly, the term "inactivate nucleases" recited in claim 1 cannot mean that the composition must inactivate both RNase and DNase in the sample because independent claim 1, permits the presence of RNase activity.

We also find informative certain claims of the related '399 patent. In particular, claim 21 of the '399 patent incorporates a "stock solution in accordance with claim 1" which, "inactivates the nucleases of the sample." Depending from claim 21, claim 26 requires that "the sample further comprises one or more nucleases, at least a portion of which is at least substantially inactivated by the stock solution." In this respect, the inactivation of at least a portion of the nucleases in a sample is consistent with the inactivation of DNase or RNase but not both.

Considering the evidence of record, we interpret "inactivates nucleases" to mean that "at least one of RNase or DNase in a sample is substantially inactivated."

4) "without degrading nucleic acids of the sample"

Independent claim 1 recites a stock solution that, "when combined with a biological sample . . . kills pathogens all without degrading nucleic

acids of the sample."[18] On its face, the phrase "without degrading nucleic acids of the sample" has potentially enormous breadth as it can be read as requiring the protection of *all* nucleic acids in the sample (100% protection), or as requiring the protection of *at least some* nucleic acids in the sample (e.g., an amount sufficient for detection). Consistent with our construction of "inactivates nucleases," we interpret the "nucleic acids" in this phrase as referring to at least one of RNA or DNA.

As we understand Patent Owner's position, one of ordinary skill in the art would understand the term to mean "as stable as possible," such that "no more than about 1 or 2% of the sample will be degraded" as "discussed in the best-preserved embodiments taught in the '256 patent." AmPOR 11–15 (citing Ex. 2033 ¶¶ 13–17; Ex. 1001, 31:57–32:46, 10:36–37, 9:57–10:1, 10:34–39; Ex. 2018, 37.; Ex. 2020, 314:17–316:16); Sur-reply 9–10.

As Petitioner points out, however, Patent Owner arrives at this construction by focusing on "the most stable embodiments" of the '256 patent to the exclusion of its broader teachings. Reply 3 (quoting AmPOR 13). Petitioner argues that Patent Owner "cannot arbitrarily impose limits of 'even more preferabl[e]" embodiments to the exclusion of other disclosed embodiments.'" *Id.* (quoting *Conoco, Inc. v. Energy & Envtl. Int'l, L.C.*, 460 F.3d 1349, 1357–1358 (Fed. Cir. 2006). We agree with Petitioner that the intrinsic record, which we address below, does not support Patent Owner's narrow reading of the claim term.

As an initial matter, during prosecution of the related '443 patent, the Examiner rejected claims reciting the "prevent[ion]" of polynucleotide

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[18] To clarify, "the sample" element of claim 1 refers to the biological sample after combination with the stock solution.

degradation under 35 U.S.C § 112, first paragraph, because "preventing 'total polynucleotide degradation . . . from happening does not appear to be the tenor of the present specification, and nowhere in the present specification is it shown that polynucleotide degradation may totally be kept from ever occurring.'" Ex. 1045, 3–5. Rather, the Examiner found, the Specification "makes clear that total protection to the polynucleotides is not expected to occur, i.e., at least some, small degree of degradation[, and] hydrolysis, etc., will occur." *Id.* 3. Accordingly, we understand that "without degrading nucleic acids of the sample" does entail absolute protection from degradation.

In support of its position, Patent Owner points to the following passage in support of its construction:

> In some instances, the population of nucleic acids prepared by the present methods may be maintained with sufficient integrity such that no more than about 1 or 2% of the sample will be degraded even when the composition is stored at a temperature from 0°C. to about 40°C. for periods of several days to several weeks.

AmPOR 13 (quoting Ex. 1001, 10:34–39). But, as Petitioner's counsel points out, "you can't import a numerical range simply because you want to avoid the prior art." Tr. 29:14–30:6. The "[i]n some instances" language of the above passage clearly indicates that limiting degradation to "1 or 2%" merely represents one possible embodiment. In this respect, a related passage makes clear that a similar measure of polynucleotide stability—"at least about 98%"— is merely a preferred embodiment, and not indicative of the full scope of the invention.

> In certain embodiments, substantially all of the polynucleotides contained within the sample will be stabilized such that the original integrity of the polynucleotides is

> preserved during the collection, lysis, storage, and transport of the processed sample. It will be desirable that this stability provides that at least about 70%, at least about 85%, more preferably at least about 90%, more preferably at least about 95%, or even more preferably, at least about 98% of the polynucleotides contained within the stored sample will not be degraded upon prolonged storage of the sample.

Id. at 9:57–10:1.

The above passage indicates that the scope of the invention includes an embodiment in which "at least about 70%" of the polynucleotides are not degraded upon prolonged storage. This does not define the lower limit encompassed by "without degrading nucleic acids of the sample." Rather, the Specification discloses a preferred embodiment wherein

> the composition containing the sample is at least sufficiently stable, or is entirely stable, to permit storage of the sample in the composition at ambient temperature or colder at least substantially (or entirely) from the time of collection to the time of analyzing a population of polynucleotides from the sample.

Id. at 9:40–45.

Consistent with the underlying goal of the invention to isolate and preserve nucleic acids for analysis "using conventional molecular biology methods," the above passage explains that the composition must merely render the target nucleic acids "sufficiently stable" for analysis. *See id.* at 1:21–38, 9:40–45; Tr. 24:16–25:11 ("[t]he fundamental goal of this invention is to stabilize nucleic acid").[19] The Specification describes known nucleic acid detection strategies as including PCR (polymerase chain reaction), RT-PCR (reverse-transcriptase PCR), and advanced detection

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[19] We do not agree with Patent Owner's counsels' unsupported assertion that only a completely intact RNA molecule can be used "for any sort of nucleic acid test or assay." *See* Tr. 80:16–82:1.

methodologies including “transcription-mediated amplifications, ligase chain reaction (LCR), microarrays, and pathogen gene chips.” *Id.* at 2:34–53, 11:52–60, 12:10–19 (RNA samples analyzed using real-time RT-PCR on an Applied Biosystems ABI 7500 instrument).

Considering the record before us, we construe “without degrading nucleic acids of the sample” as meaning that “the sample contains sufficient RNA or DNA for analysis using nucleic acid detection methodologies known to those of ordinary skill in the art as of the time of the invention.”

D. Overview of References Cited

Petitioner’s challenges rely on combinations of Birnboim, Mori, Farrell, Das, Helftenbein, and Heineman. *See* Pet. 1. In responding to Patent Owners Revised Motion to Amend, Petitioner further raises Chirgwin,[20] Casas,[21] Donofrio,[22] Laulier,[23] and Zinkevich.[24] *See* Opp. RMTA. As these references are pertinent to the knowledge of one of ordinary skill in the art,

[20] Chirgwin et al., Isolation of Biologically Active Ribonucleic Acid from Sources Enriched in Ribonuclease, Biochemistry, Vol. 18, No. 24, pp. 5294-5299 (1979). Ex. 1015.

[21] Casas, et al., “New Method for the Extraction of Viral RNA and DNA from Cerebrospinal Fluid for Use in the Polymerase Chain Reaction Assay,” Journal of Virological Methods 53: 25-36 (1995). Ex. 1052.

[22] Donofrio, et al., “Detection of Influenza A and B in Respiratory Secretions with the Polymerase Chain Reaction,” PCR Methods and Applications 1:263-268 (1992). Ex. 1056.

[23] Laulier, et al., “An Easy Method for Preserving Nucleic Acids in Field Samples for Later Molecular and Genetic Studies Without Refrigerating,” J. Evol. Biol., 8:657-663 (1995). Ex. 1060.

[24] Zinkevich and Beech, “Isolation of Intact High Molecular Weight Chromosomal DNA from Desulfovibrio spp.,” Molecular Biology Today, 1(1): 29-33 (2000). Ex. 1054.

and raised in Petitioners' Opposition to the Revised Motion to Amend, we briefly review them here. *See Qualcomm Inc. v. Apple Inc.*, 24 F.4th 1367, 1375–76 (Fed. Cir. 2022) (explaining "a petitioner may rely on evidence beyond prior art documents in an *inter partes* review, even if such evidence itself may not qualify as the 'basis" for a ground set forth in a petition" because "the assessment of a claim's patentability is inextricably tied to a skilled artisan's knowledge and skill level").

1) Overview of Birnboim (Exhibit 1003)

Birnboim discloses "compositions and methods for preserving nucleic acids at room temperature for extended periods of time and for simplifying the isolation of nucleic acids," most particularly, DNA or RNA from sputum or saliva. Ex. 1003 ¶¶ 2, 27. According to Birnboim, nucleic acid can be isolated from sputum, saliva or "from a bacterium or a virus that is residing in the buccal, nasal, or respiratory passages of the subject." *Id.* ¶ 27; *see id.* ¶ 43 (defining "nucleic acid" as meaning "a chain of the nucleotides, including deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), typically found in chromosomes, mitochondria, ribosomes, bacteria, or viruses"); ¶ 18 ("The nucleic acid to be preserved can be . . . viral RNA."); ¶ 27 ("If the nucleic acid is RNA, desirably it is mRNA or viral RNA.") ¶ 45 (discussing quantitation of "high molecular weight nucleic acid (DNA, RNA, mRNA, or viral RNA)"); claims 7, 16.

Birnboim discloses stock solutions ("nucleic acid preserving compositions") for use in a one-step method to lyse nucleic acid-containing cells or viruses, release the nucleic acids into the composition, inactivate nucleases in the sample, and stabilize the extracted nucleic acid for future

analysis. *See generally, id.* ¶¶ 11, 22, 27, 64, 114–122. With respect to stability of the extracted nucleic acid, Birnboim defines "stable" as meaning "that at least about 50% of the initial amount of high molecular weight nucleic acid (DNA, RNA, mRNA, or viral RNA) contained in a sample is still present after storing the sample at ambient temperature (i.e., 20° C. to 25°C.) for the Specified time period." *Id.* ¶ 45.

Birnboim further teaches "inclusion of an inhibitor of ribonuclease in the composition of the invention . . . when the nucleic acid to be preserved is RNA, desirably mRNA, or when the nucleic acid to be preserved is from a virus or a bacterium." *Id.* ¶ 22; *see also id.* ¶ 68 (stating that in addition to the use of various denaturing agents, "reagents such as heparin, heparan sulfate, or oligo(vinlylsulfonic acid) . . . are known to inhibit the action of deoxynucleases and /or ribonucleases").

Birnboim explains:

> When sputum is mixed with a composition of the present invention, cells are disrupted, nucleic acids are liberated from the cells, membranous material is solubilized, proteins are stripped from the nucleic acids, and protein digestion begins . . . . If transferred to a laboratory soon after collection, incubation at 55º C. for 4 to 16 hours is sufficient to allow the activated protease to digest the majority of protein to small peptides or amino acids. Under such conditions, nucleic acids and polysaccharides remain relatively intact.
>
> Once digestion is complete, nucleic acid isolation can be performed using any technique known in the art.

Id. ¶¶ 84–85.

Example 1 discloses an embodiment wherein a subject spits saliva into a collection tube which is mixed with an equal volume of stock solution. *Id.* ¶¶ 107–109. Once the container is capped and the contents shaken, the nucleic acid is "in an intermediate preserved state" and "can be maintained

in a frozen state or at any temperature up to about 60º C.” *Id.* ¶ 110. Alternatively, “[t]he container can be mailed back to the testing lab at room temperature.” *Id.* ¶ 111.

Example 3 discloses the collection and extraction of DNA using a stock solution comprising “33 mM TRIS-HCl, 0.67 M urea, 0.67 M LiCl, 0.6% sodium dodecyl sulfate, 3.3 mM CDTA, 30% ethanol, and 0.25 M sodium ascorbate, all adjusted to a final pH of 8.0.” *Id.* ¶¶ 114–122 (“Formulation 1”). Birnboim further discloses that a similar composition comprising “0.3 M TRIS-HCl, 0.67 M urea, 0.67 M NaOAc, 0.6% sodium dodecyl sulfate, 3.3 mM CDTA, 30% ethanol, and 0.1 M sodium ascorbate, all adjusted to a final pH of 8.0, stabilizes DNA for longer periods of time.” *Id.* ¶ 115 (“Formulation 2”).

In Example 4, Birnboim subjects the DNA of Example 3 to agarose gel electrophoresis, where ethidium bromide staining reveals “the characteristic band of chromosomal DNA present in all samples.” *Id*. ¶ 117, Fig. 1; *see also id.* ¶ 13 (disclosing preferred reducing agents erythiorbate, N-acetylcysteine, dithiothreitol, 2-mercaptoethanol and, “most desirably. . . ascorbic acid”), ¶ 25 (disclosing that isolated DNA is preferably stable for “more than 60 days” and “when . . . the composition does not contain ascorbic acid, the DNA is stable for more than 60 days, and desirably more than 360 days”).

In Examples 5 and 6, Birnboim prepares “[m]inimally purified DNA” from samples prepared using the nucleic acid-preserving solution by centrifuging the samples to remove insoluble material and precipitating the DNA with ethanol prior to using “Real Time” polymerase chain reactions to detect the DNA. *Id.* ¶¶ 118–121.

5) Overview of Mori (Exhibit 1011)

Mori discloses the isolation of nucleic acids from a test sample (e.g., bodily fluids, plants, animals, bacteria, viruses, and cultured cells) by treating the sample with a "nucleic acid-solubilizing reagent," which "dissolves cell membranes and nuclear membrane, and solubilizes nucleic acid." Ex. 1011, 57.[25] Exemplary nucleic acid-solubilizing reagents may include "a chaotropic salt, a surfactant, a defoaming agent, a protease and a nucleic acid stabilizing agent." *Id.* at 58; *see also id.* at 63 (indicating that the nucleic acid stabilizing agent assists in inactivating nuclease activity).

According to Mori, preferred chaotropic salts are guanidine hydrochloride, guanidine isothiocyanate and guanidine thiocyanate, but "[i]t is possible to use a chaotropic substance such as urea instead of a chaotropic salt." *Id.* at 61. Mori further discloses that the nucleic acid stabilizing agent is a reducing agent, and preferably a mercapto compound such as mercapto ethanol (*id.* at 63); and that the defoaming agent may be any number of silicon-, alcohol-, ether-, fatty oil-, fatty acid-phosphate ester-, amine-, or amide-based compounds, "preferably in a range of 0.1 to 10% by weight" (*id.* at 64).

With respect to the surfactant, Mori teaches the use of a wide variety of compounds including an anionic surfactant, an amphoteric surfactant and, preferably, either a nonionic or cationic surfactant. *Id.* at 61.

> Nonionic surfactants include a polyoxyethylene alkyl phenyl ether-based surfactant, a polyoxyethylene alkyl ether-based surfactant, and fatty acid alkanolamide, and the preferable one is a polyoxyethylene alkyl ether-based surfactant. Among the polyoxyethylene (POE) alkyl ether surfactant, POE decylether, POE lauryl ether, POE tridecyl ether, POE alkylenedecyl ether,

[25] Where possible, we refer to native pagination.

> POE sorbitan monolaurate, POE sorbitan monooleate, POE sorbitan monostearate, tetraoleic polyoxyethylene sorbit, POE alkyl amine, and POE acetylene glycol are more preferred.
>
> Cationic surfactants include cetyl trimethyl ammonium bromide, dodecyl trimethyl ammonium chloride, tetradecyl trimethyl ammonium chloride, cetyl pyridinium chloride.

Id. at 61–62. With respect to surfactant concentration, Mori states: "The concentration of the surfactant in the nucleic acid-solubilizing reagent is preferably from 0.1 to 20% by weight." *Id.* at 62.

6) Overview of Farrell (Exhibit 1026)

Farrell is a laboratory guide describing the isolation and characterization of ribonucleic acids. Ex. 1026, Title. Farrell discloses that it was widely known that nucleases, which are enzymes that degrade nucleic acids, should be purged from solutions when trying to isolate RNA. *Id.* at 48–49. Farrell discloses that numerous compounds have been used to inhibit RNase activity including, vanadyl ribonucleoside complexes, RNasin, heparin, iodoacetate, polyvinyl (dextran) sulfate, cationic surfactant, macaloid and bentonite clays, and hydrogen peroxide.

Farrell further states that "stock solutions and buffers prepared in the laboratory can be treated, directly or indirectly, with the potent chemical RNase inhibitor DEPC" or diethylpyrocarbonate. *Id.* at 55. Farrell notes that "DEPC is an efficient, nonspecific inhibitor of RNAse," but "must be destroyed completely" since "[e]ven trace amounts of residual DEPC will result in chemical modification of the base adenine" and, thus, should not be added directly to cell suspensions or lysates containing RNAs to be purified. *Id.* at 55. Farrell discloses that there are additional "legitimate reasons" not to use DEPC in the laboratory and that making solutions with nuclease-free

water is a more desirable alternative for solutions that isolate nucleic acids. *Id.* at 57. In this respect, Farrell states:

> A suitable alternative to DEPC treatment of water to render it nuclease-free is to simply buy nuclease-free water from one's favorite vendor. For those laboratories affiliated with hospitals, it is interesting to note that water labeled "sterile water for irrigation," is free of contaminants and is good for RNA work. Purified RNA may be rehydrated in this water and stored at −80°C. This water is also excellent for making dilutions of nuclease-free stock solutions.

Id.

7) Overview of Das (Exhibit 1008)

Das is directed to techniques for detecting *Mycobacterium Tuberculosis* in clinical samples using PCR amplification. Ex. 1008 ¶¶ 1, 29, 37–38. Das specifically discloses "methods of nucleic acid extraction and mix of reagents to lyse mycobacteria and purify nucleic acid from a clinical specimen." *Id.* ¶ 38. Das discloses a modified lysis buffer to lyse the mycobacteria cells in a specimen sample and extract the nucleic acid, where the lysis buffer contains a chaotrope (guanidinium isothiocyanate), detergent (N lauryl sarcosyl), reducing agent (2-mercaptoethanol), chelator (EDTA), and buffer (Tris). *Id.* ¶¶ 63–64, 89. Das discloses that "most proteins are denatured in this buffer leading to through lysis of the mycobacteria present in the specimens." *Id.* ¶ 39. In one embodiment, Das obtains saliva samples from tuberculosis patients and using the modified lysis buffer to lyse the mycobacteria cells in the samples, extract the bacteria nucleic acid, and analyze the extracted DNA using PCR. *Id.* ¶¶ 83–85, 89–98. According to Das:

> The modified lysis buffer . . . uses a strong chaotropic agent i.e guanidinium isothiocyanate. This helps to inactivate all

> mycobacteria present in a clinical specimen, lyse tough mycobacterial cell and denature and remove proteins thus results into cleaner preparation of DNA (Table 3) and also ensure safety for the operator. By heating specimen in modified lysis buffer even the toughest cells and objects like spores and baculovirus polyhedra are lysed easily.

Id. ¶ 38. Das further explains that the modified lysis buffer can "precipitate even minute amount[s] of DNA" and "results in cleaner DNA preparation with improved yield." *Id.* ¶ 39.

8) Overview of Helftenbein (Exhibit 1019)

Helftenbein discloses a vessel for withdrawing blood containing a defined volume of nucleic acid stabilizing solution comprising: a guanidinium salt (preferably guanidinium thiocyanate and/or guanidinium chloride); a buffer comprising, e.g., TRIS, HEPES, MOPS, citrate, or phosphate; a reducing agent (e.g., DTT, β-ME, or TCEP), and a detergent (e.g., Triton X-100, NP40- Tween 20, or polidocanol). Ex. 1019, 2:28–44, 3:4–48. In one embodiment, and equal amount of blood is drawn into the vessel and mixed with the stabilizing solution such that "[t]he nucleic acids contained in the inflowing blood flow were immediately converted into a stable form." *Id.* at 4:47–5:6 (Example 1).

According to Helftenbein, "[t]he nucleic acid-stabilizing substance may have added thereto an internal standard. This permits the control of the whole method from the moment of sampling up to the detection of nucleic acids." *Id.* at 2:60–63. Helftenbein illustrates this embodiment in Examples 6–8, which discloses adding naked MS2-RNA to the vessel as a positive control. *Id.* at 6:48–8:36, 8:64–9:5. Helftenbein states, for example, that

> MS2-RNA is not stable in serum. Already 2 minutes after addition of RNA to the serum the RNA is completely degraded. By the addition of stabilizing solution to the serum in the ratio of 1:1, this process can be stopped immediately, and a stabilization of the RNA can be achieved at the time when the stabilizing solution is added.

Id. at 7:1–6.

9) Overview of Heineman (Exhibit 1033)

Heineman discloses

> a method of detecting biological agents in finished water including the steps of providing a first molecular recognition element manipulated to target a biological agent in finished water; flowing at least one sample suspected of having the biological agent over the first recognition element; capturing the biological agent present in the sample with the first recognition element; and emitting a signal capable of indicating the presence of the targeted biological agent in the Sample.

Ex. 1033 ¶ 10. According to Heineman, the biological agents can be identified using an immunoassay or with "a nucleic acid-based (NA-based) assay, which detects the Specific agent by targeting a specific nucleic acid Sequence. Both immunoassay and NA-based technologies operate, for example, by conducting molecular recognition." *Id.* ¶ 15. Heineman discloses that applicable NA-based methods include PCR, RT-PCR, and aptamer-based technologies. *Id.* ¶¶ 20, 43, 47, 49, 51.

Heineman discloses combining a sample to be tested with a solution comprising one or more chaotropes, detergents, reducing agents, chelators, and buffers. *Id.* ¶¶ 12, 22, 24, 25, 28, 29. According to Heineman, the solution may further include a blocking agent such as bovine serum albumin (BSA), gelatin, or polyvinyl alcohol to reduce non-specific binding. *Id.* ¶¶ 27, 28. Heineman further discloses that the limits of detection for an

assay are often limited by non-specific adsorption (NSA), "broadly defined as the unwanted presence of a conjugate." *Id.* ¶ 63. According to Heineman, NSA can be limited by the addition of blocking agents such as BSA and gelatin. *Id.* ¶¶ 63–64. In one embodiment, the blocking agent "participates in non-specific binding reactions with the various components of the assay (e.g., the Substrate) and thereby blocks and prevents non-specific binding of the antibodies." *Id.* ¶ 27.

10) Overview of Chirgwin (Exhibit 1015)

Chirgwin discloses that disruption of cells "results in the rapid mixing of RNA and RNase. One way to eliminate nucleolytic denaturation of RNA is to denature all of the cellular proteins including RNase." *Id.* at 5294. In this respect, "[t]he rate of denaturation is maximized by the combined use of a strong denaturant, guanidinium thiocyanate, in which both cation and anion are potent chaotropic agents (Jencks, 1969), and a reductant to break protein disulfide bonds which are essential for RNase activity (Sela et al., 1956)." *Id.*

Chirgwin describes a method for preparing "[i]ntact ribonucleic acid (RNA) . . . from tissues rich in ribonuclease such as rat pancreas by efficient homogenization in a 4 M solution of the potent protein denaturant guanidinium thiocyanate plus 0.1 M 2-mercaptoethanol to break protein disulfide bonds." Ex. 1015, Abstract. In particular, Chirgwin's formulation contains: 4M guanidine thiocyanate, 0.1 M β-mercaptoethanol, 0.1% w/v Antifoam A, 25 mM sodium citrate, and 0.5% w/v of the detergent sodium N-lauroylsarcine (NLS). *Id.* at 5294–95.

Chirgwin further teaches that, after denaturation, the RNA may be "isolated free of protein by ethanol precipitation or by sedimentation through

cesium chloride," though "these steps can be varied according to the specific circumstances." *Id.* at Abstract, 5296. Chirgwin similarly notes that "for some cultured cells no homogenization is needed since the cells lyse upon addition of the guanidine solution." *Id.* at 5296

11) Overview of Casas (Exhibit 1052)

Casas discloses the simultaneous extraction of viral RNA and DNA from cerebrospinal fluid for use in a PCR assay. Ex. 1052, Title, Abstract, 26. Casas employed a formulation similar to Chirgwin's comprising 4M guanidine thiocyanate, 1 mM DTT, 25 mM sodium citrate, and 0.5% N-lauroylsarcine (NLS). Casas further added glycogen as a carrier and precipitated the isolated nucleic acid with isopropyl alcohol. *Id.* at 27.

12) Overview of Donofrio (Exhibit 1056)

Donofrio discloses the isolation and detection of influenza RNA from respiratory sequences using RT-PCR. Ex. 1056, Abstract. According to Donofrio, "[n]ine parts of denaturing solution containing 4 M guanidinium isothio-cyanate, 25 mM sodium citrate, 0.5% sarcosyl, and 0.1 M 2-mercaptoethanol was added directly to one part of frozen or unfrozen sample." *Id.* at 264. Donofrio then added yeast tRNA as a carrier, extracted the mixture with phenol, and precipitated the RNA with ethanol. *Id.*

2) Overview of Laulier (Exhibit 1060)

Citing Chirgwin, Laulier used a buffered solution of "4 M guandium-thiocyanate/2% N-lauroyl-sarcosine/50 mM Tris-HCl, pH 7.4/50 mM EDTA/0.0l% 2-mercaptoethanol," to preserve nucleic acids from "field collected samples of viruses, bacteria, yeasts, invertebrates and vertebrates." Ex. 1060, Abstract, 658. According to Laulier, "Proteins were removed by

extraction, with saturated phenol, followed by chloroform-isoamyl alcohol (19/l) at 20–25 °C. Nucleic acids were precipitated by adding 1/10 volume 3 M sodium acetate, 2.5 volumes ethanol." *Id.* at 658. "The DNA and RNA from samples kept up to 41 days without refrigeration in this way were suitable for PCR and reverse transcription PCR." *Id.* at Abstract.

3) Overview of Zinkevich (Exhibit 1054)

Zinkevich discloses the isolation of high molecular weight bacterial DNA using lysis buffer containing "5M guanidine isothiocyanate, 50mM Tris-HCl (pH 7.5), 10mM EDTA, 140mM 2-mercaptoethanol, 2% of N-lauroylsarcosine." Ex. 1054, Abstract, 30. Zinkevich further purified the DNA using a CsCl gradient prior to visualization by gel electrophoresis or PCR amplification. *Id.* at 30–33.

E. Ground 1: Obviousness in View of Birnboim, Mori, and Farrell

As to Ground 1, Petitioner challenges claims 1–10, 13, and 15–19 as unpatentable for obviousness in view of Birnboim, Mori, and Farrell. Pet. 11, 16–55; Reply 5–20. Patent Owner opposes. AmPOR 17–37; Sur-reply 1–17. Petitioner provides a detailed analysis of where each claim element is found in the cited references and discusses why one of ordinary skill in the art would have been motivated to combine those elements with a reasonable expectation of success. *See, e.g.*, Pet. 34–42 (discussing motivation to combine and reasonable expectation of success with respect to claim 1). Petitioner points out that Patent Owner only addresses Ground 1 arguments for claims 1, 2, 4, and 5, thus, "waiving any argument for other Ground 1 claims." Reply 10 (citing *In re NuVasive, Inc.*, 842 F.3d 1376, 1380–1381 (Fed. Cir. 2016). Our discussion of claims 1, 2, 4, and 5, below, is representative of the contested issues under Ground 1, and we agree with

Petitioner that Patent Owner has waived any other arguments under this Ground. *See* DI, 37 ("Any argument not raised in a timely Patent Owner Response to the Petition, or as permitted in another manner during trial, shall be deemed waived."); Paper 13, 9 (similar).

1) Overview of Petitioner's Arguments

By way of background, Petitioner and its declarant, Dr. Taylor, note that, as of the earliest possible priority date of the '256 patent, aqueous reagents for extracting, "stabilizing, and preserving nucleic acids were wide-spread and well-known in the prior art." *See, generally*, Pet. 4–7; Ex. 1002 ¶¶ 51–65 (citations omitted). Petitioner and its declarant point to, for example, the 1982 Maniatis Laboratory Manual as disclosing the isolation of RNA using a buffered, nuclease-free, aqueous solution of guanidinium isothiocyanate (a potent chaotropic agent), sodium lauryl sarkosinate (a detergent), β-mercaptoethanol (a reducing agent), and EDTA (a chelator). Pet. 4–5; Ex. 1002 ¶¶ 51–53; Ex. 1004, 189–190.

With respect to independent claim 1, in particular, Petitioner argues that Birnboim discloses stock solutions comprising the well-known elements recited in limitations [a]–[d] and [f]–[h]: chaotropes, detergents, reducing agents, chelators, short-chain alkanols, buffer, and acid or base, recited Pet. 16–23, 25, 29; Tr. 17:12–18:10. Petitioner argues that one of ordinary skill in the art would have been motivated to further include a surfactant (element 1[e]) and nuclease free water (element 1[i]) as taught by Mori and Farrell, respectively. Pet. 23–25, 29, 34–39; Tr. 20:14–21:18. According to Petitioner, one of ordinary skill in the art would have had a reasonable expectation of success that this combination would "denature[] proteins, inactivate[] nucleases, and kill[] pathogens all without degrading nucleic

acids of the sample," as required by element 1[j]. *Id.* at 30–34, 39–42. In this respect, Petitioner points to the stock solution of Birnboim's Example 3 as illustrative of "the amounts of the chaotrope, detergent, chelator, reducing agent, short-chain alkanol, and buffer in Birnboim's compositions," and as "further confirmation that a POSA would have reasonably expected the compositions to perform the functions recited in claim 1." *See* Pet. 31–32; Ex. 1002 ¶ 130; Tr. 13:17–14:3.

The stock solution of Birnboim's Example 3 comprises:

> 0.67 M urea (a chaotrope in the range of element 1[a]);
>
> 0.6% wt./vol. sodium dodecyl sulfate (a detergent in range of element 1[b]);
>
> 0.25 M sodium ascorbate (a reducing agent in the range of element 1[c]);
>
> 3.3 mM CDTA (a chelator in the range of element 1[d]); and
>
> 33 mM TRIS-HCl (a buffer in the range of element 1[d]).

Ex. 1003 ¶ 115; Ex. 1002 ¶ 130. The stock solution further contains 30% ethanol, which is higher than the range of 1 to 25% of short-chain alkanol recited in element 1[f]. *See* Ex. 1003 ¶ 115. As Petitioner notes, however, Birnboim more generally discloses that, "the alcohol is 10%-60% of the total composition volume," which overlaps with the claimed 1–25% range. *See* Pet. 32–33 (citing Ex. 1003 ¶ 20; Ex. 1002 ¶ 132). And though at pH 8.0, the solution in Birnboim's Example 3 is more alkaline than the pH 5–7 range of element 1[h], the broader disclosure of Birnboim teaches "a pH from about 5.0 to about 7.0, desirably from about 6.5 to about 6.8." Ex. 1003 ¶ 19; *see* Pet. 31 (citing Ex. 1002 ¶ 133).

With respect to element 1[e], a "surfactant present in an amount from 0.0001% to 0.3% (wt./vol.)," Petitioner argues that "[t]he '256 patent

treats surfactants and defoaming agents as synonymous reagents in the claimed solution." Pet. 23–24 (citing Ex. 1001, 5:5–16, 6:61–64, 7:26–27, claim 6); *see* Ex. 1002 ¶¶ 107–110 (citing, e.g., Ex. 1012).[26] Accordingly, Petitioner argues, Mori's recitation of either surfactants (e.g., polysorbate surfactants) or defoaming agents (e.g., silicone polymers) reads on the surfactant of element 1[e]. *Id.* Pointing to Mori's use of surfactants in an amount of "from 0.1 to 20% by weight" and a defoaming agent in amount of "0.1 to 10% by weight," Petitioner further argues that both of these concentration ranges overlap the claimed surfactant concentration range of "from 0.0001% to 0.3% (wt./vol.)," and thus satisfy the limitations of element 1[e]. *Id.* at 25 (citing Ex. 1011, 62, 64; *E.I. DuPont DeNemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018)).

Petitioner provides reasoned bases for why one of ordinary skill in the art would have combined the teachings of the Birnboim, Mori, and Farrell to arrive at the claimed invention. *See* Pet. 34–42 (citations omitted). Summarizing its arguments, Petitioner concludes that one of ordinary skill in the art

> would have been motivated to prepare solutions comprising a chaotrope, a detergent, a reducing agent, a chelator, a short chain alkanol, and a buffer (with the associated acid and base) at a pH of 5–7 with a reasonable expectation that, when combined with a biological sample, the solution would denature proteins, inactivate nucleases, and kill pathogens, all without degrading nucleic acids of the sample. Ex. 1002, ¶151. The POSA would have been motivated to use Mori's surfactants or defoaming agents along with Farrell's nuclease-free water in Birnboim's stock solution and would have had a reasonable expectation of success in doing so. Ex. 1002, ¶¶137–152.

[26] Moon et al., US 2004/010859 A1, May 27, 2004. Ex. 1012.

Pet. 41–42.

2) Chaotropes and Detergents

Patent Owner appears to argue that one of ordinary skill in the art would have had no motivation to select both a chaotrope and a detergent (as shown in Birnboim Example 3), or to modify Birnboim's example 3 to use other chaotropes or detergents. *See* AmPOR 17–23. Patent Owner points to Birnboim's teaching that exemplary "denaturing agents that may be used (alone or in combination) include . . . urea, soluble salts of dodecyl sulfate and other strong detergents, guanidinium chloride, guanidinium thiocyanate, soluble salts of perchlorate, alcohols, such as ethanol, above 10%." Ex. 1003 ¶ 68; *see id.* ¶ 20; AmPOR 17–21 (further citing Ex. 1003 ¶ 41).

Relying on Birnboim's broad use of the term "'denaturing agent' as encompassing a wide range of compounds including (1) chaotropes such as urea and guanidinium compounds, (2) detergents such as dodecyl sulfate salts, and (3) alcohols," Patent Owner concludes that "Birnboim does not teach or recognize any distinction between" detergents and chaotropes. AmPOR 17–18. Moreover, Patent Owner argues, "[n]owhere does Birnboim teach or disclose which denaturing agents should be used in combination with one another, let alone teach that a denaturing agent that works as a detergent should be combined with a denaturing agent that works as a chaotrope, or what concentrations should be used." *Id.* at 20 (citing Ex. 2015 ¶ 27).

Patent Owner does not persuade us that Birnboim's general reference to various classes of such compounds as "denaturing agents" obviates the understanding of the ordinarily skilled artisan as to their individual properties and uses of these, and other, compounds commonly employed in

stock solutions for cell lysis and subsequent nucleic acid purification (generally referred to by Petitioner and its expert as "Chirgwin-type" compositions). Sur-reply RMTA 3; Ex. 1082 ¶ 10; Ex. 2043, 335:8–336:4; 337:24–339:14.

Birnboim discloses compositions and methods for isolating and preserving nucleic acids including nucleic acid from bacteria or viruses. *See, e.g.*, Ex. 1003 ¶¶ 22, 27, 44. The exemplary composition of Example 3, contains a "strong detergent" (SDS) and a chaotrope (urea) in amounts within the ranges set forth in claim 1 and we discern no evidence suggesting that one of ordinary skill in the art would not discern the relevant differences between the two. *See* Ex. 1003 ¶ 68. To the contrary, in explaining the difference between these two classes of denaturing agents, Dr. DeFilippi testifies that:

> Detergent molecules each have a hydrophobic tail and a hydrophilic head. Detergents bring the hydrophobic portions of the protein into the aqueous phase because the hydrophobic tail of the detergent binds to hydrophobic regions of the proteins while the hydrophilic portion of the detergent interacts directly with the aqueous phase. Chaotropes disrupt the hydrogen bonding network between water molecules and reduce the stability of the native state of proteins by weakening the hydrophobic effect, permitting the hydrophobic regions of the protein that are normally internal to the protein to be turned outwards.

Ex. 2033 ¶ 27.

The prior art of record also discloses the application of these two classes of compounds in the purification of nucleic acids from biological samples. Chirgwin, for example, discloses the isolation of rat pancreas RNA using a lysis buffer comprising 4M guanidine thiocyanate, 0.1 M β-mercaptoethanol, 0.1% w/v Antifoam A, 25 mM sodium citrate, and

0.5% w/v of the detergent sodium N-lauroylsarcine (NLS), describing the guanidinium thiocyanate as a "potent protein denaturant" and the reducing agent β-mercaptoethanol as added "to break protein disulfide bonds." Ex. 1015, Abstract, 5294–95. Das discloses the use of lysis buffer containing the detergent N lauryl Sarcosyl and guanidinium isothiocyanate. *See, e.g.*, Ex. 1008 ¶ 89. Das explains that a "[d]etergent helps in solubilization of cell wall lipid and of protein and thus result in complete lysis of the mycobacterial cell wall, which is rich in different types of complex lipids," whereas, "a strong chaotropic agent i.e guanidinium isothiocyanate," is a recognized compound "for lysis and purification of nucleic [acid] from tough materials like baculovir[u]s polyhedra and mycobacteria." *Id.* ¶¶ 38–39. Goldrick similarly teaches the isolation of RNA using a mixture of a chaotropic agent (guanidinium chloride or guanidinium thiocyanate), a detergent (e.g., N-lauroyl sarcosine or sodium dodecyl sulfate), and a reducing agent (dithiothreitol or β-mercaptoethanol), whereas "[a]dditional benefits may be realized through the [addition] of a chelating agent such as EDTA, or other suitable [chelating agent] known in the art." *See, e.g.*, Ex. 1009, 4:31–34, 7:30–8:54. Goldrick explains that the chaotropic agent is added "for inactivating . . . ribonucleases," and the detergent and reducing agents act provide "nuclease inactivation enhancing" effects. *Id.* at code [57], 1:39–54, claims 1, 6, 8. Farrell, similarly discusses the action of reagents used in the isolation of RNA and, noting that guanidine thiocyanate "is the denaturant of choice for the preparation of RNA from sources enriched in RNase activity," "is routinely used at a working concentration of 4 M in water and appears repeatedly in the literature and in various commercial formulations, usually along with a reducing agent (e.g., β-

mercaptoethanol [β-ME]) and an ionic detergent (e.g., sarkosyl [*N*-laurylsarcosine]).” Ex. 1026, 58–60; *see also* Ex. 1004, 189–190 (1982 Maniatis Laboratory Manual disclosing stock solution for the isolation of RNA comprising guanidinium isothiocynate, sodium lauryl sarkosinate, β-mercaptoethanol, and EDTA); Ex. 1015, abstract (isolating RNA using “the potent protein denaturant guanidinium thiocyanate plus 0.1 M 2-mercaptoethanol to break protein disulfide bonds”).

Despite the above, Dr. DeFilippi asserts, without support, that one of ordinary skill in the art at the time of the invention would not have been aware of the relevance of the distinction between detergents and chaotropes in modifying Birnboim’s Example 3 formulations and, thus, would not have arrived at the composition of challenged claims. Ex. 2033 ¶ 27. We do not find this argument persuasive. Rather, the evidence shows that one of ordinary skill in the art would have understood the identity and use of the various chaotropes, detergents (and other reagents) recited in Birnboim for the purification of nucleic acids and the benefits of combining them in a single composition. *See, e.g.*, Ex. 1002 ¶¶ 14, 16, 17, 51–65; Tr. 110:16–112:7.

Patent Owner also argues that one of ordinary skill in the art would not have been motivated to substitute, with a reasonable expectation of success, the urea of Birnboim’s Example 3 for the guanidinium compounds of claim 2 (AmPOR 31–34), or to use the specific reducing agents of claim 4 (*id.* at 34–36), or the specific chelators of claim 5 (*id.* at 36–37). In this respect, Patent Owner argues that “[Dr.] Taylor testified that a POSA would not have any reason to change Example 3 and could only speculate as to what effect a change of concentration or a substitution of a component

would have on Birnboim's Example 3," and that such modifications would require laboratory testing. *Id.* at 19, 37; *see, e.g.*, Ex. 2020, 198:14–199:22, 230:3–231:16, 224:17–226:3, 415:7–416:4, 419:15–420:10, 515:11–518:21, 539:3–541:7, 602:6–604:21.

We do not agree with Patent Owner that the testimony it elicited at Dr. Taylor's deposition and relied on in its briefing necessarily reflects the proper standards for determining obviousness. Rather, we agree with the arguments set forth at pages 5–8 of the Reply in support of Petitioner's obviousness grounds. In particular, we find a person of ordinary skill in the art would have had sufficient reason to substitute urea with a guanidinium compound as required in claim 3, or to select the specific reducing agent or chelator required in claims 4 and 5, respectively, which is found in Birnboim itself. *See* Reply 6 (citing Pet. 11–13; Ex. 1003 ¶¶ 64–74, 115; Ex. 1002 ¶ 178); Pet. 42–45 (citing Ex. 1003 ¶¶ 20, 68 (disclosing the known chaotropes urea, guanidine thiocyanate, and guanidine chloride), ¶ 113 (disclosing exemplary reducing agents including β-ME and DTT); ¶ 16, 67 (disclosing exemplary chelators including ethylenediamine tetraacetic acid (EDTA) and cyclohexane diaminetetraacetate (CDTA), diethylenetriamine pentaacetic acid (DTPA)); Ex. 1002 ¶¶ 153–156, 160–167).

In addition to the teachings of Birnboim, the broader art of record also makes clear that numerous such reagents may be used in stock solutions for essentially the same purpose as those recited in the challenged claims. Das, Mori, Goldrick, Maniatis, and Chirgwin, for example, all disclose the use of guanidinium compounds for the isolation of nucleic acids; indeed, Mori specifies that "[i]t is possible to use a chaotropic substance such as urea instead of a chaotropic [guanidinium] salt." *See, e.g.*, Ex. 1004, 189–190;

Ex. 1008 ¶ 89; Ex. 1009, 7:30–8:54; Ex. 1011, 61; Ex. 1015, Abstract. With respect to the specific reducing agents of claim 4 and the reducing agents of claim 5, we note, for example, that Goldrick teaches the isolation of RNA using a composition comprising a guanidinium compound, a detergent, a reducing agent such as β-mercaptoethanol or DTT and, optionally, a chelator such as EDTA. Ex. 1009, 7:30–8:54, 4:31–34. Maniatis similarly discloses a solution comprising guanidinium isothiocyanate, the detergent sodium lauryl sarkosinate, "reducing agents like β-mercaptoethanol," and the chelator EDTA for the simultaneous disruption of cells and inactivation of nucleases. *See* Ex. 1004, 189; *see also* Ex. 1008 ¶ 63 (lysis buffer comprising guanidinium isothiocyanate, N lauryl sarcosyl, β-mercaptoethanol, and EDTA). These, and other, examples in the art of record make clear that those of ordinary skill in the art were familiar with the use and combinations of reagents recited in the challenged claims and, thus, support a finding of obviousness. *See* Ex. 1002 ¶¶ 51–65 (Dr. Taylor's review of the state of the art); *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1364 (Fed. Cir. 2012). ("[The claim] recites a combination of elements that were all known in the prior art, and all that was required to obtain that combination was to substitute one well-known . . . agent for another."); *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) ("That the [prior art] discloses a multitude of effective combinations does not render any particular formulation less obvious. This is especially true because the claimed composition is used for the identical purpose taught by the prior art.").

Patent Owner also suggests that any substitution of known reagents for those in Birnboim's Example 3 is unpredictable and, thus, undercuts any

reasonable expectation of success in arriving at the claimed invention. AmPOR 33–34; Sur-reply 6–9. In this respect, Patent Owner points to its experimental evidence (Exhibit 2019) showing that the substitution of 0.67 M guanidine thiocyanate for the 0.67 M urea in Birnboim's example 3 formed a precipitate and rendered the stock solution unusable for collection of nucleic acid. AmPOR 33 (citing Ex. 2033 ¶¶ 33, 24–26; Ex. 2019, 2, 8).

Exhibit 2019 lacks sufficient explanation of how the modified solutions were made—i.e., order of addition, temperature, stirring or agitation, etc. Patent Owner also fails to explain how one of ordinary skill in the art would have sought to combine the listed reagents, or whether the skilled artisan would have considered that certain reagents might be incompatible, or require a particular order of addition. Absent knowledge of the methodology employed, as compared to the usual practice of the skilled artisan in making this type of solution, these results are of limited value.

In further support of Patent Owner's unpredictability assertion, Dr. DeFilippi notes that "DTT is chemically reactive with guanidinium and would not function in composition with guanidinium salts such as those listed in Birnboim." Ex. 2033 ¶ 28. Patent Owner's counsel, however, admits that this interaction was long known in the art and "and a skilled person would not combine it with guanidinium because of its reactivity." Tr. 66:11–67:14; Ex. 1015, 5296 (Chirgwin disclosing that in place of β-mercaptoethanol "dithiothreitol can be used with the guanidine hydrochloride stock . . . but it undergoes a chemical reaction with the thiocyanate anion to produce hydrogen sulfide and a green color").[27]

[27] Chirgwin teaches that DTT is reactive with the thiocyanate counter ion of one of the two well-known guanidinium salts rather than guanidinium, per se. It does not escape our attention that, despite the teachings of Chirgwin,

Considering the level of skill in the art and the extensive use of guanidinium compounds in combination with reducing agents, detergents, and chelators discussed above, we readily infer that the skilled artisan would have been aware of such complications and known how to avoid them. To the extent some substitutions might, nevertheless, fail, "[o]bviousness 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). With respect to the substitution of well-known reagents in Birnboim's Example 3 formulations, Dr. Taylor's testimony that adjusting denaturing agents, for example, "is something that a freshman college student could do with a little bit of direction," and that substituting chaotropes or detergents is "just a standard methodology" comports with our independent understanding of the art of record. *See* Ex. 2020, 191:10–17, 338:15–20, 487:15–22.

Patent Owner also appears to argue that the NaOAc (sodium acetate) and LiCl (lithium chloride) are essential ingredients for the preservation of DNA in Birnboim's Example 3, that are not recited in the claimed compositions. AmPOR 28–29. Patent Owner does not explain adequately why these components might be essential, nor what they might be essential for. We note that, as compared to Birnboim's Example 3 Formulation 1, Formulation 2 "stabilizes DNA for longer periods of time." Ex. 1003 ¶ 115. Insofar as this embodiment has more NaOAc but entirely omits LiCl, we understand that LiCl is not an essential ingredient. We further note that Koller discloses "nucleic acid releasing compositions" comprising "a

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Patent Owner's formulation experiments in Exhibit 2019 employ guanidine *thiocyanate* but do not attempt the substitution of guanidine *hydrochloride*, for the 0.67 M urea used in Birboim's Example 3.

chaotropic agent [e.g., guanidine hydrochloride, guanidinium isothiocyanate and urea], salt, detergent, and releasing agent." Koller explains that "[t]he type of salt included in the nucleic acid releasing composition is not critical . . . . however, optimum results are obtained with either sodium chloride or sodium acetate," thus indicating that sodium acetate is also not an essential ingredient. Ex. 1016, 6:29–9:2. Taken together, we further infer that the ordinarily skilled artisan knew how to vary the concentrations of stock solution components such as NaOAc and LiCl to obtain desired results.

Although Patent Owner argues that the parties' experts propose competing hypotheses of why Birnboim included LiCl and NaOAc (AmPOR 28–29 (citing Ex. 2020, 201:1–2, 201:21–203:2; Ex. 2001 ¶ 39), these compounds were frequently used in the art—often in the context of promoting nucleic acid precipitation from aqueous samples (*see* Ex. 1013 section 4.3.1 ("separation of RNA from DNA and other impurities by selective precipitation using [2M and 8M] LiCl"), section 4.5.2 (0,15 M LiCl as a wash buffer component) (precipitating "RNA by adjusting the salt concentration to 0.3M sodium acetate"); Ex. 1004, 192 (use of NaOAc to wash/precipitate nucleic acids); Ex. 1009, 1:66–68 (same); Ex. 1018, 15:55–67 (discussing commercial RNA extraction kits comprising LiCl in combination with guanidine or urea). In any event, to the extent LiCl and/or NaOAc have functions beyond the precipitation of nucleic acids, independent claim 1 is drafted in "comprising" format, and, thus, does not exclude compounds in addition to those expressly recited.

3) "*kills pathogens*"

Patent Owner contends that Ground 1 fails because Birnboim does not teach or suggest the "kills pathogens" limitation under its proposed

construction of the term. AmPOR 24–27; Sur-reply 13–15. But as discussed above, we do not apply Patent Owner's proposed construction, and instead define "kills pathogens" as requiring that at least some viral or vegetative bacterial pathogens in a sample are killed or inactivated. *See* Section II.C.4, above. For the reasons set forth below, and in Petitioner's briefing, we find that Birnboim satisfies the "kills pathogens" limitation under our construction of the term. *See* Pet. 30–34, Reply 10–11.

As set forth in our Decision on Institution:

> Birnboim expressly teaches the isolation of nucleic acids from bacteria and viruses. *See* Ex. 1003 ¶¶ 18, 22, 27. The reference does not appear to suggest that such isolation is non-destructive, [and] we presume that at least some of these potential pathogens are "killed" in the extraction process according to the ordinary meaning of the term.

DI 24. Accordingly, Birnboim's instruction to isolate nucleic acid "from a bacterium or a virus that is residing in the buccal, nasal, or respiratory passages of the subject," necessarily "kills pathogens." *See* Ex. 1003 ¶ 27. Consistent with our interpretation, Birnboim further discloses that the disclosed compositions may be "bactericidal" and, thus, capable of killing bacteria.[28] Ex. 1003 ¶ 21; Ex. 2001 ¶ 22 (Dr. DeFilippi distinguishing Birnboim's use of "bacteriostatic" and "bactericidal" wherein, "the word 'bactericidal' itself . . . 'does not teach the killing of anything but bacteria.'").

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[28] For the purpose of our Decision, we need not address whether Birnboim's teaching that its compositions are "bacteriostatic" sufficiently inactivates bacteria as to independently satisfy the "kills pathogens" limitation. *See* Ex. 1003 ¶ 21.

Although we find the "kills pathogens" limitation satisfied within the four corners Birnboim, our determination is supported by additional evidence of record. First, we find that the parties' experimental evidence demonstrates persuasively that the stock solutions disclosed in Birnboim Example 3 (Formulation 1 and Formulation 2) kill pathogens. In this respect, Petitioner submitted evidence that both formulations killed pathogenic bacteria and viruses. *See, e.g.*, Ex. 1068, 10, 16–17 (elimination of *Bacillus subtilis* vegetative cells and *Eschericia coli*), 32–34 (elimination of H1N1 Influenza A virus); Ex. 1071 ¶¶ 7–13. [redacted] Ex. 1202–1204; Ex. 1071 ¶¶ 15–23; Ex. 1069, 272:13–173:7.[29]

Patent Owner, however, argues that Birnboim's Formulation 1 and Formulation 2 do not satisfy the "kills pathogens" limitation because MS2 virus and *B. subtilis* were not killed or inactivated by Birnboim's compositions under its test conditions. Sur-reply 14–15 (citing Ex. 2019; Ex. 1068, 15 (Table I-5); Ex. 2032, 95:3–7, 82:1–83:7, 121:2–11; Ex. 1068, 8); Ex. 1068, 48. We do not find these arguments persuasive because our construction does not require that every pathogen in a sample is killed. *See* Section II.C.4, above. Moreover, MS2 is a bacteriophage, which does not appear among the types of pathogens contemplated in the Specification. *See*

[29] Although Patent Owner argues that "Petitioner's testing of *B. subtilis* was flawed as revealed by the fact that the positive control (without Bex3 solution) saw a significant decrease in *B. subtilis*," Patent Owner does not present expert testimony or other persuasive evidence that we should discount these experiments. *See* Sur-reply 14, n.4 (citing Ex. 1068, 15 (Table I-5); Ex. 2032, 95:3–7, 82:1–83:7).

Ex. 2019, 1; Ex. 1001, 18:37–57. With respect to the difference between the parties' results in testing *B. subtilis*, Patent Owner indicates that its testing included inactivation-resistant spores, whereas Petitioner's results were based on vegetative cells. *See* Sur-reply 14, n.4. Insofar as our construction of "killing pathogens" does not encompass the killing of spores, Patent Owner's results are less informative. *See* Section II.C.4, above.

Further underscoring our determination that Birnboim's formulations satisfy the functional limitations of the challenged claims, we note Patent Owner's admission before the district court that, in the context of the '256 patent that:

> It is common knowledge to one skilled in the art that an aqueous composition that comprises a) one or more chaotropes; b) one or more detergents and/or surfactants; c) one or more reducing agents; d) one or more chelators; and e) one or more buffers [all components of the stock solution in Birnboim's Example 3] serves the purpose of denaturing proteins, inactivating nucleases, killing pathogens, and not degrading nucleic acid of a sample suspected of containing pathogens when the sample is contacted with the composition.

Ex. 1007 ¶ 17. As discussed in our Institution Decision,

> we infer that the above reference to the "common knowledge [of] one skilled in the art" encompasses the knowledge of one of ordinary skill in the art as of the filing date of the '256 patent. *See* Ex. 1007 ¶¶ 14, 266. As such, we are hard pressed to credit Patent Owner's arguments that Birnboim alone, or in combination with other asserted references, fails to teach or suggest a "stock solution, [that] when combined with a biological sample suspected of containing a pathogen, denatures proteins, inactivates nucleases, and kills pathogens all without degrading nucleic acids of the sample," as set forth in element 1[j].

DI 29–30; *see also* Pet. 34 n.4 (arguing that Patent Owner's statement before the district court is an admission that "Birnboim's stock solutions having these reagents perform the functions recited in claim 1 of the '256 patent"). And although we invited the parties to explore this issue at trial, Patent Owner merely reiterates the arguments it made in its Preliminary Response, which we rejected. *See id.* 30; Prelim. Resp. 33, n.5; Prelim Sur-reply 3–4; AmPOR 30–31. Our interpretation of Patent Owner's statement before the district court as an admission is, therefore, unchanged.

Finally, Patent Owner appears to argue that even if the formulations of Birnboim's Example 3 were shown to kill pathogens, Petitioner has not shown that the compositions of claims 2, 4, and 5 would necessarily do so. *See* Sur-reply 15. We do not agree with this argument. As discussed above, the recited compounds and their uses were well known in the art; Patent Owner fails to demonstrate that one of ordinary skill in the art would not know how to substitute the claimed components for those of Birnboim's Example 3 with a reasonable expectation of success. *See* Section II.E.2, above.

13) "*inactivates nucleases*" and "*without degrading nucleic acids of the sample*"

Patent Owner contends that Ground 1 fails because Birnboim does not teach or suggest the "inactivates nucleases" limitation under its proposed construction, which would require that all DNases *and* RNases in a sample are inactivated, thus protecting DNA and RNA in the sample from degradation. AmPOR 29–31; Sur-reply 9–13. Patent Owner relatedly contends that Birnboim fails to teach or suggest "without degrading nucleic acids of the sample" limitation under its proposed construction, which would

further limit the degradation of all RNA and DNA in a sample to 1–2%. AmPOR 27–29; Sur-reply 9–13.

But as discussed above, we do not apply Patent Owner's proposed constructions, and instead define 1) "inactivates nucleases" as requiring that at least one of RNase or DNase in a sample is substantially inactivated; and 2) "without degrading nucleic acids of the sample" as requiring that the sample contains sufficient RNA or DNA for analysis using nucleic acid detection methodologies known to those of ordinary skill in the art as of the time of the invention. *See* Sections II.C.5–6, above. For the reasons set forth below, and in Petitioner's briefing, we find that Birnboim satisfies both contested limitations (collectively, the "nucleic acid limitations") under our construction of the terms. *See* Pet. 30–34; Reply 11–15.

As an initial matter, we find sufficient support for the nucleic acid limitations within the four corners of the Birnboim reference. Birnboim is directed to isolating nucleic acids from a biological sample and stabilizing the isolated DNA or RNA for future analysis. *See* generally, Section II.D.1, above; Ex. 1003 ¶¶ 11, 22, 27, 64, 114–122. Birnboim defines "stable" as meaning "that at least about 50% of the initial amount of high molecular weight nucleic acid (DNA, RNA, mRNA, or viral RNA) contained in a sample is still present after storing the sample at ambient temperature." *Id.* ¶ 45. Although Birnboim puts no upper limit on the amount of nucleic acid preserved, we conclude that "at least about 50% of the initial amount" would contain sufficient RNA or DNA for analysis using nucleic acid detection methodologies known to those of ordinary skill in the art as of the time of the invention as required under our construction. *See, e.g., id.* ¶¶ 118–122 (Real Time PCR using DNA extracted from saliva).

Although not necessary under our construction, Birnboim also demonstrates the preservation of high molecular weight DNA (and thus the inactivation of DNases) using the method of Example 3. In particular, Birnboim subjects isolated DNA to agarose gel electrophoresis and ethidium bromide staining, which reveals "the characteristic band of chromosomal DNA present in all samples." *Id*. ¶ 117, Fig. 1.

Also not necessary under our construction, Patent Owner submits evidence that Birnboim's Example 3 formulations did not significantly inactivate RNases. *See* AmPOR 27; Ex. 2019, 11; Ex. 2033 ¶¶ 18, 26.[30] As an initial matter, Petitioner raises a serious concern regarding the amount of RNase Patent Owner added to its test samples, and reasonably suggests that Patent Owner's testing is not probative of real-world efficacy. *See* Tr. 31:22–32:11, 108:13–17; Ex. 1071 ¶ 35 (Dr. Taylor estimating that PO's testing employed 30,000–70,00-fold more RNase than in Birnboim's saliva samples); Reply 9; Sur-reply 12 (Patent Owners' admission that "inactivation [of RNase] turns on the number of RNA molecules" in a

[30] Patent Owner revisits its pre-institution assertion that, in an unrelated proceeding, Petitioner admitted that Birnboim is not enabled for preserving RNA (AmPOR 27 (citing Ex. 2013))—a contention we addressed in our Institution Decision (DI 35, n.17 (referencing Ex. 2013)). Although Petitioner argues that the statements Patent Owner relies on were "made by the ***assignee*** of the Birnboim reference," it arguably adopted these statements to support an argument that patents having the same specification as Birnboim were prosecuted in bad faith. *See* Reply 14; Ex. 2013 ¶¶ 75, 85, 122, 123, 131, 133, 134, 155; Ex. 2037 ¶¶ 8–12; Tr. 117:21–118:20. We need not decide whether the statements Patent Owner cites should be attributed to Petitioner because any such admissions would be more than balanced by our own analysis showing that Birnboim disclosed and enabled the inactivation of RNase and the preservation of RNA.

sample). Accordingly, Patent Owner's results on the inhibition of RNase activity have limited probative value.

Contrary to Patent Owner's limited test data, we find that one of ordinary skill in the art would recognize that Birnboim, taken as a whole, disclosed and enabled the inactivation of RNase and the preservation of RNA. As noted in our Decision on Institution,

> Birnboim further teaches "inclusion of an inhibitor of ribonuclease in the composition of the invention . . . when the nucleic acid to be preserved is RNA, desirably mRNA, or when the nucleic acid to be preserved is from a virus or a bacterium." *Id.* ¶22; *see also id.* ¶68 (stating that in addition to the use of various denaturing agents, "reagents such as heparin, heparan sulfate, or oligo(vinylsulfonic acid) . . . are known to inhibit the action of deoxynucleases and /or ribonucleases").

DI 13.

We further note that in addition to the urea used in Example 3, Birnboim discloses the use of other chaotropic agents, including guanidinium chloride and guanidinium thiocyanate, which were well known in the art for isolating RNA. Ex. 1003, ¶ 68; *see, e.g.*, Ex. 1004, 189; Ex. 1015, 5249. Indeed Farrell, teaches that of these two guanidinium compounds, "[guanidinium thiocyanate] is a stronger protein denaturant than guanidine hydrochloride and is the denaturant of choice for the preparation of RNA from sources enriched in RNase activity, especially pancreatic tissue (Chirgwin *et al.,* (1979))." Ex. 1026, 59. As such, the art provides ample rationale for substituting the urea in Birmboim's Example 3 formulations with a guanidinium salt in order to better preserve RNA.

Moreover, as brought to our attention by Patent Owner at oral argument, Birnboim discloses a multi-day/multi-temperature stability study wherein "[a]fter incubation, approximately 40 *uL*, of mixture was digested

briefly with ribonuclease to remove the majority of the RNA present in the sample, then applied to the indicated lane of a 0.8% agarose gel." Ex. 1003, ¶¶ 123–124 (Example 7); Tr. 78:15–17 (Patent Owner's assertion that "Birnboim requires the addition of RNase to further digest RNA that may interfere with the gel."), 88:6–89:1.[31] As such, we conclude that Birnboim discloses the inactivation of RNases and the preservation of RNA to the extent that the authors took steps to eliminate RNA from a sample in order to visualize the preserved DNA.

In view of the above, we conclude that one of ordinary skill in the art would understand Birnboim to disclose the "inactivates nucleases" and "without degrading nucleic acids of the sample" limitations of the challenged claims. The Federal Circuit has held that combining teachings in a single prior art reference "does not require a leap of inventiveness." *Bos. Sci. Scimed, Inc. v. Cordis Corp.*, 554 F.3d 982, 991 (Fed. Cir. 2009). This is especially true when the claimed composition is used for the identical purpose taught by the prior art. *Id.* Considering the record as a whole, Petitioner has shown by a preponderance of the evidence that claims 1–10,

[31] Absent evidence, Patent Owner's counsel appeared to take the position that, at least with respect to RNA, "without degrading nucleic acids in the sample" required the preservation of intact molecules, because "[i]f the molecule is cut in half, it's not preserved and you can't use the RNA for any sort of nucleic acid test or assay." Tr. 80:16–81:3. We take judicial notice that the detection of nucleic acids by PCR, for example, does not require an intact RNA or DNA molecule. *See* Tr. 81:3–82:1; Ex. 1008 ¶ 90 (designing PCR primers to amplify 373 base pair fragment of bacterial genome); Ex. 1010 (indicating that RT-PCR was well-known in the art); Ex. 3009 (Mullis KB. "*The unusual origin of the polymerase chain reaction*," 264(4) Sci Am. 56-61 (1990).

13, and 15–19 are unpatentable for obviousness in view of Birnboim, Mori, and Farrell.

F. Ground 2: Obviousness in View of Birnboim, Mori, Farrell, and further in view of Das

As to Ground 2, Petitioner challenges claim 11 (as it depends from claim 1) as unpatentable for obviousness in view of Birnboim, Mori, Farrell, and Das. Pet. 55–59; Reply 17–18. Petitioner provides a detailed analysis of where each claim element is found in the cited references and discusses why one of ordinary skill in the art would have been motivated to combine those elements with a reasonable expectation of success. *See, e.g.,* Pet. 56–59. Patent Owner opposes. AmPOR 37–40; Sur-reply 17.

Depending from claim 1, claim 11 recites that the pathogen is "hepatitis virus, papillomavirus, HIV, biological agent of SARS, corona virus, rotavirus, Influenza virus, Ebola virus, methicillin-resistant *Staphylococcus*, or *M. tuberculosis*." Focusing on Das's work on *M. tuberculosis* (*see* Section II.D.4, above)*,* Petitioner argues that

> Birnboim discloses that its solution can be used to preserve nucleic acids extracted from bacteria and viruses. Ex. 1003, ¶[0027]. Das discloses a composition for extracting and preserving nucleic acid from tuberculosis-causing mycobacteria. Ex. 1008, ¶¶[0037]-[0039]. Given the references teach virtually the same solutions for the same use, a POSA would have been motivated to use Birnboim's solution in view of Das for the specific purpose of stabilizing and preserving nucleic acid in a sample suspected of containing tuberculosis-causing pathogens. Ex. 1002, ¶205.

Pet. 56; *see also id.* 57 (comparing the composition and ranges disclosed in Das to those of challenged claim 1); Reply 17–18. Ex. 1008 ¶¶ 203, 206–207; *see also* Reply RMTA 6–7 (reviewing variations Das and other "Chirgwin-type" formulations known in the art).

Patent Owner argues that one of ordinary skill in the art would have no reason to combine or modify Birnboim in light of Das for the extraction of *M. tuberculosis.* AmPOR 38–39 (citations omitted); Sur-reply 17. In particular, Patent Owner argues that, unlike Birnboim, Das requires "heating the specimen" and "a clarification step," e.g., "treating clinical specimens, like sputum, with a decontamination mix such as a mild alkali and mucolytic agent followed by centrifugation to obtain a cleaner nucleic acid preparation" and, thus, "a POSA would not be motivated to overlay additional steps and laboratory environment of Das onto Birnboim." AmPOR 38–40; *see* Tr. 76:14–22.

We do not agree with Patent Owner's arguments. As discussed in Petitioner's Sur-reply "Das does not require heating," but merely states that heating renders its composition more effective against "the toughest cells and objects like spores and baculovirus polyhedra." Sur-reply 19–20; Ex. 1008 ¶ 38; Tr. 127:18–129:6. And given that our construction of "kills pathogens" only requires that some pathogens in a sample are killed, we do not agree with Patent Owner that Das fails to "kill pathogens" absent heating. *See* Section II.C.2, above.

Das further teaches that "clean DNA is of utmost importance for success of a PCR based assay" and that a clarification step may provide "[a] cleaner nucleic acid preparation," particularly for a "dirtier specimen like sputum." Ex. 1008 ¶ 38. As such, we do not read Das as requiring a clarification step, nor does Das even address a clarification step for detection/visualization techniques such as the agarose/ethidium bromide gel electrophoresis of Birnboim Example 4 that do not involve PCR. *See* Ex. 1003 ¶ 117, Fig. 1. Moreover, even if Das did require heating and/or

clarification, nothing in claim 11 prohibits these steps, and the increased "cleaner DNA preparation with improved yield" taught by Das provides ample motivation to combine the teachings of Das and Birnboim, as does the possibility of using the lysis buffer for the extraction of *M. tuberculosis* DNA.

In view of the above, Petitioner has shown by a preponderance of the evidence that claim 11 is unpatentable for obviousness in view of Birnboim, Mori, Farrell, and Das.

G. Ground 3: Obviousness in View of Birnboim, Mori, Farrell, and further in view of Helftenbein

For Ground 3, Petitioner challenges dependent claims 12 and 20 as unpatentable for obviousness in view of Birnboim, Mori, Farrell, and Helftenbein. Pet. 59–61; Reply 18–20. Petitioner provides a detailed analysis of where each claim element is found in the cited references and discusses why one of ordinary skill in the art would have had reason to combine those elements with a reasonable expectation of success. *See, e.g.,* Pet. 56–59. Patent Owner opposes. AmPOR 42–43; Sur-reply 18–19.

Claim 12 is directed to "[t]he stock solution of claim 1, further comprising an internal positive control." Claim 20 is direct to a diagnostic kit, "wherein the stock solution is contained in one vessel and further comprising a separate vessel containing one or more additional reagents, buffers, or compounds." Because Patent Owner does not expressly address the elements specific to claim 20, we focus our analysis on claim 12.

To the extent we understand its position, Patent Owner appears to argue that Helftenbein does not provide motivation to modify Birnboim's stock solution to include an internal positive control because Helftenbein's

Examples show the addition of control MS2-RNA to a biological sample (serum) immediately before mixing with the stock solution, rather than to the stock solution, per se. *See* AmPOR 42–43; Ex. 2033 ¶¶ 49–52. Patent Owner further argues that "the MS2-RNA in Helftenbein's Examples 5-8 is not part of Helftenbein's serum and thus does not operate as an internal control." Sur-reply 17 (citing Ex. 2033 ¶ 51).

According to Petitioner,

> Birnboim discloses that Examples 5 and 6 use a highly purified sample of DNA as a control. Ex. 1003, ¶¶[0119], [0121]. Helftenbein discloses use of naked carrier DNA or RNA as an internal positive control in its compositions. Ex. 1019, 2:60-63. ("The nucleic acid-stabilizing substance may have added thereto an **internal standard**. This permits the **control** of the whole method from the moment of sampling up to the detection of nucleic acids.")."

Pet. 59–60.

Helftenbein also discloses Examples wherein, "250 *u*l serum was spiked with 10 *u*l MS2-RNA (0.8 *ug/ul* of Roche) and incubated at room temperature. Immediately after the addition of RNA, after 2 min to 50 min, the natural RNA degradation in Serum was stopped by adding 250 ul Stabilizing Solution." Ex. 1019, 6:52–56; *see* Section II.D.5, above. Relying on the testimony of Dr. Taylor, Petitioner states that, "[i]n view of Helftenbein, a POSA would have been motivated to use naked carrier DNA or RNA as an internal positive control in Birnboim's stock solutions with a reasonable expectation of success, as disclosed in Helftenbein." Pet. 60 (citing Ex. 1002 ¶¶ 213–214).

On the record before us, Petitioner has the better position. Accordingly, and in view of the record as a whole, we find that Petitioner has shown by a preponderance of the evidence that claims 12 and 20 are

unpatentable for obviousness in view of Birnboim, Mori, Farrell, and Helftenbein.

H. Ground 4: Obviousness in View of Birnboim, Mori, Farrell, and further in view of Heineman

For Ground 4, Petitioner challenges dependent claim 14 as unpatentable for obviousness in view of Birnboim, Mori, Farrell, and Heineman. Pet. 61–63; Reply 18. Petitioner provides a detailed analysis of where each claim element is found in the cited references and discusses why one of ordinary skill in the art would have has reason to combine those elements with a reasonable expectation of success. *See, e.g.,* Pet. 56–59.

Claim 14 is drawn to "[t]he stock solution of claim 1, further comprising betadine, bovine serum albumin, an osmolyte or a combination thereof." According to Petitioner, "Heineman discloses that its solution includes the same reagents as Birnboim and within the same concentration ranges as recited in claim 1. Pet. 62 (citing Ex. 1033 ¶¶ 12, 22, 24, 25; Ex. 1002 ¶ 221). With respect to the specific limitations of dependent claim 14, Petitioner further asserts that one of ordinary skill in the art "would understand that adding a blocking agent, such as bovine serum albumin, can be desirable to prevent non-specific binding of antibodies, as Heineman expressly discloses." Pet. 62 (citing Ex. 1033 ¶ 27, Ex. 1002 ¶ 233).

Patent Owner opposes, arguing that Petitioner has failed to establish a motivation to modify Birnboim to include Heineman's blocking agents. AmPOR 42–43; Sur-reply 18. Patent Owner argues, for example, that "the purpose of Heineman's blocking agents is to block and prevent non-specific bonding of antibodies," but "Petitioner has not shown why a POSA would

find such blocking advantageous in the context of Birnboim." AmPOR 42–43 (citing Ex. 1002 ¶ 222).

Considering the evidence of record and the reasoning set forth in the Petition, we agree with Patent Owner that Petitioner has not met its burden of proving unpatentability of claim 14 by a preponderance of the evidence. We, nevertheless, find for Petitioner for the reasons set forth in our Decision on Sanctions (*see* Paper 107).

III. REVISED CONTINGENT MOTION TO AMEND

Having determined that Petitioner has shown by a preponderance of the evidence that original claims 1–13 and 15–20 of the '256 patent are unpatentable on the merits, we proceed to address Patent Owner's Revised Contingent Motion to Amend. Patent Owner proposes substitute claims 21–40 to replace original claims 1–20. RMTA 1, App'x A. Specifically, Patent Owner proposes substitute claims 21 and 35 to replace original claims 1 and 15, respectively. *Id.* at 2. According to Patent Owner, "[a]ll other amendments update the dependencies of certain dependent claims (or make minor updates to the claim language) to depend from a corresponding substitute claim." *Id.* at 3.

For the reasons below, we decline to address proposed substitute claim 34 on the merits, and find Petitioner shows by a preponderance of the evidence that proposed substitute claims 21–33 and 35–40 are unpatentable under 35 U.S.C. § 103(a). In any event, because we impose adverse judgment as sanctions against Patent Owner, we deny Patent Owner's Revised Contingent Motion to Amend in its entirety.

A. Proposed Replacement Claim 34

On the record before us, Petitioner has not shown by a preponderance of the evidence that claim 14 is unpatentable. *See* section II.H, above. Patent Owner intends proposed substitute claim 34 as a direct replacement for claim 14. *See* RMTA App'x A Because Patent Owner's submission of claim 34 is contingent a finding that claim 14 is unpatentable, we need not address the patentability of proposed claim 34. *See id.* at 1, 6,

Moreover, because Petitioner's arguments with respect to claim 34 are, at best, the same as those regarding claim 14, they would likewise fail on this record to establish motivation to modify Birnboim to include Heineman's blocking solutions. *See* Opp. RMTA 15–16 (stating that "[a]s set forth in Ground 4, Heineman discloses using bovine serum albumin (BSA as a blocking agent in the claimed stock solution").

B. Principles of Law Concerning A Motion to Amend

In an *inter partes* review, amended claims are not added to a patent as of right, but rather must be proposed as a part of a motion to amend. 35 U.S.C. § 316(d). Ordinarily, the petitioner "bears the burden of persuasion to show, by a preponderance of the evidence, that any proposed substitute claims are unpatentable." 37 C.F.R. § 42.121(d)(2); *Lectrosonics, Inc. v. Zaxcom, Inc.*, IPR2018-01129, Paper 15, 3–4 (PTAB Feb. 25, 2019) (precedential); *Bosch Auto. Serv. Sols. LLC v. Matal*, 878 F.3d 1027, 1040 (Fed. Cir. 2017).

But before considering the patentability of the substitute claims, we first must determine whether the Revised MTA meets the statutory and regulatory requirements set forth in 35 U.S.C. § 316(d) and 37 C.F.R. § 42.121. Patent Owner bears the burden of persuasion to show that: (1) the

amendment proposes a reasonable number of substitute claims; (2) the amendment responds to a ground of unpatentability involved in the trial; (3) the amendment does not seek to enlarge the scope of the claims of the patent or introduce new subject matter; and (4) the original disclosure sets forth written description support for each proposed claim. *Id.*; 35 U.S.C. § 316(d); 37 C.F.R. § 42.121(d)(1).

G. Statutory and Regulatory Requirements

A motion to amend must "propose a reasonable number of substitute claims." 35 U.S.C. § 316(d)(1)(B); *see* 37 C.F.R. § 42.121(a)(3) ("A motion to amend may cancel a challenged claim or propose a reasonable number of substitute claims."). "There is a rebuttable presumption that a reasonable number of substitute claims per challenged claim is one (1) substitute claim." *Lectrosonics*, Paper 15 at 4; *see* 37 C.F.R. § 42.221(a)(3). Patent Owner proposes no more than one substitute claim for each challenged claim. RMTA 2; *see id.* at Appendix A. Petitioner does not argue otherwise. We determine that Patent Owner proposes a reasonable number of substitute claims.

"A motion to amend may be denied where . . . [t]he amendment does not respond to a ground of unpatentability involved in the trial." 37 C.F.R. § 42.121(a)(2)(i). Patent Owner asserts that none of the references cited by Petitioner teaches or suggests the limitations added by the proposed amendments, and that the amended claims are patentable over the prior art of record. RMTA 7–14. Petitioner does not dispute that Patent Owner's amendment responds to a ground of unpatentability in this trial. We determine that the amended language in the proposed substitute claims is responsive to a ground of unpatentability involved in this trial.

An amendment may not enlarge the scope of the claims of the patent or introduce new matter. 35 U.S.C. § 316(d)(3); 37 C.F.R. §§ 42.121(b)(1), 42.121(b)(2). Patent Owner argues that proposed amendments "are all narrowing amendments," and, as a result, "[n]o substitute claim enlarges the scope of the claim that it replaces." RMTA 2. Petitioner does not contest Patent Owner's arguments on this point. We determine that each proposed substitute claim includes narrowing limitations and does not enlarge the scope of the corresponding original claim. *See* RMTA, App'x A.

Patent Owner also is required to show written description support in the original disclosure for each amended claim. 37 C.F.R. § 42.121(b). The '256 patent issued from Patent Application No. 14/969,339 (Ex. 2025, "the '339 application"). Ex. 1001, code 21. Pointing to paragraphs of the '339 application, Patent Owner argues that "the proposed substitute claims are fully supported." RMTA 4–7.

Petitioner argues that "[i]f the proposed limitation 'rendered entirely non-pathogenic and safe for human handling' requires the claimed composition to clear every sample of every type of pathogenic agent," the proposed amended claims would lack written description support, in addition to be indefinite and non-operative. Opp. RMTA 16–18; Sur-reply RMTA 9–12. We do not address this argument because, as explained below, we do not interpret the proposed limitation to require inactivation of every type of pathogen. *See infra* Section III.C.1.

Petitioner also argues that if "[t]o the extent PO argues claim 35 excludes additional processing steps between the "one-step" and detecting nucleic acids, the claims would not satisfy the written description. . .

requirement."[32] Opp. RMTA 21. We do not address this argument either because, as explained below, we do not interpret the "in one step" limitation to require the nucleic acids be detectable or detected by PCR without purification or extraction. *See infra* Section III.G.3.

After reviewing Patent Owner's identification of support for its proposed amendments (*see* RMTA 3–7), we are satisfied that, under proper claim construction (*see infra* Section II.C), the '339 application provides sufficient written-description support for proposed substitute claims 1–13 and 15–20

In sum, the RMTA meets the statutory and regulatory requirements set forth in 35 U.S.C. § 316(d) and 37 C.F.R. § 42.121.

C. Proposed Substitute Claim Elements

Patent Owner proposes substitute claim 21 to replace original claim 1, and substitute claim 35 to replace original claim 15. RMTA 2–3. Patent Owner asserts that "[a]ll other amendments update the dependencies of certain dependent claims to depend from a corresponding substitute claim." *Id.* at 3. The proposed substitute claims are substantially the same as the corresponding original claims but for the addition of three new limitations which, for convenience, we refer to as the "entirely non-pathogenic," "without further separation," "endogenous and exogenous nucleases" limitations, and "one step". *See id.* at 2–3, App'x A. We address these new limitations below and refer to Section II for all other elements.

[32] Petitioner also argues that proposed substitute claim 35 is not enabled. Opp. RMTA 21. But a proper enablement analysis requires examination of various factors under *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) and Petitioner has not done so.

1) Entirely Non-Pathogenic (claim 21)

Proposed substitute claim 21 requires that "the stock solution, when combined with a biological sample suspected of containing a pathogen, denatures proteins, inactivates nucleases, and kills pathogens <u>thereby rendering the biological sample entirely non-pathogenic and safe for human handling</u>." RMTA, App'x A. Patent Owner asserts that the '339 application, from which the '256 patent issued, provides written description support for this additional limitation. Revised MTA 5 (citing Ex. 2025, 12:4–12).

The relied-upon passage states:

> It is also desirable in the practice of the present methods that when one or more microbes, viruses, and/or pathogens are present in, on, or about the sample when collected, such microbes, viruses, and/or pathogens will be killed or sufficiently inactivated by one or more components of the composition to facilitate safe handling of the sample by the practitioner. Preferably, one or more components of the disclosed composition are effective to render a pathogenic sample substantially, or preferably entirely, non-pathogenic without the need for adding additional components to the composition. However, in certain applications, it may also be desirable to include one or more additional anti-microbial, anti-viral, or anti-fungal agents to the compositions to render them substantially non-pathogenic, and thus, same for handling by the practitioner.

Ex. 2025, 12:4–12. Neither the above paragraph nor the Revised MTA, however, explain what "entirely non-pathogenic" means. But at Oral Hearing, Patent Owner's counsel offered that the term encompasses something more that "substantially nonpathogenic," proposing that we construe the term as meaning "zero pathogenic activity," such that the sample "could not infect someone, rendering it safe for handling." Tr. 148:3–20.

We look to the '256 patent to interpret the limitations added in the Revised MTA. In Example 8, the Specification discloses "Killing of MRSA (ATCC33592) in PrimeStore™ Solution."[33] Ex. 1001, 26:59–60. According to this example, "the effectiveness of the PrimeStore™ Solution (ver. 2.2) in killing a potential bacterial contaminant," MRSA strain ATCC33592, is demonstrated when "the bacteria suspended in PrimeStore™ Solution and plated onto blood agar plates had no detectable colonies." *Id.* at 27:65–67, *see also id.* at 29:16–19 (same).

Similarly, Example 9 demonstrates that "the disclosed composition could quickly kill or inactiv[at]e microorganisms in [a chicken cloacal] sample." *Id.* at 29:35–43. According to the '256 patent, this result is illustrated is Figure 7A, which shows chicken cloacal samples "immersed in PrimeStore™ Solution (top row) or water (bottom row) and subsequently plated on blood agar plates." *Id.* at 12:36–41. Although the image quality is not ideal, it appears the plates with samples treated with the disclosed composition have no detectable colonies. *See id.* at Fig. 7A.

Thus, in view of the disclosures of the '256 patent, we conclude that a sample is rendered "entirely non-pathogenic" when the treated sample forms no detectable colonies or plaques on an applicable plate assay.

That, however, does not completely resolve the issue because the parties disagree over whether rendering a sample "entirely non-pathogenic" requires the composition to kill or inactivate all types of pathogens disclosed in the '256 patent. As noted in section II.C.4, we defined the scope of

[33] According to the '256 patent, the formulations of the compositions disclosed therein are alternatively referred to as "PrimeStore™ Solution," versions 1 and 2. Ex. 1001, 21:28–31, 51–54.

"pathogens" as disclosed in the '256 patent as comprising fungi, viruses, and vegetative bacteria, exclusive of spores.

Patent Owner argues that the prior art does not disclose or render obvious the "entirely non-pathogenic" limitation. *See generally* RMTA 9–12; Reply RMTA 3–5. Petitioner, however, presents substantial argument and evidence to the contrary. Opp. RMTA 6 (*citing* Ex. 1008 ¶ 38 ("The modified lysis buffer . . . helps to inactivate all mycobacteria present in a clinical specimen, lyse tough mycobacterial cell[s] and denature and remove proteins . . . and also ***ensure safety for the operator***."); Ex. 1083, 50 ("The strong chaotropic properties of GTC (Chirgwin et al., 1979) … ***renders the sample non-infectious and safe to handle***."); Ex. 1082 ¶¶ 18–38); Sur-reply RMTA, 3–5 (*citing, e.g.*, Ex. 1083, 50 (Chirgwin's teaching that guanidinium thiocyanate "renders the sample non-infections and safe to handle"); Ex. 1008 ¶ 38; Ex. 1016, 7:19–23).[34]

Petitioner further argues that data from tests conducted by Assured Bio Labs (ABL) for Patent Owner [redacted] Opp. RMTA 5 (citing e.g., Exs. 1201–1204; Ex. 1069, 272:13–273:7; Ex. 1082 ¶¶ 16–17). This, Petitioner contends, demonstrate that the tested samples were rendered "entirely non-pathogenic." *Id.*; *see also id.* 6 (further relying on Das (Ex. 1008 ¶ 38) and Lozano (Ex. 1083, 50) as rendering samples non-infectious and safe to handle).

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[34] Although not necessary to our analysis, Petitioner also argues that construing the claims to inactivate *all* pathogens would render them indefinite, non-operative, and invalid for lack of written description. *See* Opp. RMTA 16–20; Reply RMTA 9–12.

Patent Owner counters that data from the ABL report show Birnboim's composition did not inactivate two [redacted] types of pathogens. RMTA 10–11 (citing Ex. 2019). Thus, Patent Owner asserts, regardless of whether Birnboim's composition kills or biologically inactivates some types of viruses or bacteria, it does not "render[] the sample biologically inactivated and <u>entirely</u> non-pathogenic and safe for human handling." *Id.*

Based on this record, and as explained below, we find and agree with Petitioner's argument. Our conclusion is consistent with proposed substitute claims 31 and 36. Proposed substitute claim 31 recites that "the pathogen is hepatitis virus, papillomavirus, HIV, biological agent of SARS, corona virus, rotavirus, Influenza virus, Ebola virus, methicillin-resistant *Staphylococcus*, or *M. tuberculosis*." Proposed substitute claim 36 more broadly states that "the pathogen comprises bacteria, virus, or a fungus; optionally, wherein the bacteria is tuberculosis or the virus is influenza." These proposed substitute claims demonstrate that a sample may contain a single pathogen, for example, influenza virus, methicillin-resistant *Staphylococcus [aureus]*, or *M. tuberculosis*, the causative agent of tuberculosis. If, after contact by the composition, such a sample forms no detectable plaques (or colonies) on an applicable plate assay, the composition satisfies the requirement of rendering the sample entirely non-pathogenic.

Birnboim's composition satisfies this test. Indeed, as Petitioner points out, and Patent Owner does not dispute, ABL's test data show [redacted]

[redacted]

[35] Opp. RMTA 5 (citing Exs. 1201–1204; Ex. 1069, 272:13–273:7); *see also* Ex. 1069, 245:5–246:16 (Dr. Birkebak at ABL testifying); 247:13–248:21 (similar testimony)). We agree with Petitioner that when a pathogen in a sample is no longer detectable in the sample, the sample is biologically inactivated and rendered entirely non-pathogenic and safe for human handling. *See* Second MTA Opp. 5 (citing Ex. 1082 ¶¶ 16–17).

In sum, Petitioner has shown, by a preponderance of the evidence, that Birnboim explicitly discloses that its compositions inactivate the sample contacted and render the sample "entirely non-pathogenic and safe for human handling" as recited in proposed amended claim 21.

2) Endogenous and Exogenous Nucleases (claim 35)

Proposed substitute claim 35 requires that the composition "inactivates endogenous and exogenous RNases and DNases to prevent degradation of the nucleic acid sequence." Petitioner contends that this element is disclosed in Birnboim and numerous other prior art references. Opp. RMTA 1–5; Reply RMTA 1–3. Patent Owner contends that Birnboim does not disclose inactivating exogenous nucleases. RMTA 13–14. Considering the entirety of art and argument of record, we conclude Petitioner has the better argument.

Birnboim explains that, in the digestive tract, DNases and RNases are found in secretions of the pancreas and cells of the salivary gland and buccal

[35] Unreported validation testing on E. coli by ABL showed Birnboim's composition also inactivated E. coli. *See* Ex. 1069, 236:11–237:15.

mucosa. Ex. 1003 ¶ 68. In addition, according to Birnboim, microorganisms resident in the mouth or from recently ingested foods may contain" DNases and RNases. *Id.* Birnboim states that chelators, including EDTA, and those stronger than EDTA, such as cyclohexane diaminetetraacetate (CDTA) and diethylenetriamine pentaacetic acid (DTPA), inhibit pancreatic DNases. *Id.* ¶¶ 16, 67, 68. In addition, the activity of DNases and RNases "can also be inhibited by denaturing agents that will destroy the complex structures of these enzymes (proteins)." *Id.* ¶ 68. Thus, Birnboim explicitly discloses including denaturing agents, such as urea, SDS, guanidinium chloride, and guanidinium thiocyanate, in "the nucleic acid preserving composition" of its invention. *Id.*

Relying on these disclosures, Dr. Taylor testifies that "Birnboim expressly discloses that its compositions inactivate nucleases that are internal or external to the target cell." Ex. 1082 ¶ 6 (citing Ex. 1003 ¶ 68). Petitioner, citing Dr. Taylor's testimony, argues that "Birnboim discloses the inactivation of endogenous and exogenous DNases." Opp. RMTA 2 (citing Ex. 1003 ¶ 68; Ex. 1082 ¶¶ 5–8).

Patent Owner does not address Dr. Taylor's testimony or Petitioner's argument on this point. Instead, Patent Owner disputes Petitioner's contention that "there is no difference in inactivating an endogenous or exogenous nuclease." RMTA 2; Opp. RMTA Opp. According to Patent Owner, endogenous and exogenous nucleases are not equivalent because "coming from different sources, they may have different rates of activity and susceptibility to inactivation." Reply RMTA 2 (citing Ex. 2042 ¶ 11; Ex. 2044). We address below Patent Owner's reliance on Exhibit 2044 and Dr. DeFilippi's testimony.

As an initial matter, we note that Exhibit 2044, titled "Biofilms: Survival Mechanisms of Clinically Relevant Microorganisms," is a 27-page document. Patent Owner does not direct us any specific disclosure that supports its argument, and absent such guidance, we do not apprehend how this reference supports its position.

With respect to Patent Owner's reliance on its expert's testimony, Dr. DeFilippi states:

> One cannot equate the properties, and thus sensitivity to denaturing conditions, of endogenous and exogenous nucleases, which may include different specific enzymes from different biological sources that may be in different types of biofilms (particularly relevant in the context of a sputum sample) and thus may have different rates of activity and different rates and susceptibility to inactivation (and which may differ depending on the specific method of inactivation at issue).

Ex. 2042 ¶ 11 (citing Ex. 2044, 168). Page 168 of Exhibit 2044—or for that matter, the Exhibit in its entirety—however, does not appear to discuss nucleases. Instead, as Dr. DeFilippi testified, Exhibit 2044 "mostly related to biofilms," and did not make any reference to nucleases.[36] Ex. 1096, 1065:18–1066:6.

More importantly, we find Patent Owner's argument and Dr. DeFilippi's testimony here inconsistent with the position they took elsewhere. For example, in its Sur-reply for the case-in-chief, Patent Owner argued that inactivation of RNases "turns on the number of RN[ase] molecules, not their activity level." Sur-Reply, 12; 2. As Petitioner points

[36] To the extent Dr. DeFilippi emphasizes "different types of biofilms" (Ex. 1096, 1067:2–10; Ex. 2042 ¶ 11), neither he, nor Patent Owner, sufficiently explains the relevance of biofilms to the proposed substitute claims at issue.

out, Patent Owner does not reconcile this argument with its attempt here to distinguish endogenous and exogenous nucleases inactivation, even if the enzymes "may have different rates of activity." *See* Sur-reply RMTA, 1–2.

Similarly, pointing to the claim language "sufficient to denature proteins," Dr. DeFilippi testified: "So I'm denaturing proteins in general. And included in that would be inactivation of the nucleases." Ex. 1064, 525:1–4; *see also id.* 525:17–19 ("We are denaturing proteins, and the result of denaturing proteins would be destroying the activity of enzymes."). Birnboim and other prior art of record, confirms that one of ordinary skill in the art would agree with this testimony, that is, denaturing agents, by destroying protein structures, inactivate nucleases (which are proteins), regardless of their type or source. *See, e.g.*, Ex. 1003 ¶ 68; *see also* Ex. 1015, 5296 ("Since the early steps of the procedure are always carried out in the presence of denaturants, sterile procedures and glassware are unnecessary, but as soon as the RNA is no longer in the presence of guanidine, stringent precautions against adventitious[37] nucleases must be taken."). Thus, Dr. DeFilippi's own testimony that denaturants inactivate nucleases, which is consistent with the express teachings of the prior art, contradicts his opinion that exogenous nucleases may not be inactivated merely because they are from "different biological sources."

[37] Dr. DeFilippi appears to have misunderstood the term "adventitious." *See* Ex. 1096, 985:22–986:1 (testifying that the term "'[A]dventitious' means it takes advantage of the situation"). In fact, the term means "coming from another source and not inherent or innate" and, thus, in the present context, is synonymous with exogenous. *See* https://www.merriam-webster.com/dictionary/adventitious.

Patent Owner emphasizes that, in Example 7, Birnboim added ribonuclease to digest and thereby remove the majority of RNA present in the sample. RMTA 13. According to Patent Owner, this ribonuclease is an exogenous nuclease, and it is "clearly not inactivated." *Id.* Thus, Patent Owner concludes, the "Birnboim composition cannot be said to inactivate both endogenous and exogenous nucleases." *Id.* We disagree.

Example 7 teaches incubating a saliva sample with Birnboim's composition. Ex. 1003 ¶ 124. It is after this incubation that Birnboim added additional ribonuclease to digest RNA. *Id.* The '256 patent, on the other hand, discloses that its compositions "typically at least substantially inactivate, and preferably entirely inactivate, any endogenous or exogenous RNAses or DNAses present *in the sample*." Ex. 1001, 6:20–24 (emphasis added). Thus, the '256 patent does not contemplate inactivating nucleases added to the sample, such as the additional ribonuclease added in Birnboim Example 7, which is unrelated to the biological sample studied.[38] *See Id.* 9:13–24 (disclosing inactivating "exogenous or endogenous nucleases that may be *present in, on, or about the sample itself*") (emphasis added).

[38] Were it otherwise, such that "exogenous nucleases" encompassed additional nucleases added to the sample, the proposed substitute claims reciting inactivating exogenous nucleases would lack written description support. Those claims also would be indefinite because they do not limit the amount of additionally added nucleases. Furthermore, the '256 patent does not teach how to inactivate an overwhelmingly large amount of added nucleases, and thus, does not enable the proposed substitute claims. *See also*, Ex. 1071 ¶ 35 (Dr. Taylor's estimation that PO's testing employed 30,000–70,00-fold more RNase than in Birnboim's saliva samples).

In sum, Petitioner has shown, by a preponderance of the evidence, that compositions taught and suggested by Birnboim "inactivate endogenous and exogenous nucleases," as required by proposed substitute claim 35.

3) Without Further Separation (claim 35)

Proposed substitute claim 35 further requires that, "released nucleic acids are compatible with a nucleic acid test without further separation from the sample." The "without further separation" limitation was first presented in the original MTA. *See* MTA 3, 13–14.

Petitioner argues that Birnboim discloses this additional limitation because, in Example 7, Birnboim discloses contacting a sample with its composition, incubating the treated sample, digesting the sample with ribonuclease to remove RNA, and applying the sample to an agarose gel. OPP. MTA 11 (citing Ex. 1003 ¶ 124). According to Petitioner, the target "DNA is not separated from the sample prior to running the samples on the agarose gel." *Id.*; *see also id.* 13 ("To reduce the time and labor necessary to preliminarily test if the sample includes the target nucleic acid, a POSA would have been motivated to add a nuclease to digest the non-target nucleic acid in the sample (as Birnboim discloses in Example 7), then proceed directly to running the sample on an agarose gel. Ex. 1003 ¶124; Ex. 1071, ¶ 37."). In the Preliminary Guidance, we found Petitioner's argument persuasive. *See* PG 13–14. We explained that Birmboim's addition of ribonuclease to remove (i.e., digest) extraneous RNA does not equate to separation of the sample, as presently excluded by the language of proposed substitute claim 35. *Id.* at 14 ("We do not find that adding a ribonuclease to remove RNA causes separation of the sample.").

In the Revised MTA, Patent Owner does not address Birnboim's Example 7 as it relates to the "no further separation" limitation.[39] In the RMTA Reply, Patent Owner contends "Birnboim's use of RNase in Ex. 7 is a separation step used prior to DNA testing using gel electrophoresis that separates hydrolyzed RNA fragments from the intact DNA." Reply RMTA 5 (citing Ex. 2042 ¶¶ 16, 39–40).

For the reasons set forth below and as argued by Petitioner, Patent Owner's argument is unavailing. *See* Opp. RMTA 6–9; Sur-reply RMTA 5–6. Proposed substitute claim 35 requires first, the lysis of "a portion of cells in the sample to release nucleic acids" and second, that "the released nucleic acids are compatible with a nucleic acid test without further separation *from the sample*." (emphasis added). Claim 35, thus, makes clear that it requires lysis of cells in the sample, and is agnostic as to the amount of nucleic acids released, insofar are the sample contains sufficient nucleic acid for detection. In Birnboim's Example 7, the sample is saliva. Thus, even if we were to agree with Patent Owner that "Birnboim's use of RNase . . . separates hydrolyzed RNA fragments from the intact DNA," such separation would not be "*from the sample*." *See* RMTA 5 (Patent Owner's discussion of "without further separation from the sample" term in proposed substitute claims 78 and 98). We apply essentially the same analysis in rejecting Patent Owner's contention that "Birnboim's use of Proteinase K in Ex. 4 is a separation step." *See* Reply RMTA 5; Sur-reply 5–6.

In considering the "without separation" limitation, we are mindful that proposed substitute claim 35 recites that the DNA detection methodology is

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[39] *But see* RMTA 7 (Patent Owner discussing Example 7 as it relates to "inactivates endogenous and exogenous RNases and DNases").

"PCR amplification" rather than the agarose gel of Birnboim's Example 7. Birnboim, however, repeatedly discloses the use of well-known PCR techniques. *See, e.g.*, Ex. 1003 ¶¶ 53, 54, 79, 118–121. Although Birnboim's exemplification of PCR amplification appears to include centrifugation and precipitation steps (*see, e.g., id*. ¶ 119), we agree with Petitioner that the necessity of such additional separation steps is "purely a function of the prior art nucleic acid tests, not the claimed solution." Opp. RMTA 6–7;[40] *see also* Ex. 1015 (disclosing that post-lysis centrifugation and precipitation "steps can be varied according to the specific circumstances."); *id.* at Abstract, 5294.

In this respect, Petitioner points to the '256 patents disclosure of conventional nucleic acid tests, including the commercially-available Tigris DTS platform, which "automates the entire detection process." Opp. RMTA 7 (citing Ex. 1001, 1:21–25, 2:57–62, 9:48–51, 15:12–13, 16:31–35.). Petitioner, and its expert Dr. Taylor presents evidence that the Tigris DTS platform (and other integrated nucleic acid test systems), were available for performing testing on samples treated with prior art solutions such as

[40] On page 12 of its Reply to the Revised Motion to Amend, Patent Owner explains that the "in one step" amendment applies to all of the functional limitations *except* the PCR amplification step. Given that, as discussed in Section II.B.4, below, neither party adequately differentiates the "one step" language from the "without separation" element, it appears reasonable to infer that Patent Owner also intends that "without separation" also does not apply to PCR amplification. *See* Tr. 78:10–18, 130:11–131:6. As such, the centrifugation and precipitation steps of Birnboim's examples, would fall squarely within the scope of claim 35. For this additional reason, the prior teaches or suggests the "without further separation" limitation of proposed substitute claim 35.

Birnboim's without further separation from the sample. *Id.* (citing e.g., Ex. 1088, 450, 452, 455; Ex. 1089, 94; 1090; 4, 10); Ex. 1082 ¶¶ 25–26.

Although it is undisputed that the Tigris DTS platform performs PCR amplification as required by claim 35 (*see* Ex. 1089, 94), Patent Owner argues that Petitioner does not adequately "support its assertion that the TIGRIS or similar systems could be used with any composition described in Bi[r]nboim or Chirgwin or why a POSA would be motivated to do so." Reply RMTA 5–6 (citing Ex. 2042 ¶¶ 41–45). Considering the record as a whole, including Birnboim's teaching to use its disclosed compositions to perform PCR, the scope of the prior art and the skill of one of ordinary skill in the art, we do not agree with Patent Owner's argument. *See, e.g.* Section II.B, F, above; *see also* Opp. RMTA 8–9 (citing *In re Epstein*, 32 F.3d 1559, 1568 (Fed. Cir. 1994) ("[T]he Board's observation that appellant did not provide the type of detail in his specification that he now argues is necessary in prior art references supports the Board's finding that one skilled in the art would have known how to implement the features of the references and would have concluded that the reference disclosures would have been enabling.").

In sum, Petitioner has shown, by a preponderance of the evidence that the prior teaches or suggests the "without further separation" limitation of proposed substitute claim 35.

4) One Step (claim 35)

Proposed substitute claim 35 further recites that contacting the biological sample with the stock solution "is effective to, in one step" to effect the functional limitations of the claim. As with the "without further separation" limitation, the "one step" limitation was first presented in the

original MTA. *See* MTA 3, 13–14. To the extent the parties expressly address the "one step" limitation, their arguments and evidence is coincident with, if not subsumed by, their discussion of "without further separation." *See* RMTA 12–14; Opp. RMTA 6–9; Reply RMTA 5–6; Sur-reply RMTA 5–6. As such, our analysis of the two limitations is substantially the same. *See* Section III.B.3, above; *see* Prelim. Guide. 12–14.

In short, evidence adduced at trial confirms our initial determination that "Birnboim discloses stock solutions ('nucleic acid preserving compositions') for use in a one-step method to lyse nucleic acid-containing cells or viruses, release the nucleic acids into the composition, inactivate nucleases in the sample, and stabilize the extracted nucleic acid for future analysis." DI 13. In Section III.B.2, we determined that Birnboim's compositions "inactivate endogenous and exogenous nucleases." In Section III.B.3, we determined that one of ordinary skill in the art would be motivated, with a reasonable expectation of success to analyze nucleic acid extracted using Birnboim's stock solution (or obvious modification thereof) using PCR amplification, and without further separation from the sample. Taken together, Petitioner has shown by a preponderance of the evidence that the "one step" limitation of claim 35 is taught or suggested by the prior art.

D. Proposed Substitute Claim 21

Proposed substitute claim 21, which would replace claim 1, recites (with underlining representing addition):

> 21. A stock solution comprising components with concentrations as follows:
>
> a chaotrope present in an amount from 0.5 M to 6M;
>
> a detergent present in an amount from 0.1% to 1% (wt./vol.);

> a reducing agent in an amount from 0.5 mM to 0.3 M;
>
> a chelator present in an amount from 0.01 mM to 50 mM;
>
> a surfactant present in an amount from 0.0001% to 0.3% (wt./vol.);
>
> a short-chain alkanol present in an amount from 1 to 25% (vol./vol.);
>
> a buffer present in an amount from 1 mM to 1 M;
>
> an acid or base present in an amount that provides a pH of from 5 to 7 to the stock solution; and
>
> nuclease-free water,
>
> wherein the stock solution, when combined with a biological sample suspected of containing a pathogen, denatures proteins, inactivates nucleases, and kills pathogens thereby rendering the biological sample entirely non-pathogenic and safe for human handling, all without degrading nucleic acids of the sample.

Petitioner contends that claim 21 is unpatentable as obvious in view of Birnboim, Mori, and Farrell. Opp. RMTA 10 (citing Opp. MTA 4–8; Prelim. Guide. 12). For the reasons set for in Section II.F (with respect to the limitations common to claim 1), and in Section III.C.1 (further with respect to the newly-added limitations of claim 21), we agree with Petitioner.[41] For additional reasons discussed in sections E–G, above, and in view of the record as a whole, we further agree that proposed dependent claims 22–33 are unpatentable as obvious over the prior art. *See, e.g.*, Opp. RMTA 12–15.

Considering the entirety of the record, Petitioner has shown by a preponderance of the evidence that proposed substitute claims 21–33 are

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[41] As such, we need not address Petitioner's other obviousness arguments, including that Chirgwin's formulation inherently provides the claimed functional limitations as claimed because it is substantially similar to the sole stock solution disclosed in '728 provisional application and to Example 2 of the '256 patent. Opp. RMTA 10; Opp. MTA, 1 (citing Ex. 1049, 9; Ex. 1015, 5294–95; Ex. 1001, 21:37–58).

unpatentable as obvious in view of the prior art, including Birnboim, Mori, Farrell, Das, Helftenbein, Heineman.

E. Proposed Substitute Claim 35

Proposed substitute claim 35, which would replace claim 15, recites (with underlining and strikethrough representing addition and deletion, respectively):

> 35. A method for detecting a nucleic acid sequence that is indicative of the presence of the pathogen in the sample comprising, at an ambient temperature, contacting the biological sample with an amount of the stock solution of claim 21~~1~~ forming a composition which is effective to, in one step:
>
> i) kill pathogens,
>
> ii) lyse a portion of cells in the sample to release nucleic acids comprising the nucleic acid sequence, wherein the released nucleic acids are compatible with a nucleic acid test without further separation from the sample; and
>
> iii) inactivate nucleases in the sample without degrading or modifying nucleic acids of the sample, wherein the amount of the stock solution inactivates endogenous and exogenous RNases and Dnases to prevent degradation of the nucleic acid sequence, and wherein ~~so that~~ the nucleic acid sequence of the pathogen is detectable by PCR amplification.

Petitioner contends that claim 35 is unpatentable as obvious in view of Birnboim, Mori, and Farrell. Opp. RMTA 11 (citing Opp. MTA 8–13; Prelim. Guide. 14). For the reasons set for in Section II.F (with respect to the limitations common to claim 1), and in Section III.C.2–4 (further with respect to the newly-added limitations of claim 35), we agree with Petitioner.[42] For additional reasons discussed in sections E–G, above, and in

[42] As such, we need not address Petitioner's other obviousness arguments, including that Chirgwin's formulation inherently provides the claimed

view of the record as a whole, we further agree that proposed dependent claims 36–40 are unpatentable as obvious over the prior art. *See, e.g.*, Opp. RMTA1 16.

Considering the entirety of the record, Petitioner has shown by a preponderance of the evidence that proposed substitute claims 35–40 are unpatentable as obvious in view of the prior art, including Birnboim, Mori, Farrell, Das, Helftenbein, Heineman.

IV. PATENT OWNER'S MOTION TO EXCLUDE

Patent Owner filed a Motion to Exclude Evidence. Paper 82 ("MTE"). Specifically, Patent Owner moves to exclude Birnboim, the primary prior art reference relied on in the Petition. MTE 1–2. Patent Owner also moves to exclude certain test results from ABL, a third-party laboratory Patent Owner engaged to perform tests on several biological samples, as well as the deposition transcripts of three ABL employees. *Id.* at 6–8, 11–15. Patent Owner further moves to exclude test results from Nelson Labs, a third-party laboratory Petitioner engaged to perform tests on two biological samples. *Id.* at 3–6. Additionally, Patent Owner moves to exclude certain declarations of Petitioner's expert witness, Dr. Taylor. *Id.* at 6–8. Patent Owner also moves to exclude numerous articles published in peer-reviewed journals and published U.S. patent applications. *Id.* at 2–3, 8–11.

Patent Owner, as the party moving to exclude evidence, bears the burden of proving that it is entitled to the relief requested, namely, that the

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functional limitations as claimed because it is substantially similar to the sole stock solution disclosed in '728 provisional application and to Example 2 of the '256 patent. Opp. RMTA 11–12; Opp. MTA, 1 (citing Ex. 1049, 9; Ex. 1015, 5294–95; Ex. 1001, 21:37–58).

material sought to be excluded is inadmissible under the Federal Rules of Evidence. *See* 37 C.F.R. §§ 42.20(c), 42.62(a). For the reasons explained below, Patent Owner has not met that burden. Thus, Patent Owner's MTE is denied.

A. Exhibit 1003

Exhibit 1003 is Birnboim, the primary reference Petitioner relies on. Patent Owner moves to exclude Birnboim "to the extent Petitioner relies on Birnboim's specification to *prove the truth* of testing data stated and described therein without submitting and affidavit by an individual having first-hand knowledge of how the data was generated, which contravenes 37 C.F.R. §42.61(c)." MTE 1. According to Patent Owner, Petitioner cannot rely on the test results reported in Birnboim's specification and figures because Petitioner has not provided any affidavit from a person with first-hand knowledge of the experiments discussed therein. *Id.* We are not persuaded.

Petitioner relies on Birnboim, a U.S. patent application, to prove what its specification describes, which renders Birnboim admissible. *See* 37 C.F.R. § 42.61(c) (stating a patent application is admissible as evidence "only to prove what the specification or drawing describes"); *see also* 77 Fed. Reg. 48,612, 48,624 (Aug. 14, 2012) (explaining that § 42.61(c) addresses the "problem in which a party mistakenly relies on a specification to prove a fact other than what the specification says").

In seeking to exclude Birnboim, Patent Owner faults Petitioner for "repeatedly rel[ying] on *other references*" to support the arguments "regarding Birnboim's performance of functional limitations." MTE 1 (emphasis added). This appears to contradict Patent Owner's argument that

"Petitioner relies on *Birnboim's specification* to *prove the truth* of testing data stated and described therein." *Id.* (the first emphasis added).

The examples Patent Owner points to do not show that Petitioner relies on Birnboim's specification to prove a fact other than what its specification describes. Indeed, Patent Owner points to Paper 66, Petitioner's Opposition to Patent Owner's Revised Contingent Motion to Amend, where Petitioner allegedly "incorporat[ed] by reference argument in Taylor Decl. (Ex. 1082 ¶ 5) purporting to interpret and rely upon Birnboim ¶¶ [0020] and [0068])." MTE 2 (citing Opp. RMTA 2). In his Declaration, Dr. Taylor testified that "Birnboim discloses compositions that 'inactivate nucleases'—including DNases and RNases." Ex. 1082 ¶ 5 (citing Ex. 1003 ¶¶ 20, 68). In paragraph 68, Birnboim teaches "[t]he action of deoxyribonucleases and ribonucleases can also be inhibited by denaturing agents that will destroy the complex structures of these enzymes (proteins). Hence, denaturing agents are included in the nucleic acid preserving composition of the invention." Ex. 1003 ¶ 68. It goes on to list examples of denaturing agents. *Id.*; *see also id.* ¶ 20. Thus, Petitioner and Dr. Taylor rely on Birnboim to prove what its specification describes, as permitted under 37 C.F.R. § 42.61(c).

Patent Owner similarly contends that Petitioner "incorporat[ed] by reference argument in Taylor Decl. (Ex. 1082 ¶ 5) purporting to interpret and rely on Birnboim ¶¶ [0020] and [0068]." MTE 2 (citing Opp. RMTA 2). In his Declaration, Dr. Taylor testified that "Birnboim discloses stock solutions that "inactivate nucleases"— including DNases and RNases." Ex. 1082 ¶ 21 (citing Ex. 1003 ¶¶ 20, 68). Birnboim' s paragraph 68 (largely quoted in paragraph 5 of Dr. Taylor's Declaration), discloses that such

nucleases can be inhibited by denaturing agents, used "alone or in combination," including, for example, strong chelators, alcohols, and "denaturing agents that will destroy the complex structures of these enzymes." Ex. 1003 ¶ 68. Paragraph 20, for example, states that

> The denaturing agent of the composition can be selected from the group consisting of urea, dodecyl Sulfate, guanidinium chloride, guanidinium thiocyanate, perchlorate, and an alcohol. Desirably, the denaturing agent is urea, dodecyl sulfate, or an alcohol, wherein the alcohol is 10%-60% of the total composition volume. The alcohols can be methanol, ethanol, n-propanol, isopropanol, n-butanol, trifluoroethanol, phenol, or 2,6-di-tert-butyl-4-methylphenol.

Id. ¶ 20. Again, Patent Owner does not explain how Petitioner's reliance on these disclosures is to prove a fact other than what the specification describes.

Because Petitioner relies on Birnboim to prove what its specification describes, we deny Patent Owner's Motion to Exclude Exhibit 1003.

B. Exhibits 1008, 1015, 1050, 1052, 1054, 1056–1058, 1060, 1083, 1085–1092, and 1095

1) Exhibits 1050, 1057–1058, 1083, 1085–1087, 1090–1092, and 1095

Exhibits 1050, 1057–1058, 1083, 1085–1087, 1090–1092, and 1095 are articles published in peer-reviewed journals. We do not rely on these articles in rendering this Decision. Thus, we dismiss this aspect of Patent Owner's Motion to Exclude as moot.

2) Exhibits 1008, 1015, 1052, 1054, 1056, 1060

Patent Owner argues Exhibits 1008 (Das), 1015 (Chirgwin), 1052 (Casas), 1054 (Zinkevich), 1056 (Donofrio), and 1060 (Laulier) "should be excluded to the extent that Petitioner relies on them for the truth of the

testing data they report, for the same reasons discussed above as to Ex. 1003." MTE 3 (citing 37 C.F.R. § 42.61(c)). Rule § 42.61(c) does not apply to Chirgwin, Casas, Zinkevich, Donofrio, or Laulier, as these are all articles published in scientific journals. *See* 37 C.F.R. § 42.61(c) (discussing the admissibility of "specification or drawing of a United States patent application or patent"). Nor has Patent Owner explained adequately why any of these references should be excluded as irrelevant or prejudicial under FRE 401 or 403, respectively. *See* MTE 3. Thus, we deny Patent Owner's Motion to Exclude Exhibit 1015, 1052, 1054, 1056, and 1060.

Although Rule § 42.61(c) does apply to Das, a published U.S. patent application, Patent Owner does not identify which "testing data" in Das Petitioner attempts to prove the truth of. Because Patent Owner has not met its burden of proving that it is entitled to the relief requested, we deny Patent Owner's Motion to Exclude Exhibits 1008. *See* 37 C.F.R. §§ 42.20(c), 42.62(a).

C. Exhibits 1069, 1072, 1073, AND 1200-1211[43]

Patent Owner engaged ABL to conduct biological testing in support of Patent Owner Response and its revised MTA. *See* Ex. 2019. In connection with Petitioner's deposition of three ABL employees (Exs. 2026–2028), the parties contacted the Board with a dispute as to the work product objections Patent Owner raised in these depositions. *See* Exs. 3004–3006. The Board held a conference call to discuss those objections on March 30, 2022. *See* Paper 33, 2–3.

[43] Patent Owner moves to exclude Exhibit 1200. MTE 11. Exhibit 1200, however, does not exist in this proceeding. Thus, we dismiss Patent Owner's motion in this regard as moot.

During that conference, Patent Owner argued that Exhibit 2019, "the testing report signed by the three ABL employees is relevant only for what is explicitly stated in the report itself and the report does not address patent validity." *See* Paper 33, 3. Patent Owner further argued that the ABL witnesses originally testified that "(1) they did not do other testing for Patent Owner's counsel that was considered or relied upon for Exhibit 2019 and (2) 'no other testing exists relating to the conclusions or results presented in Ex. 2019.'" *Id.* at 4 (citing Ex. 2026, 53:20–54:11; 25:4–28:22; 120:8–122:25; Ex. 2028, 17:20–20:8; Ex. 2027, 109:21–11:14; 20:4–22:10; 39:8–40:6; 42:1–25; 43:21–45:15).

Patent Owner asserted that "any work done by ABL not explicitly disclosed in Ex. 2019 qualifies as work product because it was done 'in anticipation of litigation or for trial by or for another party or its representative (including the other party's attorney, consultant, surety, indemnitor, insurer, or agent).'" *Id.* (citing FRCP 26(b)(3); *Hickman v. Taylor*, 329 U.S. 495 (1947)). Thus, Patent Owner concluded that "other ABL work, if any, is clearly distinct from the testimony provided in the report (Ex. 2019) and remains protected work product." *Id.*

After the parties briefed the matter (Papers 28, 32), we issued an Order explaining that we "do not agree with Patent Owner because the legal precedent and the deposition transcripts run counter to Patent Owner's position." Paper 34, 4. We noted that the deposition transcripts do not support Patent Owner's statements. *Id.* at 5–9 (citing Ex. 2026, 53:20–54:11; Ex. 2027, 39:8–40:6; Ex. 2028, 17:20–20:8). In fact, the transcripts show Patent Owner attempted to cabin the witnesses to only the explicit disclosure of Exhibit 2019. *Id.* at 9.

Under the circumstances, we authorized Petitioner additional questioning on certain testing and ordered Patent Owner to serve any relevant inconsistent information as required by 37 C.F.R. § 42.51(b)(iii). *See* Paper 34, 11. Subsequently, Patent Owner served Exhibits 1201–1211 on Petitioner. After further deposing the three ABL employees, Petitioner filed the transcripts of those depositions (Exs. 1069, 1072, 1073). Patent Owner seeks to exclude these Exhibits. MTE 6–8, 11–15.

1) Exhibits 1072 and 1073

Exhibits 1072 and 1073 are deposition transcript of two ABL employees. We do not rely on these two Exhibits in rendering this Decision. Thus, we dismiss this aspect of Patent Owner's Motion to Exclude Exhibits 1072 and 1073 as moot.

2) Exhibits 1205 and 1208

Exhibit 1205 is a publicly available spreadsheet listing tested organisms, testing solutions, and the resulting organism concentration. Exhibit 1208 is a publicly available reproduction of a peer-reviewed scientific article.

Patent Owner moves to exclude Exhibits 1205 and 1208 as being protected work product. MTE 11–15. "A motion to exclude evidence must be filed to preserve any objection. The motion must identify the objections in the record in order and must explain the objections." 37 C.F.R. § 42.64(c). Patent Owner did not object to Exhibits 1205 and 1208 as being work product. *See* Paper 42, 8–9[44] (objecting to these Exhibits only "under FRE 401/402/403, needlessly cumulative evidence, little to no probative

[44] Patent Owner does not include page numbers in Papers 41 and 42. We cite to the pages as if they were numbered properly.

value, and probative value outweighed by prejudicial effect" and "under FRE 802 and § 42.61(c) to the extent relied on for the truth of statements therein"). Indeed, Patent Owner acknowledges these Exhibits are publicly available. *See* Paper 41, 2 ("Exhibits 1205 and 1208 need not be sealed.").

Because Patent Owner fails to explain adequately how the information disclosed in Exhibits 1205 and 1208 constitutes work product, we deny Patent Owner's Motion to Exclude these Exhibits.

3) Exhibits 1201–1204, 1206, 1207, and 1209–1211

Exhibit 1201 is a list of reagents and amounts used to create solutions used for testing by ABL. Exhibit 1202 is a spreadsheet listing tested organisms, testing solutions, and the resulting organism concentration. Exhibit 1203 is a graphic representation of testing results of solutions used on specific tested organisms. Exhibit 1204 is a graphic representation of testing results of solutions used on specific tested organisms. Exhibit 1206 is a standard operating procedure on how to perform testing protocol at ABL. Exhibit 1207 is a spreadsheet [redacted] [redacted]. Exhibit 1209 is a [redacted] spreadsheet. Exhibit 1210 is a product testing data sheet from ABL. Exhibit 1211 is a spreadsheet showing data analysis of several runs of quantitative PCR assays determining the impact of the presence of [redacted] RNase.

As explained above, Patent Owner initially only produced test results that supports its position in Patent Owner Response. Following our Order (Paper 33), Patent Owner produced test results that are adverse to its position. Now Patent Owner claims the contradictory test results are protected by work product privilege. MTE 11–15. Patent Owner argues its

counsel "explored different theories and options in preparing its response to the Petition and engaged ABL to assist in that exploration." *Id.* at 14. According to Patent Owner, "ABL tested a variety of hypotheses in consultation with [Patent Owner] Longhorn's counsel to assist in this process. Such testing is quintessentially consulting expert work product immune from discovery." *Id.* In its Reply in support of the Motion to Seal, Patent Owner also contends:

> PO objects to (and seeks to preserve its right to appeal as to) the consulting testing itself (including litigation strategy considerations embodied in what was tested and how) as its attorney work product, which protects confidential litigation strategy and preparation materials broadly, not just *communications with counsel*. *U.S. v. Nobels*, 422 U.S. 225, 238 n.11 (1975) (work product doctrine "distinct from and broader than" attorney-client privilege); Paper 31 (making work product arguments PO seeks to preserve for appeal).

Paper 61 ("Seal Reply"), 2. We are not persuaded by Patent Owner's assertion of work-product privilege.

Patent Owner does not sufficiently explain why test results that support its arguments are not protected under any privilege, whereas the results from tests conducted around the same time and by the same entity that contradict its position are. Indeed, Patent Owner does not appear to have "tested a variety of hypothesis" so much as it tested all the compounds, solutions, and organisms disclosed in Birnboim. Several of the compounds produced results inconsistent to Patent Owner's arguments in its Response. Simply because a test produces results contrary to a party's initial hope, does not mean the party was exploring different theories and options. Rather, Patent Owner tested one theory—that certain embodiments disclosed in

Birnboim would not work—and withheld all the test results inconsistent with that theory.

Our rules specifically prohibit such conduct. Indeed, under 37 C.F.R. § 42.51(b)(1)(iii), "a party must serve relevant information that is inconsistent with a position advanced by the party during the proceeding concurrent with the filing of the documents or things that contains the inconsistency."

Of course, Rule § 42.51(b)(1)(iii) "does not make discoverable anything otherwise protected by legally recognized privileges such as attorney-client or attorney work product." But, as explained in detail in the concurrently issued Order granting Petitioner's Motion for Sanctions, the work-product doctrine is not absolute and generally allows discovery of "factual" or "non-opinion" work product. Paper __, __ (citing *In re EchoStar Comms. Corp.*, 448 F.3d 1294, 1301 (Fed. Cir. 2006)); *see also id.* at ___ (explaining the scope of attorney work product protection before the Office is "limited" and "cannot be used to shield factual information from discovery that is inconsistent with positions taken by a party before the Board" because "shielding the factual information from the Board violates the duty of candor and good faith to the Office").

The information in Exhibits 1201–1204, 1206, and 1207, and 1209–1211 relates to tests run by ABL with compounds that are identical to or variations of those disclosed in Birnboim. Because the test results relay facts, and not "mental impressions, conclusions, opinions, or legal theories of an attorney or other representative" the work-product doctrine is designed to protect, we deny Patent Owner's Motion to Exclude

these Exhibits. *See EchoStar*, 448 F.3d at 1301 (citing Fed. R. Civ. P. 26(b)(3)).

4) Exhibit 1069

Exhibit 1069 is the deposition transcript of Joshua M. Birkebak, Ph.D. Dr. Birkebak is an ABL employee in the management role involved in conducting tests for Patent Owner. Ex. 2019, 1.

Relying on the same argument "[a]s discussed in greater detail as to Exhibit[s] 1200–1211," Patent Owner moves to exclude "sections of Dr. Birkebak's April 26, 2022 deposition transcript that describe the consulting testing and exhibits reflecting the consulting testing that PO asserts constitute its protected work product." MTE 5–6 (citing Ex. 1069, 200:1–278:12).

For the same reason explained above as related to Exhibits 1201–1204, 1206, and 1207, and 1209–1211 (*see supra* Section IV.D.3), we deny Patent Owner's Motion to Exclude Exhibit 1069.

5) Exhibits 1071 and 1082

Exhibits 1071 and 1082 are Declarations of Petitioner's expert witness, Dr. Taylor. Dr. Taylor's discusses the testing performed by ABL and refers to Birnboim, Chirgwin, as well as other references in these Declarations.

Patent Owner moves to exclude paragraphs 15–30 of Exhibit 1071 and paragraph 16 of Exhibit 1082 "[f]or the same reasons discussed . . . as to Exhibits 1200–1211." MTE 6, 7–8. For the same reason explained above as related to Exhibits 1201–1204, 1206, and 1207–1211 (*see supra* Section IV.C.3), we are not persuaded by this argument.

Also, "[f]or the same reasons discussed . . . as to Exhibit 1003," Patent

Owner moves to exclude paragraphs 38–72 of Exhibit 1071 and paragraphs 10 and 18 of Exhibit 1082 because Dr. Taylor allegedly "improper[ly] reli[ed] . . . on data reported in Birnboim, Chirgwin, and [other] references . . . *for their truth*." MTE 6–8 (citing 37 C.F.R. § 42.61(c)). Rule § 42.61(c) does not apply to the Taylor Declarations because they are not "specification or drawing of a United States patent application or patent." *See* 37 C.F.R. § 42.61(c). Thus, we are not persuaded by this argument either.

Patent Owner further moves to exclude paragraphs 2–72 of Exhibit 1071 "as irrelevant (FRE 401) and prejudicial far beyond any probative value (FRE 403) Taylor's arguments regarding new grounds for invalidity (and new prior art references) not asserted in the Petition." MTE 6–7. Patent Owner, however, has not sufficiently explained what "new grounds for invalidity" it refers to.

In addition, many of the over seventy paragraphs Patent Owner seeks to exclude are not related to the alleged "new grounds for invalidity (and new prior art references)." Indeed, as Patent Owner complains, in paragraphs 15–30, Dr. Taylor discusses the "testing performed for PO's counsel by Assured Bio Labs." *Id.* at 6. As another example, in paragraphs 37–42, 62–65, and 71, of Exhibit 1071, Dr. Taylor discusses Birnboim, Chirgwin, Das, and Goldrick, all of which are asserted in the Petition. *See*, *e.g.*, Pet. 5, 10, 20–23, 27–28, 43. Thus, it is unclear which paragraphs of Exhibit 1071 Patent Owner actually moves to exclude as irrelevant and prejudicial. Accordingly, we deny Patent Owner's Motion to Exclude Exhibits 1071 and 1082.

D. Exhibit 1068

Exhibit 1068 is a testing report from Nelson Labs, a third-party laboratory Petitioner engaged to perform tests on two microorganisms: *B. subtilis* vegetative cells and *E. coli*, and signed by the study monitor, Christopher M. Beasoleil, B.S. *See* Ex. 1068, 54. Patent Owner contends that we should exclude Exhibit 1068 under FRE 802, 701/702, and 37 C.F.R. §§ 42.65; 42.61(c), because it is "not based on the declarant's perception." MTE 3–5; Reply MTE 2–4. We do not find Patent Owner's argument persuasive in view of Mr. Beasoleil's (admittedly belated) declaration attesting to oversight and participation in preparing the report. *See* Ex. 1077. Mr. Beasoleil's declaration, states, for example:

> I have personal knowledge of all protocols, experiments, and results reported in Exhibit 1068 (Nelson Labs Study Monitor Report for In-Vitro Evaluations of Two Test Products for Their Antimicrobial Properties, dated May 3, 2022). For example, I participated in the drafting and revision of the protocols provided in Exhibit 1068, I oversaw the experiments performed in Exhibit 1068, and I participated in the preparation and revision of the portions of Exhibit 1068 reporting the experimental results. I have experience in all protocols described in Exhibit 1068, and I confirm that all protocols correspond to industry standards for Time-Kill and antimicrobial assays. In performing of the experiments reported in Exhibit 1068, I monitored the laboratory work as it was being performed, and I oversaw the laboratory work over the duration of the experiments. I confirm that all laboratory work was performed according to industry standards for Time-Kill and antimicrobial assays. I prepared the report provided in Exhibit 1068, and in the process of preparing this report, I prepared or oversaw the preparation of the results summaries provided in Exhibit 10689. I confirm that the results are accurately reported in Exhibit 1068.

Ex. 1077 ¶ 3. Patent Owner had ample opportunity to question Dr. Beasoleil regarding the content and preparation of Exhibit 1068, and the resulting testimony amply confirms his role in overseeing the underlying experiments and preparing the report. *See* Ex. 2032, 22:17–23:14, 46:11–25, 170:11–171:16, 247:16–248:8, 289:12–23.

Patent Owner's arguments regarding "appropriate foundation for the reliability of the analysis" are also unavailing for the reasons set forth on pages 4 and 5 of Petitioner's Opposition to Patent Owner's Motion, which we adopt. *See* Opp. MTE, 4–5; Reply MTE 3. Moreover, Patent Owner's contentions regarding the specific details of the methods referenced in the report go to the weight we should accord to this exhibit, rather than its admissibility. *See* MTE, 5 (citing Ex. 2032 198:22–199:17). Accordingly, we deny Patent Owner's Motion to Exclude Exhibit 1068.

V. PATENT OWNER'S MOTION TO SEAL

Patent Owner filed an unopposed Motion for entry of a Protective Order. Paper 35. According to Patent Owner, the parties have agreed upon a protective order that deviates from the Board's default protective order. *Id.* Patent Owner filed a marked-up comparison of the proposed and default protective orders (Ex. 2030) and a clean copy of the proposed protective order (Paper 37). The Protective Order as set forth in Paper 37 is hereby entered. It shall govern the conduct of the proceeding unless otherwise modified.

Patent Owner filed Motion to Seal. Paper 41 ("Mot. Seal"). Petitioner filed an Opposition to the Motion (Paper 49, "Opp. Seal."), and Patent Owner filed a Reply in support of its Motion to Seal (Paper 61, "Reply Seal").

There is a strong public policy for making all information filed in an *inter partes* review open to the public, especially because the proceeding determines the patentability of claims in an issued patent and, therefore, affects the rights of the public. Generally, all papers filed in an *inter partes* review shall be made available to the public. *See* 35 U.S.C. § 316(a)(1); 37 C.F.R. § 42.14. Our rules, however, "aim to strike a balance between the public's interest in maintaining a complete and understandable file history and the parties' interest in protecting truly sensitive information." Consolidated Patent Trial Practice Guide ("Trial Practice Guide")[45] 19. Thus, a party may move to seal certain information (37 C.F.R. § 42.14); but only "confidential information" is protected from disclosure (35 U.S.C. § 326(a)(7)). Confidential information means trade secret or other confidential research, development, or commercial information. 37 C.F.R. § 42.2.

The standard for granting a motion to seal is "for good cause." 37 C.F.R. § 42.54(a). The party moving to seal bears the burden of proof and must explain why the information sought to be sealed constitutes confidential information. 37 C.F.R. § 42.20(c). Moreover, "[r]edactions to documents filed in this proceeding should be limited to the minimum amount necessary to protect confidential information." Trial Practice Guide 91. Patent Owner has not met these requirements.

As we understand the motion, Patent Owner seeks to seal the entirety of Exhibits 1202–1204, 1206, 1207, 1209, and 1210, which relate to the ABL testing Patent Owner originally withheld from discovery and is at issue in the copending Order on Sanctions. *See* Mot. Seal, 1–2; Opp. Seal 6–11.

[45] Available at https://www.uspto.gov/TrialPracticeGuideConsolidated.

As we further understand the motion, Patent Owner seeks to partially seal Exhibits 1069, 1072, and 1073 (Deposition testimony of ABL employees), Exhibit 1071 (Dr. Taylor's Second Declaration), Exhibits 1201 and 1211 (additional data relating to the originally withheld testing), Paper 44 (Petitioner's Reply), and Paper 43 (Petitioner Opposition to Motion to Amend. *See* Opp. Seal. 11–15. We further note that some 17 papers in this case, including briefing on Petitioner's motion for sanctions, were filed "Board and Parties Only."

Patent Owner asserts that good cause for sealing these materials exists "to preserve Patent Owner's ability to appeal the overruling of its privilege/work product objections to disclosure and production of the information and documents proposed to be sealed." Mot. Seal 2, 3. Petitioner does not oppose the motion in principle, but argues—with justification—that Patent Owner provides insufficient detail or justification for the full scope of material it seeks to seal. Opp. Seal 1–2. Petitioner asserts that

> Patent Owner's Motion to Seal falls far short of providing "a detailed discussion" that "[e]xplains why good cause exists" for blocking this information from the public. *See Garmin* at 4. Patent Owner's request to keep this information from the public domain should be denied, subject to Patent Owner (a) providing a more specific justification for sealing the information, and (b) providing redacted documents in which the extent of redactions is no more than necessary to preserve, pending appeal, the confidentiality of information that is the subject of Patent Owner's privilege assertions.

Id. at 6.

By way of example, Patent Owner seeks to seal portions of Exhibit 1069, which is Dr. Birkebak's testimony on ABL's testing results. Patent Owner alleges that, in this deposition, Petitioner sought information "subject to work product immunity." Reply Seal 4–5. As such, Patent Owner

redacts 78 pages of the testimony, leaving 35 pages available to the public. *Id.* One topic Patent Owner redacts relates to ABL's testing of *E. coli*. Ex. 1069, 235:5–237:15. Dr. Birkebak testified that the *E. coli* testing "was not performed as part of the official testing as requested by [Patent Owner's counsel]." *Id.* at 236:14–17. Thus, as Petitioner points out, "Patent Owner cannot possibly allege that any testing on *E. coli* is subject to any privilege or work product immunities." Opp. Seal 13. But that is exactly what Patent Owner does. *See* Reply Seal 5 (broadly alleging "PO limited its redactions to testimony regarding that consulting testing").

Petitioner also proposes a plan for how each item of the subject documents should be treated. *Id.* at 6–15. Patent Owner disagrees, arguing that Petitioner is trying to set a "waiver trap" and, for the first time, describes adequately the material sought to be sealed and, with some degree of particularity, the reasons therefore. *See* Reply Seal 2–5.

Petitioner's arguments are non-trivial, and though we are mindful of our charge to make pertinent information available to the public, we balance these considerations against Patent Owner's desire to preserve its rights subject to appeal.

We further note that page 19 of our Trial Practice Guide provides:

> 1. <u>Public availability</u>: The record of a proceeding, including documents and things, shall be made available to the public, except as otherwise ordered. 37 C.F.R. § 42.14. Accordingly, a document or thing will be made publicly available, unless a party files a motion to seal that is then granted by the Board.
>
> . . .
>
> 3. <u>Motion to seal</u>: A party intending a document or thing to be sealed may file a motion to seal concurrent with the filing of the document or thing. 37 C.F.R. § 42.14. The document or thing will be provisionally sealed on receipt of the motion and remain so pending the outcome of the decision on motion.

Relevant to the above, some seventeen papers in this proceeding have been filed "Board and Parties Only," with no corresponding motion to seal. *See* Papers 28, 31, 33, 38, 39, 48, 49, 55, 61, 66, 74, 81, 83, 87, 93, 100, and 104. Collectively, these Papers discuss the materials sought to be sealed at length and in such substantial detail that sealing only the requested Exhibits would be improvident.

In consideration of the above, we determine that Patent Owner has not established good cause for sealing the information at issue. Indeed, the Board is not even certain what scope of information is intended. Patent Owner's motion is denied.

We note, however, Patent Owner appears to request sealing of the identified Exhibits only "long enough to allow PO to appeal after a final written decision." Seal Reply 5; *see also* Seal Mot. 3 ("Patent Owner seeks to seal this information to preserve its opportunity to seek appellate review of the Board's Order as to Patent Owner's privilege/work product objections."). That request is granted with respect to Exhibits 1202–1204, 1206, 1207, 1209, and 1210, and unredacted versions of Exhibits 1069–1073, 1201, 1211, Paper 43, and Paper 44. Depending on the outcome of the appeals, Patent Owner may renew its Motion to Seal within thirty days of the conclusion of all appeals. In the event that Patent Owner does not timely renew its Motion to Seal, the documents filed under seal in this proceeding will be unsealed forty-five days after the conclusion of all appeals.

As noted above, numerous papers in this case were filed as "Board and Parties Only," with no corresponding motion to seal. For example, in its Reply in support of the Motion to Seal, Patent Owner states "Petitioner has since filed as Board/Parties Only briefs and transcripts discussing the same

information, which should likewise remain sealed." Reply Seal 2–3. There, Patent Owner identifies Petitioner's Reply (Paper 38), the first MTA Opposition (Paper 39), and the Motion for Sanctions (Paper 55).[46] Such a single sentence does not amount to a motion to seal, which is required under the Trial Practice Guide. *See* TPG 19 ("A party intending a document or thing to be sealed may file a motion to seal concurrent with the filing of the document or thing."). Other Papers, including Petitioner's Opposition to Patent Owner's Motion to Seal (Paper 49) as well as Patent Owner's Reply in Support of the Motion to Seal (Paper 61), were filed as "Board and Parties Only," without even a sentence mentioning any basis for sealing these Papers.

If desired, within ten business days, either party, or both parties jointly,[47] may file a motion to seal any document filed as Board and Parties Only but not presently accompanied by a motion to seal. Any such motion shall explain in detail and on a document-by-document basis what good cause supports granting the motion. In addition, the moving party or parties shall provide redacted versions of any document not requested to be sealed in its entirety, or explain where such redacted versions are available in the record. Any redactions must be limited to the minimum necessary. *See* TPG 91.

The parties may, within ten business days of this Decision, jointly propose redactions for this Final Written Decision. In the absence of such

[46] Petitioner filed a redacted version of the Reply (Paper 45), the first MTA Opposition (Paper 44), and the Motion for Sanctions (Paper 59).

[47] We strongly encourage the parties to meet and confer regarding the extent of redactions, and if possible, to file any motion to seal either unopposed or jointly.

proposal, at the expiration of ten business days from the date of this Decision, the entirety of the Final Written Decision will be made available to the public.

VI. CONCLUSION[48]

Having considered the evidentiary record before us and the parties' respective positions on each ground asserted in the Petition, we find that Petitioner has shown by a preponderance of the evidence that claims 1–13 and 15–20 of the '256 patent are unpatentable in view of the cited prior art. Claim 14 is further subject to adverse judgment, as are all other claims and proposed amended claims, as a sanction for the reasons set forth in our Order on Sanctions, filed concurrently. In summary:

Claims	**35 U.S.C. §**	**References/Basis**	**Claims Shown Unpatentable**	**Claims Not Shown Unpatentable**
1–10, 13, 15–19	§ 103(a)	Birnboim, Mori, Farrell	1–10, 13, 15–19	
11	§ 103(a)	Birnboim, Mori, Farrell, Das	11	
12, 20	§ 103(a)	Birnboim, Mori, Farrell, Helftenbein	12, 20	

[48] Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner's attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding*. *See* 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. §§ 42.8(a)(3), (b)(2).

Claims	35 U.S.C. §	References/Basis	Claims Shown Unpatentable	Claims Not Shown Unpatentable
14	§ 103(a)	Birnboim, Mori, Farrell, Heineman		14[49]
1–20	na[50]	sanctions	1–20	
Overall Outcome			1–20	

With respect to proposed substitute claims 21–33 and 35–40 are denied. We do not reach the merits of proposed substitute claim 34. In summary:

Revised Motion to Amend Outcome	Claim(s)
Original Claims Cancelled by Amendment	
Substitute Claims Proposed in the Amendment	21–40
Substitute Claims: Motion to Amend Granted	
Substitute Claims: Motion to Amend Denied	21–33, 35–40
Substitute Claims: Not Reached	34

I. ORDER

Accordingly, it is hereby:

ORDERED that all challenged claims (claims 1–20) of the ’256 patent are *deemed unpatentable* based on Adverse Judgment under 37 C.F.R. § 42.12 for the reasons set forth in our Order on Sanctions (Paper 107), entered concurrently, and *will be cancelled*;

[49] Claim 14 is deemed unpatentable in view of our Order on Sanctions, filed concurrently.
[50] As noted in section I.D, above, we separately address sanctions under 37 C.F.R. § 1.56, § 11.106(c), § 11.303, § 42.11(a), and § 42.51(b)(1)(iii).

FURTHER ORDERED that Patent Owner's Revised Contingent Motion to Amend is *denied* as based on Adverse Judgment under 37 C.F.R. § 42.12 for the reasons set forth in our Order on Sanctions;

FURTHER ORDERED that Petitioner has demonstrated by a preponderance of the evidence that claims 1–13, and 15–20 of the '256 patent are unpatentable under 35 U.S.C. § 103 based on the grounds set forth in the Petition;

FURTHER ORDERED that Patent Owner's Revised Contingent Motion to Amend is *denied* on the merits;

FURTHER ORDERED that Patent Owner's Motion to Exclude Exhibits 1003, 1008, 1015, 1052, 1054, 1056, 1060, 1068, 1069, 1071–1073, 1082, 1088, 1089, and 1200–1211 is *denied*;

FURTHER ORDERED that Patent Owner's Motion to Exclude Exhibits 1050, 1057–1058, 1083, 1085–1087, 1090–1092, and 1095 is *dismissed* as moot;

FURTHER ORDERED that Patent Owner's Motion to Exclude is *denied*;

FURTHER ORDERED that Patent Owner's Motion to Seal Exhibits 1069, 1071–1073, 1201–1204, 1206, 1207, and 1209–1211 is *denied*;

FURTHER ORDERED that within ten business day of this Order, either party may file a motion to seal any document filed as Board and Parties Only but not presently accompanied by a motion to seal;

FURTHER ORDERED that this Order, as well as Exhibits 1202–1204, 1206, 1207, 1209, and 1210, and unredacted versions of Exhibits

1069–1073, 1201, 1211, Paper 43, and Paper 44 will remain sealed until the completion of all appeals;

FURTHER ORDERED that Patent Owner may renew its Motion to Seal within thirty days of the conclusion of all appeals;

FURTHER ORDERED that within ten business days of this Order, the parties shall jointly propose a minimally redacted version for public dissemination; and

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

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