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PUBLIC VERSION
Paper 110
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.

IPR2021-00850
Patent 8,293,467 B2

Before GEORGIANNA W. BRADEN, ZHENYU YANG, and
WESLEY B. DERRICK, *Administrative Patent Judges*.

YANG, Administrative Patent Judge.

JUDGMENT

Adverse Judgment
Ordering All Challenged Claims Cancelled Based on Adverse Judgment

FINAL WRITTEN DECISION
Determining Some Challenged Claims Unpatentable
Denying Patent Owner's Revised Contingent Motion to Amend
35 U.S.C. §§ 318(a)

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:

On the merits, we determine that Petitioner has demonstrated by a preponderance of the evidence that claims 1–17 and 24–42 of the U.S. Patent No. 8,293,467 are unpatentable under 35 U.S.C. § 103. Petitioner also has shown by a preponderance of the evidence that proposed substitute claims 43–59 and 66–84 are unpatentable under 35 U.S.C. § 103.

Nonetheless, in the concurrently-issued Sanctions Order (Paper 109), 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 *inter partes* reviews, but selectively and improperly withheld material results that were inconsistent with its arguments. For the reasons set forth in our Sanctions Order, we order, as adverse judgment, that all challenged claims are cancelled and Patent Owner's Revised Motion to Amend is denied.

I. PROCEDURAL BACKGROUND

Spectrum Solutions LLC ("Petitioner") filed a Petition (Paper 1 ("Pet.")), seeking an *inter partes* review of claims 1–42 of U.S. Patent No. 8,293,467 B2 (Ex. 1001 ("the '467 patent")). Longhorn Vaccines & Diagnostics, LLC ("Patent Owner") filed a Preliminary Response. Paper 7 ("Prelim. Resp."). We instituted trial to review the challenged claims. Paper 13 ("DI"). Thereafter, Patent Owner filed its Response (Paper 103[1] ("PO Resp.")), Petitioner filed a Reply to Patent Owner's Response (Paper 40 ("Reply")), and Patent Owner filed a Sur-reply to Petitioner's Reply (Paper 104[2] ("Sur-reply")).

Patent Owner also filed a Contingent Motion to Amend (Paper 21 ("original MTA")), and Petitioner filed an Opposition to the MTA (Paper 41 ("first MTA Opp." or "first MTA Opposition")). We issued a Preliminary Guidance on the MTA, indicating our initial, preliminary, non-binding views that Petitioner had established a reasonable likelihood that the proposed substitute claims are unpatentable. Paper 50 ("PG").

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[1] Patent Owner originally filed its Response on February 11, 2022. Paper 22. It later sought, and we granted, leave to amend the Patent Owner Response. Papers 53, 62. After filing the Amended Patent Owner Response (Paper 66), Patent Owner again sought, and we granted, leave to correct certain citations therein (Ex. 3009). Patent Owner filed a corrected Amended Patent Owner Response. Paper 103. In this Decision, we cite to Paper 103 and treat all citations to Papers 22 and 66 in the Papers and Exhibits as citations to Paper 103.

[2] Patent Owner originally filed the Sur-reply on June 17, 2022. Paper 55. It later sought, and we granted, leave to correct certain citations therein (Ex. 3009). Patent Owner filed a corrected Sur-reply. Paper 104. In this Decision, we cite to Paper 104 and treat all citations to Paper 55 in the Papers and Exhibits as citations to Paper 104.

Thereafter, Patent Owner filed a Revised Contingent Motion to Amend (Paper 56 ("Revised MTA")) and Petitioner filed an Opposition to the Revised MTA (Paper 68 ("second MTA Opp." or "second MTA Opposition")). Patent Owner filed a Reply in support of its Revised MTA (Paper 79 ("MTA Reply")), and Petitioner filed a Sur-reply to the MTA Reply (Paper 95 ("MTA Sur-reply")).

Patent Owner filed a Motion to Seal (Paper 43); Petitioner opposed (Paper 51); and Patent Owner filed a Reply in support of its Motion (Paper 63).

Patent Owner also filed a Motion to Exclude Evidence (Paper 83 ("MTE")); Petitioner opposed (Paper 89); and Patent Owner filed a reply in support of the MTE (Paper 97).

Petitioner filed a Motion for Sanctions (Paper 57); Patent Owner opposed (Paper 77); and Petitioner filed a Reply in support of its Motion (Paper 85). On August 16, 2022, the panel held a hearing on the sanctions motion, and the transcript of that hearing is of record also. Paper 102. Concurrently with this Decision, we issue a separate decision discussing the Sanctions Motion. *See* Paper 109 ("Sanctions Order").

An oral hearing on the merits for this and related proceedings was held on August 19, 2022, and the transcript of that hearing is of record. *See* Paper 106 ("Tr.").

II. RELATED MATTERS

According to the parties, Patent Owner asserted the '467 patent against Petitioner in *Longhorn Vaccines & Diagnostics, LLC v. Spectrum Solutions LLC*, C.A. No. 2:20-cv-00827 (D. Utah). Pet. 1; Paper 4.

Petitioner also filed IPR2021-00847, -00851, -00854, -00857, and -00860, challenging claims of related U.S. Patents Nos. 8,084,443; 8,415,330; 8,669,240; 9,212,399; and 9,683,256, respectively. We denied review in IPR2021-00851 but instituted trial in the other four cases. Concurrently with this Decision, we issue Final Written Decisions in those proceedings.

III. ADVERSE JUDGMENT

Petitioner moved for sanctions, seeking (1) judgment against Patent Owner; (2) a holding that a particular reference meets particular claim limitations; and (3) compensatory expenses, including attorney fees. Paper 57, 1–2. We considered the issue after further briefing (Papers 77, 85) and a hearing on the motion (Paper 102). As set forth under separate cover and issued 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), 42.51(b)(1)(iii). *See* Sanctions Order 59–60.

Under 37 C.F.R. §§ 42.5, 42.11, and 42.12, and based on the Sanctions Order and determinations made therein, we enter Adverse Judgment against Patent Owner as to all challenged original claims and deny Patent Owner's Revised Contingent Motion to Amend. *See id.* Nonetheless, for the sake of completeness, and to add further context to our Sanction's Order, we address below the merits of the Petition and the Revised Contingent Motion to Amend.

IV. BACKGROUND

A. The ’467 Patent

The ’467 patent relates 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, 1:27–31.

The ’467 patent acknowledges that prior-art methods existed, but states those 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. *Id.* at 1:49–2:28. The ’467 patent also states that “clinical laboratory methods for pathogen detection were labor-intensive, expensive processes that required highly knowledgeable and expert scientists with specific experience.” *Id.* at 2:29–32.

Against this background, the ’467 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.” *Id.* at 3:14–18. In particular, the ’467 patent discloses a one-step, aqueous composition 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. at 1:31–38, 6:35–43. The Specification further discloses exemplary compositions 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 alkylbenzene 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. at 4:23–7:40.

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.

B. Illustrative Claims

Claims 1, 24, 29 and 31 of the ’467 patent are independent. They are reproduced below:

> 1. A method for denaturing proteins, inactivating nucleases and killing pathogens in one step without degrading nucleic acid of a biological sample containing proteins, nucleases, and nucleic acid, and suspected to contain pathogens, comprising:
>
> providing a mixture containing one or more chaotropes, one or more detergents, one or more reducing agents, one or more chelators, and one or more buffers, together present in an amount sufficient to denature proteins, inactivate nucleases, kill pathogens, and not degrade nucleic acid;
>
> contacting the biological sample with the mixture which denatures proteins, inactivate nucleases, kill pathogens, and does not degrade nucleic acid of the biological sample; and
>
> detecting the presence and identity of or absence of the pathogens in the biological sample.

Ex. 1001, 32:56–33:6.

> 24. A method for denaturing proteins, inactivating nucleases and killing pathogens in one step without degrading nucleic acid of a biological sample containing proteins, nucleases, and nucleic acid, and suspected to contain pathogens, comprising:
>
> providing a mixture containing one or more chaotropes, one or more detergents, one or more reducing agents, one or more chelators, one or more buffers, one or more short-chain alkanols, and one or more surfactants, together present in an amount sufficient to denature proteins, inactivate nucleases, kill pathogens, and not degrade nucleic acid;

contacting the biological sample with the mixture which denatures proteins, inactivate nucleases, kill pathogens, and does not degrade nucleic acid of the biological sample, and

detecting the presence and identity of or absence of the pathogens in the biological sample, wherein,

said one or more chaotropes are selected from the group consisting of guanidine thiocyanate, guanidine isocyanate, guanidine hydrochloride, and any combination thereof;

said one or more detergents are selected from the group consisting of sodium dodecyl sulfate, lithium dodecyl sulfate, sodium taurodeoxycholate, sodium taurocholate, sodium glycocholate, sodium deoxycholate, sodium cholate, sodium alkylbenzene sulfonate, N-lauroyl sarcosine, and any combination thereof;

said one or more chelators are selected from the group consisting of ethylene glycol tetra acetic acid, hydroxyethylethylenediaminetriacetic acid, diethylene triamine penta acetic 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, and any combination thereof; and

said one or more buffers are selected from the group consisting of tris(hydroxymethyl)aminomethane, citrate, 2-(N-morpholino)ethanesulfonic acid, N,N-Bis(2-hydroxyethyl)-2-aminoethanesulfonic acid, 1,3-bis(tris(hydroxymethyl)methyl amino)propane, 4-(2-hydroxyethyl)-1-piperazine ethanesulfonic acid, 3-(N-morpholino) propanesulfonic acid, bicarbonate, phosphate, and any combination thereof; and

said one or more short-chain alkanols are selected from the group consisting of methanol, ethanol, propanol, butanol, pentanol, or hexanol, and any combination thereof;

which are together present in an amount sufficient to denature proteins, inactivate nucleases; kill pathogens, and not

substantially degrade nucleic acid of the biological sample upon contacting the mixture.

Id. at 34:28–35:12.

> 29. A method for denaturing proteins, inactivating nucleases and killing pathogens in one step without degrading nucleic acid of a biological sample containing proteins, nucleases, and nucleic acid comprising:
>
> providing a mixture containing one or more chaotropes, one or more detergents, one or more reducing agents, one or more chelators, and one or more buffers, together present in an amount sufficient to denature proteins, inactivate nucleases, kill pathogens, and not degrade nucleic acid;
>
> providing the biological sample suspected to contain pathogens;
>
> contacting the biological sample with the mixture which liberates nucleic acid of the pathogens for PCR analysis;
>
> PCR amplifying the nucleic acid, if present; and
>
> determining the presence or absence of the pathogens in the biological sample.

Id. at 35:45–61.

> 31. A method for denaturing proteins, inactivating nucleases and killing pathogens in one step without degrading nucleic acid of a biological sample containing proteins, nucleases, and nucleic acid, and suspected to contain pathogens, comprising:
>
> providing a mixture containing one or more chaotropes, one or more detergents, one or more reducing agents, one or more chelators, and one or more buffers, together present in an amount sufficient to denature proteins, inactivate nucleases, kill pathogens, and not degrade nucleic acid, wherein the one or more chaotropes are present in an amount from about 0.5 M to about 6 M, the one or more detergents are present in an amount from about 0.1% to about 1% (wt./vol.); the one or more reducing agents are present in an amount from about 0.5 mM to about 0.3 M; the one or more chelators are present in an amount from about 0.01 mM to about 1 mM;

and the one or more buffers are present in an amount from about 1 mM to about 1M.

Id. at 36:4–23.

C. Instituted Challenges to Patentability

We instituted trial to determine whether the challenged claims are unpatentable based on the following basis:

Claim(s) Challenged	35 U.S.C. §[3]	Reference(s)
1, 2, 4, 7, 17–20, 22, 23, 29, 31, 34–39	102(b)	Birnboim[4]
1–9, 15–23, 29–39	103(a)	Birnboim
10, 11, 24, 25, 28	103(a)	Birnboim, Mori[5]
12	103(a)	Birnboim, Das[6]
27	103(a)	Birnboim, Mori, Das
13, 14	103(a)	Birnboim, Helftenbein,[7] Birnboim 2006[8]
26	103(a)	Birnboim, Mori, Helftenbein
40–42	103(a)	Birnboim, Mori, Helftenbein, Birnboim 2006

In support of their respective positions, Petitioner relies on the Declarations of Richard F. Taylor, Ph.D. (Exs. 1002, 1071) and Christopher M. Beausoleil (Ex. 1077); and Patent Owner relies on the Declaration of

[3] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. §§ 102 and 103, effective March 16, 2013. The '467 patent issued before the effective date of the AIA. Ex. 1001, code (45). Thus, pre-AIA version of §§ 102 and 103 applies.
[4] US 2004/0038269 A1, published Feb. 26, 2004 (Ex. 1003).
[5] WO 2005/111210 Al, published Nov. 24, 2005 (Ex. 1011).
[6] US 2005/0123928 Al, published Jun. 9, 2005 (Ex. 1008).
[7] US 6,776,959 B1, issued Aug. 17, 2004 (Ex. 1019).
[8] WO 2006/096973 A1, published Sept. 21, 2006 (Ex. 1023).

Louis DeFilippi, Ph.D. (Ex. 2001), and the Amended Supplemental Expert Report of Dr. Louis DeFilippi (Ex. 2033[9]).

V. ANALYSIS

The Board has jurisdiction under 35 U.S.C. § 6 and issues this Final Written Decision pursuant to 35 U.S.C. § 318 and 37 C.F.R. § 42.73. For the reasons provided below, we conclude Petitioner has established by a preponderance of the evidence that claims 1–17 and 24–42 of the ’467 patent are unpatentable. We find Petitioner, however, has not met its burden to show that claims 18–23 are unpatentable. Nonetheless, as noted above, we enter Adverse Judgment against Patent Owner as to all challenged original claims. *See Supra* Section III.

A. Principles of Law

To prevail in this *inter partes* review, Petitioner "shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence." 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d) (2019).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying

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[9] Patent Owner originally filed the Supplemental Declaration of Dr. Louis DeFilippi (Ex. 2015) on February 11, 2022. It later sought, and we granted, leave to amend that declaration. Papers 53, 62. Patent Owner filed an Amended Supplemental Declaration of Dr. Louis DeFilippi (Ex. 2033). In this Decision, we cite to Exhibit 2033 and treat all citations to Exhibit 2015 in the Papers and Exhibits as citations to Exhibit 2033.

factual determinations, including (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) when in evidence, objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *KSR*, 550 U.S. at 406.

This analysis, however, "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 406; *see also In re Preda*, 401 F.2d 825, 826 (CCPA 1968) ("[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."). 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." *KSR*, 550 U.S. at 420.

Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *In re Magnum Oil Tools International, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (citations omitted).

We analyze the instituted grounds of unpatentability in accordance with these principles.

B. Level of Ordinary Skill in the Art

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

Here, Petitioner asserts that, at the relevant time,

> [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.

Pet. 7 (citing Ex. 1002 ¶¶ 37–38).

Patent Owner disagrees with Petitioner's definition of the skill level in two aspects. First, Patent Owner argues "a POSA would not have experience with 'development' of nucleic acid extraction formulations." PO Resp. 3. Patent Owner points out that Petitioner's declarant, Dr. Taylor, does not have such experience. *Id.* That Dr. Taylor personally may not have been involved with this type of assay or formulation development, however, 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, 3012;[10] *Okajima*, 261 F.3d at 1355.

Second, Patent Owner alleges that requiring an ordinarily skilled artisan to have "experience" with the literature is ambiguous. PO Resp. 3. 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 Petitioner's proposed definition of the skill level may be misconstrued, we substitute "awareness" for "experience."

In sum, an ordinarily skilled artisan at the critical time 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. Such an artisan also is presumed to be aware of all the pertinent prior art, including literature concerning nucleic acid extraction and analysis.

We further note that, at the 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.

C. Claim Construction

In an *inter partes* review, we construe a claim term "using the same claim construction standard that would be used to construe the claim in a

[10] Farrell, RNA Methodologies: A Laboratory Guide for Isolation and Characterization (3rd ed., 2005) (Ex. 3012 ("Farrell")). Petitioner filed Farrell as Exhibit 1026 in all the related cases but did not do so in this proceeding. We add the reference into the record to facilitate the discussion.

civil action under 35 U.S.C. [§] 282(b).” 37 C.F.R. § 42.100(b) (2020). Under that standard, the words of a claim “are generally given their ordinary and customary meaning,” which is “the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc).

Petitioner does not propose any claim construction in the Petition. In our decision to institute, we gave all claim terms their respective plain and ordinary meaning. *See* Paper 13, 7 & n.7. During trial, the parties dispute the meaning of the terms “kill pathogens,” “not degrade nucleic acids,” and “inactivate nucleases.” *See* PO Resp. 4–17; Reply 1–5. We address each of these terms below.

1. Kill Pathogens

Each challenged claim requires a composition with reagents “together present in an amount sufficient to . . . kill pathogens” of a biological sample “suspected to contain pathogens.” The Specification of the ’467 patent does not expressly define “kill pathogens” and the parties did not formally construe this term 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 infectio[u]s pathogens.’” Prelim. Resp. 15.

On the limited record before us, we concluded that the challenged claims do not require “the claimed composition to clear every sample of every type of pathogenic agent.” DI 20. Applying its 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.* at 20, 33. For the reasons discussed below, we further refine our initial construction.

We first address what pathogens are within the scope of "kill pathogens." During the hearing, Patent Owner's counsel clarified that "kill pathogens" only applies to those classes of pathogen disclosed in the Specification. Tr. 104:8–105:11, 134:11–15. According to Patent Owner's counsel, those classes are "viruses, bacteria, and spores." *Id.* at 122:9–135:15.

By way of explanation, some bacteria have the capacity to form spores (endospores) under adverse environmental conditions. *See* Ex. 1046, 50:6–23. 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"); Ex. 1046, 54:13–56:3 (Dr. Birkebak at Assured Bio Labs ("ABL")[11] testifying that spores are more resistant to desiccation and disinfection).

Contrary to the assertion of Patent Owner's counsel that the Specification disclosed spores, we do not identify any disclosure of bacterial spores in the '467 patent. In addition, Dr. DeFilippi, Patent Owner's declarant, 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

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

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, 136:1–137:8. Also pertinent to our understanding of "kill pathogens," Dr. DeFilippi testified that "[a] spore in the form of a spore is not pathogenic" but a "prepathogen." Ex. 1064, 186:19–187:10.

Discussing killing bacteria and inactivating viruses,[12] the Specification 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.* at 18:30–48 (listing various microorganisms that may be present in a biological sample), claim 17 ("the biological sample contains viral particles, virally infected cells, bacteria, bacterially infected cells, fungal organisms"). In light of the above, we understand "kill pathogens" to encompass the killing or inactivation of fungi, viruses, or vegetative bacteria capable of causing disease—but excluding bacterial spores, which are neither pathogens (according to Dr. DeFilippi) nor disclosed in the Specification.

Having addressed the scope of "pathogens," we turn to Patent Owner's contention that "kill pathogens" means "rendering the sample substantially non-pathogenic 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." PO Resp. 11

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[12] 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 purposes of this Decision we consider inactivation synonymous with killing.

(citing Ex. 2033 ¶ 10); *see also id.* at 21 n.1 (alternatively defining the term "as rendering the sample (that may contain pathogens) safe for shipment and handling (non-pathogenic)"); Tr. 134:19–135:14 (Patent Owner explaining that "substantially nonpathogenic . . . doesn't mean entirely").[13] According to Patent Owner,

> [t]he intrinsic record is clear that "kill pathogens" in the context of the "compositions of the present invention" does not refer merely to killing any two or more individual pathogen organisms, but to rendering the sample safe for transportation and handline [sic], or "inactivation of potentially infectious biological pathogens [of the sample suspected of containing pathogens] for safe handling and transport of specimens."

PO Resp. 4 (quoting Ex. 1001, 26:21–23) (third alteration in original).

Pointing to exemplary embodiments, the Title, and the Abstract of the '467 patent, Patent Owner contends that the "fundamental purpose" of the invention is to "provide a solution that simultaneously renders the sample (that may contain pathogens) safe for shipment and handling (non-pathogenic) while at the same time preserving nucleic acids and inactivating nucleases in the sample." *Id.* at 4–9 (citing Ex. 1001, Title, Abstract, 2:15–28, 3:1–10, 6:35–40, 9:25–39, 14:57–67, 15:61–16:9, 26:17–25); *see also* Sur-reply 5 ("[T]he '467 Patent repeatedly recognizes as one of its fundamental purposes rendering samples potentially containing dangerous pathogens safe for unsecured shipment to laboratory facilities.").

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[13] The '467 patent defines "substantially non-pathogenic" as "leaving less than about 10 percent, less than about 5 percent, etc., of the pathogenic activity." Ex. 1001, 19:67–20:3. Thus, we agree with Petitioner that "substantially non-pathogenic" would render the claims indefinite. *See* Reply 1 n.1 (citing Ex. 1001, 19:65–20:3).

As support, Patent Owner relies on *Praxair, Inc. v ATMI, Inc.*, 543 F.3d 1306 (Fed. Cir. 2008). PO Resp. 6–7; Sur-reply 4.

In support of its proposed construction, Patent Owner also relies on extrinsic evidence, including 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. *Id.* at 9–11 (citing 49 C.F.R. §§ 173.134(a)(1), (b)(4), (b)(5); Ex. 2016, 7). Specifically, Patent Owner asserts that "at the time of invention[,] it was known in the art that rendering a sample substantially non-pathogenic 'so it cannot cause disease when exposure to it occurs' was the regulatory standard for transport without Division 6.2 (Infectious Substance) restrictions of samples potentially containing pathogens." *Id.* at 10 (citing Ex. 2033 ¶¶ 8–10).

Petitioner disagrees with Patent Owner's analysis. Reply 1–2. According to Petitioner, the unclaimed goal of "safe handling and transport" is merely desirable, and not fundamental. *Id.* (citing Ex. 1001, 9:20–31, 14:57–15:2, 16:1–16). Thus, Petitioner argues Patent Owner's proposed construction improperly imports limitations into the claims. *Id.* at 1. Petitioner asks us to continue to give the term "kill pathogens" its plain meaning, that "some pathogens are killed." *Id.* Based on the evidence of record, we find Petitioner's argument more persuasive.

It is settled that the specification "is the single best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315. Extrinsic evidence, on the other hand, is less reliable and less significant in claim construction. *Id.* at 1317–19. Considering the extrinsic evidence Patent Owner refers to, including 49 C.F.R. § 173 and the USDOT packaging requirement, in view

of the Specification, we find that they provide limited value. This is because in summarizing its invention, the '467 patent discloses that it

> 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.

Ex. 1001, 3:16–27. Although a statement's location is not determinative, statements that describe the invention as a whole, such as those in the Summary of the Invention, rather than statements that describe only preferred embodiments, are more likely to support a limiting definition of a claim term. *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 864 (Fed. Cir. 2004). The Summary of the Invention of the '467 patent, however, does not mention, let alone focus on, "kill pathogens."

Indeed, nowhere in the '467 patent Specification does it state any one goal is mandatory. Instead, it discloses

> [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 (emphases added).

Using the conjunction "or," the '467 patent discloses "inactivating potentially infectious biological pathogens" as one of three alternative goals. The rest of the paragraph stating that achieving "two or more, or all three, of these goals" is preferable confirms our reading. Elsewhere, the '467 patent discloses that "[t]he compositions of the present invention provide clinical/environmental collection solutions that efficiently achieve ***at least three, and preferably all four*** of the following" benefits, including, "kill or inactivate potentially-infectious pathogens." *Id.* at 15:61–16:9 (emphasis added); *see also id.* at 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).

The '467 patent discloses that it is "desirable" that "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." *Id.* at 9:25–31. Thus, we agree with Petitioner that "kill pathogens" for "safe handling and transport" does not amount to the "fundamental purpose" of the '467 patent. *See* Reply 1–2.

Our conclusion is consistent with the Federal Circuit's decision in *Praxair*. There, the court addressed the term "flow restrictor," finding 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 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.* The court, however, 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. Thus, in line with the reasoning in *Praxair*, we reject Patent Owner's proposed construction, which would require us to import a desired goal from the Specification into the challenged claims.

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

2. Not Degrade Nucleic Acid

Each challenged claim requires a composition with reagents "together present in an amount sufficient to . . . not degrade nucleic acid." Patent Owner acknowledges "a POSA's understanding that it is not possible to achieve exactly 0% degradation." PO Resp. 12. According to Patent Owner, that understanding, however, does not render the term "not degrade nucleic acid" "so meaningless as to allow any amount of degradation (10% or 20% or 50% or 80%)." *Id.* (citing Ex. 2033 ¶¶ 13–17). Instead, Patent Owner argues that an ordinarily skilled artisan would understand the term as referring to "as stable as possible, such as disclosed in the most stable embodiments in the '467 Patent disclosure," which "preserves 'at least about 98% of the polynucleotides' upon prolonged storage and 'no more than about 1 or 2% of the sample will be degraded.'" *Id.* at 13 (internal citations omitted).

Petitioner counters that Patent Owner's proposed construction "arbitrarily impose[s] numerical limits of 'even more preferabl[e]' embodiments to the exclusion of other explicitly disclosed embodiments." Reply 3 (second alteration in original). We agree with Petitioner.

As an initial matter, the '467 patent defines "nucleic acid" as DNA or RNA. *See* Ex. 1001, 17:39–49 (stating "the term 'nucleic acid' includes ***one or more types*** of: polydeoxyribonucleotides (containing 2-deoxy-D-ribose), polyribonucleotides (containing D-ribose)" and others) (emphasis added); *see also id.* at 17:49–54 (stating that exemplary nucleic acids include various types of DNA, RNA, "and any combination thereof").

Patent Owner relies on certain passages of the '467 patent to support its proposed construction. *See* PO Resp. 12 (citing Ex. 1001, 10:37, 9:62–67). Patent Owner, however, isolates the selected sentences from their contexts. For example, Patent Owner refers to the '467 patent for stating "no more than 1 or 2% of the sample will be degraded" (*id.* (citing Ex. 1001, 10:37)), while ignoring that is only "[i]n some instances" (Ex. 1001, 10:34). Similarly, according to Patent Owner, the '467 patent discloses "at least about 98% of the polynucleotides contained within the stored sample will not be degraded upon prolonged storage of the sample." PO Resp. 12 (citing Ex. 1001, 9:62–67). Yet, Patent Owner conveniently omits the immediately preceding language, describing the quoted portion as merely an "even more prefer[red]" embodiment.[14] *See* Ex. 1001, 9:65.

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[14] In each instance here, when quoting the '443 patent disclosure, Patent Owner alters the first letter of the first word by capitalizing it to make a complete sentence. *See* PO Resp. 12 (citing Ex. 1001, 10:37, 9:62–67). In

In fact, the ’467 patent discloses:

> 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.

Id. at 9:57–67.

Patent Owner does not explain sufficiently why an ordinarily skilled artisan would understand the term “not degrade nucleic acid” to require preserving “at least about 98% of the polynucleotides,” when the ’467 patent nowhere defines the lower limit of that term and explicitly states that preserving “at least about 70%” polynucleotides is within the scope of its invention. *See id.* Moreover, the ’467 patent states that preserving “at least about 70%” polynucleotides is “desirable.” *Id.* at 9:62–63. Thus, we agree with Petitioner that Patent Owner “cherry-picks ‘the most stable embodiments,’ but ignores other portions of the specification.” *See* Reply 3.

Patent Owner argues that Petitioner’s declarant, Dr. Taylor, “agreed that the Specification provides a definition of ‘does not degrade nucleic acid’ using the term ‘i.e.’” PO Resp. 13–14. Patent Owner relies on the sentence in the ’467 patent, which discloses that its composition stabilizes the nucleic

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our view, it appears unlikely that Patent Owner merely overlooked the context of each cropped phrase. We remind the parties the importance of representing facts truthfully before the Board. *See* 37 C.F.R. § 42.11(a).

acids so they "remain at least substantially non-degraded (i.e., at least substantially stable) even upon prolonged storage of the composition." *Id.*

To the extent Patent Owner equates "not degrade nucleic acid" with the notion that nucleic acid is "substantially stable," this does not support Patent Owner's assertion that "not degrade nucleic acid" requires preserving "at least about 98% of the polynucleotides." Indeed, the '467 patent discloses that "preventing substantial degradation would refer to less than about 15 weight percent, less than about 10 weight percent, preferably less than about 5 weight percent, etc., being lost to degradation." Ex. 1001, 19:62–65.

The '467 patent summarizes its invention as providing a formulation to preserve nucleic acids of a sample "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.* at 3:19–27. In other words, the underlying goal of the '467 patent invention is to isolate and preserve nucleic acids for analysis "using conventional molecular biology methods." *See id.* at 1:27–31.

Indeed, in a preferred embodiment, the Specification discloses

> 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.

In view of the Specification, we construe "not degrade nucleic acid" to mean preserving sufficient RNA or DNA for analysis using conventional nucleic acid detection methods known to an ordinarily skilled artisan at the time of the invention.

3. Inactivate Nucleases

Each challenged claim requires a composition with reagents "together present in an amount sufficient to . . . inactivate nucleases." Patent Owner argues that "nucleases" in the plural "would for a POSA refer to types of nucleases, rather than multiple nuclease molecules." PO Resp. 15 (citing Ex. 2033 ¶¶ 19–21). Emphasizing "the consistent pairing of RNA/DNA in the Specification," Patent Owner asserts "[t]he intrinsic record of the '467 Patent consistently refers to both DNA and RNA with regards to inactivation of nucleases and preservation of nucleic acid." *Id.* at 15–16 (citing Ex. 1001, 6:35–43, 14:57–15:1, 26:17–24; Ex. 2033 ¶¶ 19–22). Patent Owner further refers to the testimony of Dr. Taylor, Petitioner's declarant, for stating that because the term "[n]ucleases is plural," he understands "both DNA and RNA nucleases are involved." *Id.* at 17 (citing Ex. 2020, 298:16–28). Thus, Patent Owner asks us to construe the term "inactivate nucleases" to require "inactivation of both RNA and DNA nucleases." *Id.* at 16.

Petitioner contends that Patent Owner's proposed construction "is contrary to the plain language of the claims and the specification." Reply 4. Petitioner argues that Patent Owner cannot rely on Dr. Taylor for claim construction. *Id.* at 5. Instead, Petitioner refers to the '467 patent for disclosing that its compositions "typically at least substantially inactivate, and preferably entirely inactivate, any endogenous or exogenous RNAses ***or*** DNAses present in the sample." *Id.* at 4 (quoting Ex. 1001, 6:23–26). According to Petitioner, "the specification uses the plural RNa***ses*** or DNa***ses***, consistent with the limitation 'nuclea***ses***,'" because "there are many RNases that degrade RNA and many DNases that degrade DNA." *Id.*

Considering the totality of the evidence, and as explained below, we agree with Petitioner that "inactivate nucleases" encompasses inactivating DNases or RNases (or both) in a sample.

As an initial matter, it is undisputed that there are entire families of both RNases and DNases. *See* Ex. 1064, 143:22–144:21, 146:7–16; *see also* Ex. 3012, 48 ("RNases are a family of enzymes present in virtually all living cells."). Thus, "nucleases," in its plural form, can refer to multiple RNases or multiple DNases.

More importantly, the Specification states one of the benefits of its solutions is "[p]reservation of RNA and/or DNA integrity within the sample." *See* Ex. 1001, 15:14–15; *see also id.* at 5:62–63 (referring to nucleic acids as "RNA and/or DNA"), 6:34 (discussing "RNA and/or DNA analysis"), 7:46–47 (stating the composition is "for the collection of nucleic acids such as RNA and/or DNA"), 8:13–14 (describing lysing cells "to release RNAs and/or DNAs from the sample"). Thus, in view of the Specification, we interpret "DNA/RNA" as "DNA and/or RNA," and do not require it to encompass both DNA and RNA.

Indeed, the Specification explicitly discloses that

> [t]he 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, 6:23–30 (emphasis added); *see also id.* at 9:21–24 ("Preferably, one or more components of the disclosed composition are effective to kill,

inactivate, or substantially inhibit the biological activity of a DNAse ***or*** an RNAse, when such a protein is present in the sample.") (emphasis added).

In sum, guided by the Specification, we determine the term "inactivate nucleases," encompasses, but does not require, inactivating both RNase and DNase. Instead, we construe the term to mean inactivate RNase or DNase.

D. Relevant Disclosures of Prior Art

1. Birnboim

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, isolated nucleic acid can be that of the sputum or saliva donor 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, mitocho[n]dria, ribosomes, bacteria, or viruses"), 18 ("The nucleic acid to be preserved by the composition 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 "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" to mean "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 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.

In Example 1, Birnboim discloses an embodiment wherein a subject spits saliva into a collection tube which is mixed with an equal volume of the nucleic acid-preserving composition. *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.

In Example 3, Birnboim discloses the collection and extraction of DNA using a nucleic acid-preserving composition 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. Birnboim also 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.

In Example 4, Birnboim subjects the DNA extracted from saliva collected in the composition of Example 3 and stored for 14 days to agarose gel electrophoresis and ethidium bromide staining, noting "the characteristic band of chromosomal DNA present in all samples." *Id.* ¶ 117, Fig. 1.

In Examples 5 and 6, Birnboim analyzes samples 62 and 30 days, respectively, after collection. *Id.* ¶¶ 118–121. Birnboim subjects "[m]inimally purified DNA" to real time PCR. *Id.* According to Birnboim, the results using real time PCR demonstrate the suitability of the DNA for PCR analysis. *Id.* ¶ 119.

2. <u>Mori</u>

Mori teaches isolating 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. 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.

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 teaches that the nucleic acid stabilizing

agent is a reducing agent, preferably a mercapto compound such as mercapto ethanol. *Id.* at 63 (stating a reducing agent has "functions to inactivate the nuclease activity"). Mori further teaches 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. Specifically, Mori teaches using a silicon-based defoaming agent, such as dimethyl polysiloxane (*id.*), which, Petitioner asserts, and Patent Owner does not dispute, is a silicone polymer (*see* Pet. 49).

Mori teaches an anionic surfactant or a cationic surfactant as a preferred surfactant. Ex. 1011, 61. According to Mori,

> [n]onionic 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, 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. Mori states that "[t]he concentration of the surfactant in the nucleic acid-solubilizing reagent is preferably from 0.1 to 20% by weight." *Id.* at 62.

3. Das

Das is directed to techniques for detecting *Mycobacterium Tuberculosis* in clinical samples using PCR amplification. Ex. 1008 ¶¶ 1, 29, 37–38. Specifically, Das teaches "methods of nucleic acid extraction and

mix of reagents to lyse mycobacteria and purify nucleic acid from a clinical specimen." *Id.* ¶ 38. Das teaches a modified lysis buffer to lyse the mycobacteria cells in a specimen sample and extract the nucleic acid, where the lysis buffer contains guanidinium isothiocyanate (chaotrope), N lauryl sarcosyl (detergent), β-ME (reducing agent), EDTA (chelator), and Tris (buffer). *Id.* ¶¶ 63–64, 89. According to Das, "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.

4. <u>Helftenbein</u>

Helftenbein teaches a vessel for withdrawing blood, the vessel containing a guanidinium salt (preferably guanidinium thiocyanate and/or guanidinium chloride), a buffer (such as Tris, HEPES, MOPS, citrate, or phosphate buffer), a reducing agent (such as DTT, β-ME, or TCEP), and/or

detergent (such as Triton X-100, NP40, Tween 20, or polidocanol) as components. Ex. 1019, Abstract, 2:38–44, 3:4–35. According to Helftenbein, these reagents form a nucleic acid-stabilizing substance (N-sS). *Id.* at 2:46–48, 4:60–64. In one embodiment, Helftenbein teaches when blood is drawn into the vessel and mixed with an equal volume of N-sS, "[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).

Helftenbein teaches adding an internal standard to N-sS. According to Helftenbein, "[t]his permits the control of the whole method from the moment of sampling up to the detection of nucleic acids." *Id.* at 2:60–63.

5. Birnboim 2006

Birnboim 2006 teaches aqueous composition "for the extraction of nucleic acid from a sample of bodily fluid, such a[s] saliva, wherein the extracted nucleic acid is stable for at least fourteen days at room temperature." Ex. 1023, Abstract. According to Birnboim 2006, the composition "permits direct use of the extracted and stored DNA in an amplification reaction without further processing." *Id.*

6. Other Prior Art

Petitioner also presents numerous other prior art references. Although they do not form the bases of the asserted unpatentability challenges, we consider them in our analyses because they provide the background knowledge of an ordinarily skilled artisan. *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").

For example, the 1982 Maniatis Laboratory Manual teaches isolating RNA using a buffered, nuclease-free, aqueous solution of guanidinium isothiocyanate (a chaotrope), sodium lauryl sarkosinate (a detergent), β-ME (a reducing agent), and EDTA (a chelator). Ex. 1004, 189–90.

Chirgwin teaches that disruption of cells "results in rapid mixing of RNA and RNase." Ex. 1015, 5294. According to Chirgwin, "[o]ne way to eliminate nucleolytic degradation of RNA is to denature all of the cellular proteins including RNase." *Id.* Chirgwin explains that "[t]his approach would be successful only if the rate of denaturation exceeds the rate of RNA hydrolysis by RNase." *Id.* "The rate of denaturation," Chirgwin continues, "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 intact RNA "from tissues rich in ribonuclease such as the 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." *Id.* at Abstract. In particular, Chirgwin's formulation contains 4 M guanidine thiocyanate, 0.5% of sodium N-lauroylsarcosine, 25 mM sodium citrate, 0.1 M β-ME, and 0.1% Antifoam A. *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. In addition, "for some cultured cells no homogenization is needed since the cells lyse upon addition of the guanidine solution." *Id.* at 5296.

Farrell is a laboratory guide describing the isolation and characterization of RNA. Ex. 3012, Title. Farrell teaches 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. According to Farrell, various compounds have been used to inhibit RNase activity, including vanadyl ribonucleoside complexes, RNasin, heparin, iodoacetate, polyvinyl (dextran) sulfate, cationic surfactant, macaloid and bentonite clays. *Id.* at 50–53. Furthermore, readily available reagents, such as hydrogen peroxide, and mixtures of sodium hydroxide and SDS also inhibit RNase activity. *Id.* at 53.

Farrell states that "stock solutions and buffers prepared in the laboratory can be treated, directly or indirectly, with the potent chemical RNase inhibitor [diethylpyrocarbonate] DEPC." *Id.* at 55. Farrell notes that "DEPC is an efficient, nonspecific inhibitor of RNAse," but "must be destroyed completely" after the treatment, because "[e]ven trace amounts of residual DEPC will result in chemical modification of the base adenine." *Id.* For the same reason, Farrell cautions that DEPC should not be added directly to cell suspensions or lysates containing RNAs to be purified. *Id.* at 56.

Farrell teaches that there are additional "legitimate reasons" not to use DEPC in the laboratory. *Id.* at 57. Instead, according to Farrell,

> [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.

Other references, such as Goldrick (Ex. 1009) and Koller (Ex. 1016), provide further background of the knowledge in the relevant field. Goldrick teaches methods and compositions for the “recovery of nucleic acid from in vitro reaction mixtures that contain nucleases.” Ex. 1009, 1:8–11. Goldrick’s compositions include chaotropes, reducing agents, detergents, chelating agents, and buffers. *Id.* at 4:57–5:28, 7:30–8:54. Goldrick also incorporates into its composition a “carrier” that “serves to promote precipitation of minute amounts of RNA.” *Id.* at 3:38–48.

Koller teaches “methods and compositions for isolation of nucleic acids from cells.” Ex. 1016, Abstract. Koller’s composition “contain[s] a chaotropic agent, salt, detergent and a reducing agent.” *Id.* at 7:1–3.

E. Alleged Obviousness over Birnboim

Petitioner asserts that claims 1–9, 15–17, and 29–39 would have been obvious over Birnboim.[15] Pet. 32–42, 45–48. After reviewing the entire record developed at trial, and as explained below, we determine that Petitioner has shown, by a preponderance of the evidence, that Birnboim teaches or suggests each limitation of claims 1–9, 15–17, and 29–39. Petitioner has also shown that an ordinarily skilled artisan would have had a

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[15] Petitioner also asserts claims 18–23 would have been obvious over Birnboim. Pet. 42–45. We address those claims separately. *See infra* Section V.F.

reason to modify the teachings of Birnboim and would have had a reasonable expectation of success when doing so.

1. Claim 1

Petitioner argues that Birnboim teaches preserving nucleic acids from a bacterium or a virus. Pet. 9–10 (citing Ex. 1003 ¶ 27); *see also id.* at 19 (the same). According to Petitioner, just like the ’467 patent, Birnboim teaches "using chaotropes, detergents, reducing agents, chelators, and buffers in their one-step aqueous compositions." *Id.* at 34 (citing Ex. 1003 ¶¶ 64–74, 115). And, just like the ’467 patent, Petitioner continues, Birnboim teaches "employ[ing] a combination of well-known compounds and use them in accordance with their well-understood functions" of denaturing proteins, killing pathogens, and preserving nucleic acids to "yield predictable results." *Id.* (citing Ex. 1003 ¶¶ 114–121).

Patent Owner alleges multiple faults with Petitioner's challenge. PO Resp. 19–28, 31–37. Specifically, Patent Owner contends that applying its claim construction, Birnboim does not teach "kill pathogens." *Id.* at 19–21. Patent Owner also argues that Birnboim's composition degrades nucleic acids, and does not inactivate nucleases. *Id.* at 25–28. Patent Owner further contends that Petitioner fails to show (1) Birnboim teaches chaotropes; or (2) an ordinarily skilled artisan would have modified Birnboim's Example 3 with a reasonable expectation of success. *Id.* at 31–37. On this record, we find Petitioner's arguments more persuasive.

a. Chaotropes and Detergents

As Petitioner points out, Birnboim teaches that its compositions stabilize nucleic acids and inhibit nucleases and microbial growth. Pet. 10 (citing Ex. 1003 ¶ 64). Birnboim specifically teaches that its compositions

contain (1) denaturing agents to lyse cells, denature proteins, inactivate nucleases, and inhibit microbial growth (*id.* (citing, e.g., Ex. 1003 ¶¶ 64, 68, 73, 84)); (2) reducing agents to prevent nucleic acid degradation (*id.* at 11 (citing Ex. 1003 ¶¶ 13, 14, 70–72)); (3) chelating agents to stabilize nucleic acids and inhibit microbial growth (*id.* (citing Ex. 1003 ¶¶ 64, 67, 68, 73)); and (4) buffers to maintain an appropriate pH to prevent nucleic acid degradation (*id.* (citing Ex. 1003 ¶ 64)). *See id.* at 19 (summarizing reagents and their functions in Birnboim's compositions). We agree with Petitioner, and Patent Owner does not dispute, that these well-known reagents perform well-understood functions. *See* Ex. 1003 ¶¶ 64–74.

Birnboim's Example 3 teaches a composition comprising urea, which is a chaotrope, and SDS, which is a detergent. *Id.* ¶ 115. Patent Owner contends that Birnboim does not teach "the use of chaotropes and detergents as individual and separate components." PO Resp. 34. Patent Owner argues that Birnboim's Example 3 just "happens to include" urea and SDS, both of which are labeled as "denaturing agents," a term Birnboim uses "extremely broadly." *Id.* at 33–34. According to Patent Owner, "[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." *Id.* at 34 (citing Ex. 2033 ¶ 27).

To the extent Patent Owner argues that an ordinarily skilled artisan would not have had a reason 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, we do not agree. An ordinarily skilled artisan would have understood the individual properties and uses of, as well as

relevant differences between, a chaotrope and a detergent. Indeed, 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.

Dr. DeFilippi, however, asserts, without any support, that "a POSA at the time of the invention was not aware of the relevance of this distinction." *Id.* That statement is contradicted by the prior art of record. Das, for example, teaches a lysis buffer containing the detergent N lauryl sarcosyl and the chaotrope 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 . . . 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 . . . and also ensure safety for the operator." *Id.* ¶¶ 38–39.

Similarly, Goldrick teaches isolating RNA using a mixture of, among other reagents, a chaotropic agent (guanidinium chloride or guanidinium thiocyanate) and a detergent (e.g., N-lauroyl sarcosine or SDS).

See, e.g., Ex. 1009, 7:30–8:54. Goldrick explains that the chaotropic agent is for inactivating nucleases, and the detergent and other ingredients, such as reducing agents, "aid in the inactivation of the nucleases." *Id.* at Abstract, 1:39–54; *see also id.* at claim 9 (reciting "the nuclease inactivation enhancing detergent is SDS or N-lauroyl sarcosine").

In addition, Farrell similarly discusses "homogenization in lysis buffers consisting of guanidinium thiocyanate or guanidinium hydrochloride is widely accepted as the method of choice." Ex. 3012, 58. Farrell explains that "[s]olutions containing guanidine HCl or guanidine thiocyanate (GTC) are often referred to as chaotropic buffers because of their biologically disruptive nature." *Id.* at 59; *see also* Ex. 1004, 189–90 (1982 Maniatis Laboratory Manual teaching solution for isolating RNA comprising guanidinium isothiocyanate, sodium lauryl sarkosinate, β-ME, and EDTA).

Furthermore, Koller teaches nucleic acid releasing compositions containing a chaotrope, detergent, reducing agent, and chelator salt. Ex. 1016, 7:1–5. According to Koller, "[t]he chaotropic component of the nucleic acid releasing composition is both an effective protein denaturant and a strong inhibitor of nucleases. The effect of a chaotropic agent on growing cells is an almost instantaneous dissolution of the cells." *Id.* at 7:19–23. Koller teaches urea as a useful chaotropic agent. *Id.* at 7:23–25. Koller also teaches that for the nucleic acid releasing composition, it is "beneficial to incorporate a surface-active anionic detergent to further aid in lysis and disruption of the cells," and SDS is such a detergent. *Id.* at 8:8–15.

Thus, the preponderance of the evidence shows that an ordinarily skilled artisan at the critical time would have understood the identity, as well

as the individual properties and use, of the various chaotropes and detergents (and other reagents), as well as the benefits of combining them in a single composition for isolating nucleic acids.

b. Kill Pathogens

Petitioner asserts that Birnboim's compositions inhibit and kill microbes in the sample. Pet. 33 (citing Ex. 1003 ¶¶ 21, 64, 73). Patent Owner counters that "Applying the Correct Claim Construction, Birnboim Does Not Teach Killing Pathogens." PO Resp. 19. As support, Patent Owner submits data from tests conducted by ABL of compositions prepared according to Birnboim Example 3. *Id.* at 20–21. Patent Owner asserts that "[t]he testing showed that Birnboim's composition failed to kill the vast majority of both viral and bacterial pathogen organisms in a sample." *Id.* at 21. Thus, Patent Owner concludes "Birnboim's compound did not render a sample substantially non-pathogenic." *Id.* (citing Ex. 2033 ¶ 24). We disagree with Patent Owner's conclusions and analysis.

We explained in our Decision on Institution that "Birnboim expressly discloses isolating nucleic acid from bacteria and viruses. Ex. 1003 ¶¶ 18, 22, 27. It does not suggest such isolation as non-destructive, and we presume that at least some pathogens are 'killed' in the extraction process according to the plain and ordinary meaning of the term." DI 20. In other words, 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" would kill the bacterium or the virus. *See* Ex. 1003 ¶ 27. Consistent with our interpretation, Birnboim further teaches that its compositions may be "bactericidal," i.e., capable of killing bacteria. *Id.* ¶ 21. Thus, Birnboim teaches "kill pathogens."

Additional evidence of record supports our determination. Indeed, ABL test data initially withheld by Patent Owner [redacted]. Exs. 1202–1204; Ex. 1069, 272:13–273:7; Ex. 1071 ¶¶ 15–23.

Patent Owner downplays these data. PO Resp. 20 ("Even if Petitioner could show that Birnboim teaches a compound that would lyse some small subset of individual pathogen cells from a sample, that is a far cry from, and nothing in Birnboim teaches, rendering a sample substantially non-pathogenic."). Instead, it emphasizes other ABL test data showing Birnboim's compositions do not kill MS2 and *B. subtilis*. Sur-reply 6 (citing Ex. 2019); *see also* Ex. 2033 ¶ 24 (Dr. DeFilippi testifying that two Birnboim compositions were not able to "inactivate or kill MS2 viruses or *B. subtilis* bacteria").

As a preliminary matter, we note MS2 is a bacteriophage. Ex. 2019, 1. Other than ABL stating MS2 is "commonly used as a surrogate for human pathogenic virus" (*id.*), Patent Owner does not directly address whether MS2 is the type of pathogens contemplated in the Specification. In addition, ABL apparently included spores in its testing of *B. subtilis*. As explained above, under our construction, "kill pathogens" does not encompass the killing or inactivation of spores. *See supra* Section V.C.1. Thus, ABL's data on these two microorganisms have limited value.

Nonetheless, even if we were to accept Patent Owner's assertion that Birnboim's compositions failed to kill both viral (MS2) and bacterial (*B. subtilis*) pathogen organisms in a sample, we still must reject its conclusion that Birnboim's compositions do not "kill pathogens." *See* PO

Resp. 20–21. As explained above, "kill pathogens" does not require that every pathogen in sample is killed. Instead, it merely requires killing or inactivating some fungal, viral, or vegetative bacterial pathogens in a sample. *See supra* Section V.C.1. [redacted]

c. Not Degrade Nucleic Acid

Petitioner argues that Birnboim teaches this limitation because its compositions "preserve sufficient quantities of nucleic acids for subsequent analysis." Pet. 33 (citing Ex. 1003 ¶¶ 88, 116–121). Patent Owner contends that nothing in Birnboim teaches this limitation because its compositions do not preserve RNA and only preserve 50% of the DNA in a sample. PO Resp. 25. Based on this record, we agree with Petitioner's argument.

Birnboim is directed to isolating nucleic acids from a sample and stabilizing the isolated nucleic acids for future analysis. *See* 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 (i.e., 20° C. to 25° C.) for the specified time period." *Id.* ¶ 45; *see also id.* ¶¶ 2 (teaching its compositions are "for preserving nucleic acids at room temperature for extended periods of time"), 25 (teaching that, in one embodiment, the isolated DNA is stable "for more than 14 days, desirably more than 30 days, and more desirably more than 60 days," and in another embodiment, when its composition does not contain ascorbic acid, a specific reducing agent, "the DNA is stable for more than 60 days, and desirably more than 360 days").

As explained above, the ’467 patent does not define the lower limit of the nucleic acid that must be preserved to be encompassed by “not degrade nucleic acid.” *See supra* Section V.C.2 (citing Ex. 1001, 9:62–63 (stating preserving “at least about 70%” polynucleotides is “desirable”)). Instead, the term “not degrade nucleic acid” means preserving sufficient RNA or DNA for analysis using conventional nucleic acid detection methods known to an ordinarily skilled artisan at the time of the invention. *Id.* Under our construction, Birnboim’s compositions satisfy this limitation.

Indeed, Birnboim teaches isolating nucleic acids “for any application requiring a nucleic acid sample,” including, for example, “forensic applications, medical applications (including genetic screening and disease typing), and paternity testing.” Ex. 1003 ¶ 88. In addition, as Petitioner correctly points out, “Birnboim Examples 4–6 establish that the DNA is successfully stabilized and preserved sufficiently to analyze the DNA via gel electrophoresis (Example 4) and via PCR (Examples 5 and 6).” Pet. 20 (citing Ex. 1003 ¶¶ 116–122). Thus, we are persuaded that Birnboim’s compositions do “not degrade nucleic acid” beyond the extent allowed by the challenged claims.

Patent Owner points to Birnboim’s Example 3, which includes NaOAc (sodium acetate) and LiCl (lithium chloride) in the composition.[16] PO Resp. 26–27. Patent Owner argues that these ingredients, not recited in

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[16] Claim 1 recites a mixture “containing” five categories of reagents. The term “containing,” like the transition phrase “comprising,” is open-ended. *Mars Inc. v. H.J. Heinz Co.*, 377 F.3d 1369, 1376 (Fed. Cir. 2004). Thus, the claimed mixture includes the listed reagents, but does not exclude others.

challenged claim 1, are responsible for the preservation of DNA. *Id.* We are not persuaded.

As a preliminary matter, we note that, for its obviousness challenge, Petitioner relies on not only Example 3, but also the general teachings of Birnboim. *See* Pet. 33–34 (citing Ex. 1003 ¶¶ 2, 21, 64–74, 84, 88, 114–121). And the general teachings of Birnboim do not suggest that either NaOAc or LiCl must be present in the composition.

Nonetheless, in our Decision to Institute, we explained that an ordinarily skilled artisan would have understood the roles of NaOAc and LiCl. DI 22. Patent Owner argues that is not true. PO Resp. 27. According to Patent Owner, the parties' experts propose competing hypotheses of why Birnboim includes LiCl and NaOAc. *Id.* (citing Ex. 2001 ¶ 39; Ex. 2020, 201:1–2, 201:21–203:2). We disagree with Patent Owner's argument.

NaOAc and LiCl are salts frequently used in the art, often in the context of promoting nucleic acid precipitation from aqueous samples. *See, e.g.*, Ex. 1004, 192 (using NaOAc to wash/precipitate nucleic acids); Ex. 1009, 1:66–68 (same); Ex. 1013, 4.3.1 ("separation of RNA from DNA and other impurities by selective precipitation using [2 M and 8 M] LiCl"), 4.5.2 (0.15 M LiCl as a wash buffer component, precipitating "RNA by adjusting the salt concentration to 0.3 M sodium acetate"); Ex. 1018, 15:55–67 (discussing commercial RNA extraction kits comprising LiCl in combination with guanidine or urea).

In Birnboim's Example 3, the formulation with NaOAc "stabilizes DNA for *longer periods of time*" than the formulation with LiCl. Ex. 1003 ¶ 115 (emphasis added). That result, however, does not mean a formulation without NaOAc does not sufficiently stabilize sufficient DNA "for analysis

using conventional nucleic acid detection methods known to an ordinarily skilled artisan at the time of the invention," which is all that is required to satisfy the limitation of "not degrade nucleic acid." *See supra* Section V.C.2.

In addition, Koller teaches nucleic acid releasing compositions comprising "a chaotropic agent, salt, detergent and reducing agent." Ex. 1016, 7:1–3. Koller explains that salt is "at a concentration effective to aid in the dissociation, purification and eventual dissolution of the isolated nucleic acids." *Id.* at 8:27–29. The type of salt included in the composition, Koller continues, "is not critical." *Id.* at 8:33–34; *see also id.* at 8:35–9:2 ("For example[,] sodium chloride, sodium acetate, potassium acetate, ammonium acetate or other derivatives thereof, would suffice, however, optimum results are obtained with either sodium chloride or sodium acetate."). Patent Owner does not present competent evidence or otherwise explain adequately how NaOAc and LiCl would be responsible for preserving DNA.

In sum, we find Petitioner has met its burden in showing that the ingredients recited in claim 1, as taught in Birnboim, do "not degrade nucleic acid."

d. Inactivate Nucleases

Petitioner argues that Birnboim teaches protecting nucleic acid from "breakdown" by nucleases. Pet. 33 (citing Ex. 1003 ¶ 68). We agree with Petitioner.

Under our construction, the term "inactivate nucleases" means inactivating RNase or DNase. *See supra* Section V.C.3. The parties do not dispute that Birnboim teaches inactivating DNase. *See* Ex. 1003 ¶ 68

(teaching that strong chelators and denaturing agents inactivate DNases). For this reason alone, Birnboim teaches "inactivate nucleases."

Moreover, Birnboim explicitly teaches that its composition may "include[] an inhibitor of ribonuclease." Ex. 1003 ¶ 22. According to Birnboim, "[t]he inclusion of an inhibitor of ribonuclease in the composition of the invention is particularly desirable 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.* Birnboim explains that 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 teaches including denaturing agents, such as urea, SDS, guanidinium chloride, and guanidinium thiocyanate, in "the nucleic acid preserving composition" of its invention. *Id.*

Patent Owner contends that, in an unrelated district-court proceeding, Petitioner admitted that Birnboim is not enabled for inactivating RNases to preserve RNA. PO Resp. 25 (citing Ex. 2013). Petitioner counters that the statements Patent Owner relies on were "made by the ***assignee*** of the Birnboim reference." Reply 9 (citing Ex. 2013 ¶¶ 85, 122, 123, 131). In our opinion, Petitioner embraced those statements to support an argument that patents having the same specification as Birnboim were prosecuted in bad faith. *See, e.g.*, Ex. 2013 ¶¶ 75, 133–141, 155. Despite so, as explained below, we find all of the prior art as a whole, enables inactivating RNases to preserve RNA.

"In general, a prior art reference asserted under § 103 does not necessarily have to enable its own disclosure, i.e., be 'self-enabling,' to be relevant to the obviousness inquiry." *Raytheon Techs. Corp. v. Gen. Elec.*

Co., 993 F.3d 1374, 1380 (Fed. Cir. 2021). Instead, "such a reference may be used to supply claim elements enabled by other prior art or evidence of record." *Id.* In this case, other prior art of record shows an ordinarily skilled artisan were enabled to use the reagents taught in Birnboim to inactivate RNases.

Indeed, Birnboim teaches denaturing agents, including guanidinium chloride and guanidinium thiocyanate, can inhibit RNase activity. Ex. 1003 ¶ 68. Farrell lists reagents "commonly used to minimize or eliminate RNase activity." Ex. 3012, 58. According to Farrell, "[f]or cells enriched in RNase, and even those that are not, homogenization in lysis buffers consisting of guanidinium thiocyanate or guanidinium hydrochloride is widely accepted as the method of choice." *Id.* Farrell teaches that "[a]t a working concentration of about 4 to 6 M (in water)," guanidinium hydrochloride is "an excellent inhibitor of RNase activity during purification of nucleic acids." *Id.* at 59. Farrell further teaches that guanidinium thiocyanate, as "a stronger protein denaturant than guanidine hydrochloride," "is the denaturant of choice for the preparation of RNA from sources enriched in RNase activity, especially pancreatic tissue (Chirgwin *et al.*, 1979)." *Id.* Farrell states that guanidinium thiocyanate "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])." *Id.*; *see also* Ex. 1004, 189 (teaching making 4 M guanidinium isothiocyanate to inactivate RNase); Ex. 1015, 5294, 5298 (teaching preparing intact RNA "from tissues rich in ribonuclease such as

the rat pancreas by efficient homogenization in a 4 M solution of the potent protein denaturant guanidinium thiocyanate plus 0.1 M 2-mercaptoethanol").

Thus, we find that an ordinarily skilled artisan would have understood Birnboim to teach inactivating, not only DNases, but also RNases. For this additional reason, Birnboim teaches "inactivate nucleases."

Patent Owner argues that "Birnboim's Example 3 composition does not deactivate RNases." PO Resp. 27–28. As support, Patent Owner relies on ABL testing data, allegedly showing "a solution prepared according to Birnboim's Example 3 allows RNA in a sample to fully degrade within hours, demonstrating that the RNAses in the sample must not have been effectively deactivated." *Id.* (citing Ex. 2033 ¶¶ 19–22).

Relying on Dr. Taylor's testimony, Petitioner contends that "PO's results are unsurprising as its testing artificially spiked the RNase activity in the test samples to over 30,000 times that ordinarily found in saliva." Reply 10 (citing Ex. 1071 ¶ 35; Ex. 1073, 70:20–72:4; Ex. 1201; Ex. 1206; Ex. 1208, 207). We credit Dr. Taylor's testimony that ABL tested RNase "many thousands fold higher than the appropriate amount" because it is supported by the cited evidence. *See* Ex. 1071 ¶ 35 (citing Exs. 1075, 1208).

Patent Owner does not squarely address this issue in its Sur-reply. While making another argument, however, Patent Owner does contend that "inactivation [of RNase] turns on the number of RNA molecules." Sur-reply 3. This argument supports Petitioner's position that Patent Owner's testing data are unreliable because ABL tested an artificially high amount of RNases. *See* Reply 10; *see also* Ex. 1071 ¶ 35 (Dr. Taylor testifying "it is not possible to conclude that Assured Bio's RNase inactivation experimental design would provide any reliable experimental

evidence of Birnboim's solution not being capable of inactivating RNases or preventing degradation of RNA in a sample containing saliva"). Thus, we find Patent Owner's results on the inhibition of RNase activity to have limited probative value.

Furthermore, Dr. DeFilippi's testimony supports our finding that Birnboim teaches inactivating RNases. Indeed, 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.* at 525:17–19 ("We are denaturing proteins, and the result of denaturing proteins would be destroying the activity of enzymes."). Specifically, Dr. DeFilippi testified that he "would not suspect that one DNase or RNase in particular would be denatured relative to the other one not being denatured because we're denaturing proteins." *Id.* at 523:14–17.

In sum, based on this record, we find Petitioner has shown that Birnboim teaches "inactivate nucleases."

e. Reason to Modify and Reasonable Expectation of Success

Patent Owner argues that the Petition fails to show a reason to modify Birnboim's Example 3 with reasonable expectation of success.
PO Resp. 31–37. But, as explained above, for its obviousness challenge, Petitioner relies on the general teachings of Birnboim, as well as Example 3. *See supra* Section V.E.1.c.

Claim 1 of the '467 patent recites five general categories of reagents: chaotropes, detergents, reducing agents, chelators, and buffers. It requires these reagents to perform recited functions: denature proteins, inactivate nucleases, kill pathogens, and not degrade nucleic acid. As explained above,

Petitioner has shown that Birnboim teaches all the reagents recited, and those reagents together perform the recited functions. *See supra* Sections V.E.1.a–V.E.1.d.

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.*

Such is the case here. Petitioner argues, and we agree, Birnboim teaches "employ[ing] a combination of well-known compounds and use them in accordance with their well-understood functions" to "yield predictable results." Pet. 34. Thus, we find an ordinarily skilled artisan would have had a reason to use these known compounds to perform their known functions taught in the prior art with a reasonable expectation of success. *See KSR*, 550 U.S. at 417 ("If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability.").

f. Summary

After reviewing the record, we determine Petitioner demonstrates by a preponderance of the evidence that Birnboim teaches or suggests all limitations of claim 1, and that an ordinarily skilled artisan at the critical time would have had a reason to implement these teachings to arrive at the subject matter of claim 1 with a reasonable expectation of success. Patent Owner does not present evidence on objective indicia of nonobviousness. Thus, for the reasons discussed above, we determine Petitioner demonstrates by a preponderance of the evidence that claim 1 would have been obvious over Birnboim.

2. <u>Claim 2</u>

Claim 2 depends from claim 1, and further recites the concentration ranges for the five ingredient categories. Petitioner argues that Birnboim Example 3 teaches "a specific composition with a chaotrope, detergent, reducing agent, and buffer in amounts that fall within the claimed range[s]." Pet. 21; *see also id.* (comparing the ranges recited in claim 2 with the amounts taught in Birnboim) (citing Ex. 1003 ¶ 115). Acknowledging that "the concentration of the chelator (CDTA) in Birnboim's Example 3, at 3.3 mM, is higher than the range in claim 2 (0.01–1 mM)," Petitioner refers to Birnboim's teaching elsewhere that for CDTA, "concentrations in the 1–20 mM range are sufficient" and "other concentrations would work." *Id.* (citing Ex. 1003 ¶ 67). Thus, Petitioner contends that an ordinarily skilled artisan "would have been motivated to use a chelator at the claimed concentration of 0.01 mM–1 mM" and would have had a reasonable expectation of success when doing so. *Id.* at 34–35.

Patent Owner counters that "Birnboim provides no suggestion to reduce the concentration of CDTA by more than two-thirds." PO Resp. 37 (citing Ex. 2033 ¶ 29). We disagree.

Birnboim teaches that

> [t]he amount or concentration of chelator will depend upon the strength of the chelator, which would need to be determined empirically. For CDTA, concentrations in the 1–20 mM range are sufficient, however other concentrations would work, and the compositions of the invention are not intending to be limited to this range.

Ex. 1003 ¶ 67. CDTA is the chelator in Example 3. *Id.* ¶ 115. Thus, contrary to Patent Owner's assertion, Birnboim, in fact, explicitly teaches using

CDTA at the concentration of 1–20 mM, which overlaps with the "about 0.01 mM to about 1 mM" range recited in claim 2.

In cases involving overlapping ranges, the Federal Circuit has "consistently held that even a slight overlap in range establishes a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003); *see also In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997) (concluding a prior art reference that teaches the range 100–600 Å renders obvious a claimed invention with the range 50–100 Å); *In re Woodruff*, 919 F.2d 1575, 1577–78 (CCPA 1990) (concluding a prior art reference that teaches the range "about 1–5%" renders obvious a claimed invention with the range "more than 5% to about 25%").

The case for obviousness based on encompassing or overlapping ranges shifts the burden of production to the patentee to rebut the case, and this is applicable in the context of an *inter partes* review. *See E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1008 (Fed. Cir. 2018) ("'[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence' of teaching away, unexpected results, or other pertinent evidence of nonobviousness.") (quoting *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013)). Likewise, there is a rebuttable presumption grounded on a claimed range overlapping a range disclosed in the prior art. *Id.*

"The presumption [of obviousness] can be rebutted if it can be shown that the prior art teaches away from the claimed range, or the claimed range produces new and unexpected results." *Ormco Corp. v. Align Tech., Inc.*,

463 F.3d 1299, 1311 (Fed. Cir. 2006); *see also Peterson*, 315 F.3d at 1330–31 (the same). Here, Patent Owner has done neither.

Patent Owner contends "[t]he Petition and Taylor Declaration conclude that a POSA would try other concentrations and expect them to work without explaining why this motivates a POSA to reduce the chelator concentration to less than a third of the concentration in Example 3." PO Resp. 37 (citing Pet. 34–35; Ex. 1002 ¶ 170). We, again, disagree with Patent Owner's contention.

Both Petitioner and Dr. Taylor cite Birnboim for teaching CDTA at the concentration of 1–20 mM, which overlaps with the claimed range of 0.01–1 mM. Pet. 34–35 (citing Ex. 1003 ¶ 67); Ex. 1002 ¶ 170 (citing Ex. 1003 ¶ 67). As the Federal Circuit explained, "[s]uch overlap itself provides sufficient motivation to optimize the ranges." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012); *see also Peterson*, 315 F.3d at 1330 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of . . . ranges is the optimum combination."). Indeed, Birnboim's teaching that "[t]he amount or concentration of chelator . . . would need to be determined empirically" comports with the guidance from our reviewing court. *See* Ex. 1003 ¶ 67.

Moreover, both Petitioner and Dr. Taylor cite Das and Goldrick as examples of prior art that teaches an ordinarily skilled artisan "to use a chelator such as CDTA or EDTA at a concentration within the claimed range in aqueous solutions further comprising a chaotrope, a detergent, a reducing agent, and a buffer to preserve and stabilize nucleic acids." Pet. 35 (citing Ex. 1008 ¶¶ 63–64, claims 6–7; Ex. 1009, 5:5–11, 7:33–47,

11:64–68); Ex. 1002 ¶ 170 (citing the same). Thus, Petitioner has shown by a preponderance of the evidence that an ordinarily skilled artisan would have had a reason to change the concentration of the chelator in Birnboim's Example 3.

Patent Owner further contends that the effect of decreasing the concentration of chelator in Birnboim's Example 3 is unpredictable and "testing would be necessary." PO Resp. 32–38. Relying on Dr. Taylor's testimony that "the concentrations going up, going down . . . that would take research," Patent Owner argues that there would be no reasonable expectation of success. *See id.* at 36 (citing Ex. 2020, 399:22–400:12); *see also id.* at 33 (arguing that "the effect [of modifying Birnboim's Example 3] would be unknown and testing would be necessary") (citing Ex. 2020, 199:4–22). Patent Owner's argument is unavailing.

The Federal Circuit's opinion in *Pfizer, Inc. v. Apotex, Inc.* sheds light on the issue and guides our analysis. *See* 480 F.3d 1348 (Fed. Cir. 2007). There, the court asked where "a formulation must be tested by routine procedures to verify its expected properties . . . how far does that need for testing go toward supporting a conclusion of non-obviousness?" *Id.* at 1365. In answering that question, the court explained that "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Id.* at 1364.

In the instant case, we face the same question. Under the guidance of *Pfizer*, we find that, although there is some degree of unpredictability, "the mere possibility that [a chelator at certain concentration may not work] does not demand a conclusion that those that do are necessarily non-obvious." 480 F.3d at 1366. This is especially true here, where Birnboim explicitly

teaches a concentration range that overlaps with the claimed range. *See* Ex. 1003 ¶ 67 (also stating "other concentrations would work"). Moreover, other prior art of record confirms chelators at lower concentrations, including those that fall within or overlap with the claimed range, work for their intended purposes. *See* Ex. 1008 ¶¶ 63, 64, claims 6, 7 (teaching using EDTA in the range of 0.1–20 mM and specifically at 1 mM to extract DNA); Ex. 1009, 5:5–11, 7:33–47, 11:64–68 (teaching using EDTA at 0.1 mM for RNA preservation).

We also find Patent Owner's reliance on Dr. Taylor's testimony misplaced. Dr. Taylor testified that "the changing of -- keeping the chelator in that -- in that range should theoretically at least have no real effect on the . . . formulation." Ex. 2020, 481:6–13. He also testified that based on his own experience in using chelators, he did not see a problem in "[i]ncreasing or decreasing" the concentration of chelators, even though "there would have to be experimental work to prove it." *Id.* at 481:24–482:21; *see also id.* at 199:19–22 (Dr. Taylor testifying that "testing out the concentrations . . . would need to be done by laboratory work"). But, as in *Pfizer*, the experimental work Dr. Taylor referred to in his testimony is the type an ordinarily skilled artisan would have routinely used to verify the expectation of success, which is different from "the trial and error procedures often employed to *discover* a new compound where the prior art gave no motivation or suggestion to make the new compound nor a reasonable expectation of success." *See Pfizer*, 480 F.3d at 1367.

Indeed, the experimentation needed to arrive at the subject matter of claim 1, that is, changing the chelator concentration to one taught in Birnboim, is "nothing more than routine application of a well-known

problem-solving strategy" and not the work "of an inventor." *Id.* at 1368 (internal quotation marks omitted). Thus, the facts of this case show an ordinarily skilled artisan would have had a reasonable expectation of success that 1 mM chelator, such as CDTA, would work for its intended purpose.

In sum, Petitioner demonstrates by a preponderance of the evidence that Birnboim teaches or suggests all limitations of claim 2, and that an ordinarily skilled artisan would have had a reason to implement these teachings to arrive at the subject matter of claim 2 with a reasonable expectation of success. Patent Owner does not present evidence on objective indicia of nonobviousness. Thus, for the reasons discussed above, we determine Petitioner demonstrates by a preponderance of the evidence that claim 2 would have been obvious over Birnboim.

3. Claims 3, 5, and 6

Claim 3 depends from claim 2 and further recites specific chaotropes, including guanidine thiocyanate and guanidine hydrochloride. Petitioner argues that Birnboim teaches guanidine thiocyanate and guanidine hydrochloride in its compositions. Pet. 35 (citing Ex. 1003 ¶¶ 20, 68).

Claim 5 depends from claim 2 and further recites specific reducing agents, including β-ME and DTT. Petitioner argues that Birnboim teaches β-ME and DTT as exemplary reducing agents for use with its compositions. *Id.* at 37 (citing Ex. 1003 ¶ 13).

Claim 6 depends from claim 2 and further recites specific chelators, including ethylenediamine tetraacetic acid (EDTA) and diethylene triamine pentaacetic acid (DTPA). Petitioner argues that Birnboim teaches using either EDTA or DTPA as the chelator in its compositions. *Id.* at 38 (citing Ex. 1003 ¶¶ 16, 67).

Petitioner also contends that an ordinarily skilled artisan would have had a reason to use the specific reducing agents, chaotropes, or chelators at the concentration ranges recited in claim 2, and would have had a reasonable expectation of success in doing so. *Id.* at 35–39 (citing Ex. 1002 ¶¶ 173–175, 181–183, 185–187; Ex. 1003 ¶¶ 13, 67, 115; Ex. 1008 ¶¶ 60–64, claims 6, 7; Ex. 1009, 5:5–11, 7:33–47, 11:64–68).

Patent Owner points out that Birnboim's Example 3 uses sodium ascorbate (a salt of ascorbic acid) as the reducing agent, urea as the chaotrope, and CDTA as the chelator, none of which are recited in claims 3, 5, and 6. PO Resp. 38, 41, 43 (citing Ex. 1003 ¶ 115). According to Patent Owner, Birnboim does not teach or suggest substituting these reagents with those recited in claims 3, 5, and 6, and an ordinarily skilled artisan would not have had a reasonable expectation of success when doing so. *Id.* at 38–44. We disagree with Patent Owner.

Again, as noted above, for its obviousness challenge, Petitioner relies on not only Example 3, but also the general teachings of Birnboim. *See supra* Section V.E.1.c. As such, Birnboim itself teaches using the specific reducing agent, chaotrope, or chelator recited in claim 3, 5, or 6. *See* Ex. 1003 ¶¶ 13 (exemplary reducing agents including ascorbic acid, β-ME, and DTT), 20, 68 (known chaotropes urea, guanidine thiocyanate, and guanidine chloride), 16, 67 (exemplary chelators including EDTA, CDTA, and DTPA).

In addition, other prior art of record also makes clear that numerous such reagents may be used for essentially the same purpose as those recited in the challenged claims. With respect to the specific chaotropes of claim 3, Das, Mori, Goldrick, Maniatis, and Chirgwin, for example, all teach using

guanidinium compounds for the isolation of nucleic acids. *See, e.g.*, Ex. 1004, 189–90; Ex. 1008 ¶ 89; Ex. 1009, 7:30–8:54; Ex. 1011, 61; Ex. 1015, Abstract. Specifically, Mori teaches guanidinium salt as the preferred chaotropic salt, and guanidine thiocyanate as especially preferred. Ex. 1011, 61. Mori, however, states that "[i]t is possible to use a chaotropic substance such as urea instead of a chaotropic salt." *Id.*

With respect to the specific reducing agents of claim 5 and the specific chelators of claim 6, Goldrick, for example, teaches isolating RNA using a composition comprising a guanidinium compound, a detergent, a reducing agent such as β-ME or DTT and, optionally, a chelator such as EDTA. Ex. 1009, 7:30–8:54, 4:31–34. Similarly, Maniatis teaches a solution comprising guanidinium isothiocyanate, the detergent sodium lauryl sarkosinate, "reducing agents like β-mercaptoethanol," and the chelator EDTA for simultaneously disrupting cells and inactivating nucleases. *See* Ex. 1004, 189; *see also* Ex. 1008 ¶ 63 (lysis buffer comprising guanidinium isothiocyanate, N lauryl sarcosyl, β-ME, and EDTA).

According to Patent Owner, Birnboim prefers ascorbic acid[17] as the "most desirabl[e]" reducing agent, and prefers other, non-guanidine denaturing agents ahead of guanidine compounds. PO Resp. 41–42 (citing Ex. 1003 ¶¶ 13, 72). But, "the fact that a specific embodiment is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered." *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (brackets

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[17] According to Patent Owner, sodium ascorbate, which is used in Birnboim's Example 3, "is the same thing as ascorbic acid." PO Resp. 41 n.3.

omitted); *see also In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012) ("[J]ust because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes.").

Based on the prior art of record, we find that an ordinarily skilled artisan would have been familiar with the use and combinations of reagents recited in the challenged claims. *See* Ex. 1002 ¶¶ 48–73 (Dr. Taylor's review of the state of the art). Thus, we find claims 3, 5, and 6 would have been obvious because they each "recite[] 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." *See Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1364 (Fed. Cir. 2012).

Patent Owner argues 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. PO Resp. 32–44; Sur-reply 13–16. To the extent this argument overlaps with the one addressed above when discussing claim 2, our analysis there applies with equal force here; specifically, necessary experimental work an ordinarily skilled artisan routinely employs to verify the expected properties of the substitute reagents does not undermine a reasonable expectation of success. *See supra* Section V.E.2.

Patent Owner further argues that there would not have been a reasonable expectation of success because its "test results show that substitution of guanidine in Birnboim's Example 3 causes the Example 3 composition to form a precipitate, removing the precipitated reagents from the aqueous composition and making the composition unusable for

collection of nucleic acid." PO Resp. 40 (citing Ex. 2033 ¶¶ 24–26, 37; Ex. 2019).

We acknowledge the results in Exhibit 2019 but disagree with the conclusion Patent Owner draws from it. Patent Owner argues that "the guanidine compounds are active compounds that are likely to react with other reagents in the composition." *Id.* (citing Ex. 2033 ¶ 28; Ex. 2020, 224:17–225:7). For example, 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 ¶ 20." Ex. 2033 ¶ 28. This interaction, however, was well-known in the art. *See, e.g.*, Ex. 1015, 5296 (Chirgwin teaching that in place of β-ME, "[d]ithiothreitol 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").

Considering the level of skill in the art and the extensive use of guanidinium compounds in combination with reducing agents, detergents, and chelators as discussed above, we find an ordinarily skilled artisan would have been aware of such complications and known how to avoid them. Indeed, as Patent Owner points out, Dr. Taylor testified that an ordinarily skilled artisan "should take into account the reactivity of guanidinium before combining it with other reagents." PO Resp. 40–41 (citing Ex. 2020, 223:17–224:15). Yet, Patent Owner does not show that it has accounted for this well-known reactivity when considering the simple substitution of 0.67 M guanidine thiocyanate for the 0.67 M urea in Birnboim's Example 3.

In addition, Patent Owner focuses on the composition in Birnboim's Example 3 as the starting material. We repeat that, for its obviousness challenge, Petitioner relies on not only Example 3, but also the general teachings of Birnboim. *See supra* Section V.E.1.c. When an ordinarily skilled artisan is not limited to start from Example 3, other prior art of record shows that guanidine compounds have been routinely used in compositions for extracting and preserving nucleic acids. *See supra* Section V.E.1.a.

For example, Das teaches a lysis buffer containing about 4 M guanidinium isothiocyanate (chaotrope), about 1 % N lauryl sarcosyl (detergent), about 10 mM β-ME (reducing agent), about 1 mM EDTA (chelator), and about 50 mM Tris.Cl pH 7.6 (buffer). Ex. 1008 ¶ 64; *see also id.* ¶ 63 (teaching guanidinium isothiocyanate in the range of about 0.5–8 M). Thus, we accord limited value to the results in Exhibit 2019 in view of both the limitations of its experimental design and the prior art teachings of successful use of guanidine compounds. *See supra* Section V.E.1.a.

To the extent some substitutions might fail, it is important to keep in mind that expectation of success need only be reasonable, not absolute. *Pfizer*, 480 F.3d at 1364. With respect to the substitution of well-known reagents in Birnboim's Example 3 formulations, Dr. Taylor testified 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." *See* Ex. 2020, 191:10–17, 338:15–20, 487:15–22.

In sum, Petitioner demonstrates by a preponderance of the evidence that Birnboim teaches or suggests all limitations of claims 3, 5, and 6, and

that an ordinarily skilled artisan would have had a reason to implement these teachings to arrive at the subject matter of these claims with a reasonable expectation of success. Patent Owner does not present evidence on objective indicia of nonobviousness. Thus, for the reasons discussed above, we determine Petitioner demonstrates by a preponderance of the evidence that claims 3, 5, and 6 would have been obvious over Birnboim.

4. Claim 32

Claim 32 depends from claim 31, and further recites

> wherein the one or more chaotropes comprise guanidine thiocyanate, guanidine isocyanate, guanidine hydrochloride, or any combination thereof;
>
> the one or more detergents comprise sodium dodecyl sulfate, lithium dodecyl sulfate, sodium taurodeoxycholate, sodium taurocholate, sodium glycocholate, sodium deoxycholate, sodium cholate, sodium alkylbenzene sulfonate, N-lauroyl sarcosine, or any combination thereof;
>
> the one or more reducing agents comprise 2-mercaptoethanol, tris(2-carboxyethyl)phosphine, dithiothreitol, dimethylsulfoxide, tris(2-carboxyethyl)phosphine, or any combination thereof;
>
> the one or more chelators comprise ethylene glycol tetra acetic acid, hydroxyethylethylenediaminetriacetic acid, diethylene triamine penta acetic 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 any combination thereof;
>
> the one or more buffers comprise tris(hydroxymethyl)aminomethane, citrate, 2-(N-morpholino)ethanesulfonic acid, N,N-Bis(2-hydroxyethyl)-2-aminoethanesulfonic acid, 1,3-bis(tris(hydroxymethyl)methyl amino)propane, 4-(2-hydroxyethyl)-1-piperazine ethanesulfonic

acid, 3-(N-morpholino) propanesulfonic acid, bicarbonate, phosphate, or any combination thereof;

and the mixture is buffered to a pH of from about 5 to 7.

Ex. 1001, 36:24–48 (paragraphing added).

Petitioner asserts that Birnboim teaches the "specific compounds for the different ingredients in the mixture" as well as the pH level of the mixture, and thus, renders claim 32 obvious. Pet. 35–39, 46–47. Specifically, Petitioner points to its showing for claims 3 (chaotropes), 4 (detergents), 5 (reducing agents), 6 (chelators), and 7 (buffers). *Id.* at 46–47 (citing Ex. 1002 ¶ 217). Petitioner also points to its showing for claim 15 for the pH level. *Id.* at 47 (citing Ex. 1002 ¶¶ 218–219).

Patent Owner points out that claim 32 "recites particular groups of reagents that are missing from Birnboim's Example 3—including at least the chaotrope, the reducing agent, and the chelator." PO Resp. 48 (citing Ex. 1002 ¶ 215; Ex. 1003 ¶ 115; Ex. 2033 ¶ 58). Patent Owner points to a footnote of our Decision to Institute, where we stated that "we agree with Patent Owner that an ordinarily skilled artisan 'would not have used the Birnboim Example 3 composition as a starting point and arrived at the composition utilized by the method of claim 24,'[18] because 'doing so would have required substituting the chaotrope . . . the reducing agent, and the chelator.'" DI 32 n.16 (quoting Prelim. Resp. 42; footnote added). Relying on this statement, Patent Owner argues that Petitioner provides no reason to

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[18] We addressed claim 24 in the Decision to Institute because it is one of the independent claims. Similar to claim 32, claim 24 lists specific compounds in several compound class, from which constituents must be selected. *See* Ex. 1001, 34:28–35:12.

modify all three components in Birnboim's Example 3 together to arrive at the mixture of claim 32. PO Resp. 48 (citing DI 32 n.16).

Patent Owner appears to have misunderstood footnote 16 of our Decision to Institute. There, we merely agreed with Patent Owner that an ordinarily skilled artisan would not have started with Birnboim's Example 3. But Petitioner does not argue Birnboim's Example 3 is the starting point for its obviousness challenge; instead, as we have pointed out repeatedly above, Petitioner relies on the entire teachings of Birnboim, citing previous sections of the Petition, which in turn cite to teachings throughout Birnboim. *See, e.g.*, *supra* Section V.E.1.c. Our Decision to Institute reflects this view.

Indeed, acknowledging Petitioner's reliance on Birnboim's general teachings, we concluded that "Petitioner's mapping of these individual compounds to Birnboim's disclosures appears reasonable." DI 31–32 (citing Pet. 25, 35, 38–40, which in turn, cite Ex. 1003 ¶¶ 13, 16, 20, 67, 68, 115). In other words, we understood then, as we do now, that Petitioner's arguments in its obviousness analysis are not limited to Birnboim's Example 3. *See* Reply 20 (citing Ex. 1003 ¶¶ 16, 19, 20, 70).

Of course, in the Decision to Institute, we also stated that, on the preliminary record, we were "not persuaded that Petitioner has shown sufficiently a reason that would have prompted an ordinarily skilled artisan to combine the discrete ingredients all at once." DI 32. But we cautioned that our determination at that stage was not final and "could change upon further development of the record during trial," and encouraged the parties to "further address the relevant issues of all challenges." *Id.* at 33–34. Based on the entire record before us now, and as explained below, we determine that

Petitioner has met its burden in showing the obviousness of claim 32 by a preponderance of the evidence.

During trial, Petitioner asserts that challenged claims, like claim 32 here, do not "deal[] with precise compositions." Tr. 21:11–14. Instead, according to Petitioner, combining multiple different reagents in each category listed in the Markush-type limitations, claim 32 would encompass "over 13,000 possible combinations."[19] Reply 20 (citing Ex. 1071 ¶ 5). Petitioner contends the '467 patent "relies on the skill in the art," and does not teach anything additional, "to put them together." Tr. 19:8–15, 21:8–10, 16–18. And Birnboim, Petitioner argues, similarly relies on the ability of an ordinarily skilled artisan to put the reagents together. *Id.* at 21:1–6. As such, Petitioner continues, what the '467 patent claims "is identical to what Birnboim teaches." *Id.* at 21:14–15; *see also id.* at 21:7 (arguing the challenged claim "mirrors what Birnboim has").

In its Sur-reply, Patent Owner continues to characterize the Petition as relying on modifying Birnboim's Example 3. Sur-reply 8–9, 18. With this misinterpretation, Patent Owner relies on cases that are inapposite. *Id.* at 8–9, 12–13, 16 (citing *DSS Tech. Mgmt., Inc. v. Apple Inc.*, 885 F.3d 1367 (Fed. Cir. 2018); *Intel Corp. v. Tela Innovations, Inc.*, IPR2019-01521, Paper 65 at 9 (PTAB Mar. 9, 2021)).

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[19] Dr. Taylor testifies that the "13,608 different formulations" included in claim 32 are calculated based on the "3 chaotropes, 9 detergents, 4 reducing agents, 14 chelators, and 9 buffers" that "are explicitly named," and "do not account for claim language that 'any combination' of reagents in a given class may be used." Ex. 1071 ¶ 5. According to Dr. Taylor, "[a]ccounting for such combinations would greatly increase the number of potential formulations." *Id.*

For example, in *DSS*, the Federal Circuit reversed the Board's obviousness finding because the Board "relied on ordinary creativity as a wholesale substitute for reasoned analysis and evidentiary support, and did so when dealing with a limitation missing from the prior art references specified." 885 F.3d at 1377 (internal quotation marks omitted). In the instant case, however, no limitation is missing and no modification is required. Indeed, Birnboim teaches a nucleic acid stabilizing composition comprising chelators, reducing agents, denaturing agents, and buffers. Ex. 1003 ¶ 64. It also teaches the functions of each category of the reagents and lists exemplary compounds, some of which are recited in claim 32. *Id.* ¶¶ 13, 16, 19, 20, 64, 66–68, 115. Because Birnboim teaches all limitations-at-issue, *DSS* is distinguishable.

Patent Owner's reliance on *Intel* is similarly misplaced. There, the Board found the petitioner did not sufficiently establish that an ordinarily skilled artisan "would have combined and modified the *different embodiments*" depicted in separate figures. *Intel*, Paper 65 at 9 (emphasis added). Here, Petitioner relies on not different embodiments, but the general teachings, of Birnboim. Thus, *Intel* is distinguishable too.

After considering the entire record developed during trial, we agree with Petitioner that the facts in this case are akin to those in *Merck*. Reply 22 (citing *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804 (Fed. Cir. 1989)). In *Merck*, each claim-at-issue recited a composition comprising amiloride, a known potassium conserving diuretic, and hydrochlorothiazide, a known potassium excreting diuretic. 874 F.2d at 805–806. The prior-art patent taught a genus of compounds, and specifically claimed amiloride. *Id.* at 806. It also taught that those compounds were useful in combination

with potassium excreting diuretic agents, and identified hydrochlorothiazide as an example that can be combined with the genus of compounds. *Id.* The district court found the prior art taught "more than 1200 combinations," and did not highlight either amiloride or hydrochlorothiazide as preferred embodiment. *Id.* at 806–807. As a result, it concluded that the claims-at-issue would not have been obvious. *Id.* at 807.

The Federal Circuit reversed. *Id.* According to the Federal Circuit, the prior art expressly taught the advantages of co-administering its genus of compounds with potassium excreting diuretic agents. *Id.* Thus, the Federal Circuit reasoned that "any of the 1200 disclosed combinations" would produce a formulation with desirable properties. *Id.* It stated "[t]hat 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." *Id.*

Similarly in this case, Birnboim expressly teaches a nucleic acid stabilizing composition comprising the categories of reagents and lists exemplary compounds in each category, which overlap with those recited in claim 32. Ex. 1003 ¶¶ 13, 16, 19, 20, 64, 67, 68, 115. Birnboim also teaches the functions of each category of the reagents, as well as the advantages of combining them together. Ex. 1003 ¶ 64 (stating the resulting compositions "provide the advantageous properties of chemical stabilization of nucleic acids and the inhibition of nucleases . . . and microbial growth"). Applying the reasoning in *Merck*, the fact that Birnboim teaches a large number of effective combinations does not render any one of its formulations, some of which are encompassed by claim 32, less obvious. *See Merck*, 874 F.2d

at 807. This is especially true because each category of reagents performs the same functions in claim 32 as those taught in Birnboim, and the claimed composition is used for the same purpose as that taught in Birnboim. *See In re Susi*, 440 F.2d 442, 445 (CCPA 1971) (affirming an obviousness rejection because even though the prior art teaches a "huge" genus, it included "at least some of the compounds recited in appellant's generic claims and it is of a class of chemicals to be used for the same purpose as appellant's additives").

Thus, for the reasons discussed above, we determine Petitioner demonstrates by a preponderance of the evidence that claim 32 would have been obvious over Birnboim.

5. Claims 4, 7–9, 15–17, 29–31, and 33–49

Petitioner asserts that Birnboim renders obvious claims 4, 7–9, 15–17, 29–31, and 33–49. Pet. 36–37, 39–42, 45–48. Petitioner provides a detailed analysis, showing that Birnboim teaches the additional limitations recited in these claims. *Id.* (citing Ex. 1002 ¶¶ 176–179, 190–192, 195, 196, 198, 199, 208–210, 212–214, 221, 222, 224, 225; Ex. 1003 ¶¶ 19–21, 27, 43, 68, 73, 115–121). According to Petitioner, an ordinarily skilled artisan would have had a reason to combine or modify Birnboim's teachings to arrive at the claimed invention with a reasonable expectation of success. *Id.* (citing Ex. 1002 ¶¶ 178, 179, 191, 192, 195, 196, 198, 199, 208–210, 212–214, 221, 222, 224, 225; Ex. 1003 ¶¶ 19, 20, 27, 43, 115–121; Ex. 1008 ¶¶ 39, 63–64, claims 6, 7; Ex. 1010, 8:18–24).

Patent Owner does not address these claims separately in its Response. In our Decision to Institute, we warned that "[a]ny argument not raised in a timely Patent Owner Response to the Petition, or as permitted in

another manner during trial, shall be deemed waived even if asserted in the Preliminary Response." DI 33. Thus, we agree with Petitioner that Patent Owner has waived any argument for these claims. Reply 20; *see also In re NuVasive, Inc.*, 842 F.3d 1376, 1380–81 (Fed. Cir. 2016) (holding patent owner waived arguments on issues not raised in its response after institution).

After reviewing the record, we agree with Petitioner's analyses and adopt them as our own. *See* Pet. 36–37, 39–42, 45–48. Thus, we determine Petitioner demonstrates by a preponderance of the evidence that Birnboim renders obvious claims 4, 7–9, 15–17, 29–31, and 33–49.

6. Summary

After reviewing the record, we determine Petitioner demonstrates by a preponderance of the evidence that Birnboim teaches or suggests all limitations of claims 1–9, 15–17, and 29–39, and that an ordinarily skilled artisan would have had a reason to implement these teachings to arrive at the subject matter of those claims with a reasonable expectation of success. Patent Owner does not present evidence on objective indicia of nonobviousness. Thus, for the reasons discussed above, we determine Petitioner demonstrates by a preponderance of the evidence that claims 1–9, 15–17, and 29–39 would have been obvious over Birnboim.

F. Alleged Anticipation by and/or Obviousness of Claims 18–23 over Birnboim

Petitioner argues that Birnboim anticipates claims 18–20, 22, and 23. Pet. 26–28. In addition, Petitioner argues that Birnboim renders claims 18–23 obvious. Pet. 42–45. Based on this record, and as explained below, we determine Petitioner has not shown, by a preponderance of the

evidence, that Birnboim anticipates claims 18–20, 22, and 23, or renders obvious claims 18–23.

Claim 18 depends from claim 17, and further recites "wherein contacting comprises detectably liberating nucleic acid contained within the particles, cells or organisms of the biological sample." Petitioner argues that Birnboim anticipates, or renders obvious, claim 18. Pet. 26–27, 42. As support, Petitioner refers to Birnboim for teaching that "[w]hen 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." *Id.* at 26 (citing Ex. 1003 ¶ 84). Petitioner further relies on Birnboim's Examples 4–6 for teaching "detecting the presence of nucleic acid in the contacted saliva samples through gel electrophoresis or PCR." *Id.* at 26–27 (citing Ex. 1002 ¶¶ 134, 135; Ex. 1003 ¶¶ 116–122).

Patent Owner disagrees. According to Patent Owner, "Birnboim's Example 3 does not reach anything like detectable liberation of nucleic acid of the sample until after additional steps (addition of a protein digester, purification, and precipitation) that follow contacting a sample with the solution." PO Resp. 30 (citing Ex. 1003 ¶¶ 117, 119); *see also id.* at 45 (the same). Thus, Patent Owner concludes, "contacting with the composition of Example 3 does not detectably liberate nucleic acid," as required in claim 18. *Id.* at 44 (citing Ex. 2033 ¶ 48); *see also id.* at 29–30 (the same).

In response, Petitioner emphasizes that claim 18 "requires a method 'comprising' certain steps." Reply 10–11, 18. Petitioner argues that, because of the open-ended language, "[e]ven if Birnboim requires further processing

before detecting nucleic acids," it still anticipates, or renders obvious claim 18. *Id.* We do not agree with Petitioner's argument.

Claim 18 requires "contacting comprises detectably liberating nucleic acid." Although Petitioner is correct that the use of transitional phrase "comprises" does not exclude additional unrecited elements (*id.* at 11, 18), the plain language of the claim still requires "detectably liberating nucleic acid" in the "contacting" step. As Patent Owner points out, the Board previously addressed a similar issue in a related case IPR2021-00851. PO Resp. 29–30.

In that case, challenged claim 1 is directed to an aqueous composition, wherein upon contact of the composition with a biological sample, it "creates an effective concentration of the composition that, in one step, disinfects said sample, inactivates nucleases of said sample, and extracts the nucleic acids from the other macromolecules such that a target sequence of the nucleic acids is detectable by a nucleic acid test." IPR2021-00851, Ex. 1001, 31:57–67. The panel denied institution in that case, explaining, among other reasons, that

> Petitioner's position as to the extraction, in one step, of the nucleic acid such that a target sequence is detectable by a nucleic acid test, however, does not follow from Birnboim's disclosure. While it is evident that Birnboim's nucleic acid-preserving solution both lyses cells and preserves nucleic acids for extended periods of time such that the nucleic acid can later be detected, in each of Examples 4–6, there are additional steps before the nucleic acid test. In Example 4, Birnboim treats a portion of samples prepared using the nucleic acid-preserving solution with proteinase K, removes insoluble matter by centrifugation, and precipitates the DNA with ethanol prior to subjecting the DNA to agarose gel electrophoresis and ethidium bromide staining to find "the characteristic band of

> chromosomal DNA present in all samples." Ex. 1003 ¶ 117, Fig. 1. 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 polymerase chain reactions to detect the DNA. *Id.* ¶¶ 118–121. These additional steps are consistent with Birnboim's disclosure as a whole, which elsewhere describes its "nucleic acid preserving compositions" as facilitating the extraction and recovery of nucleic acids and teaches that "[o]nce digestion is complete, nucleic acid isolation can be performed using any technique known in the art." *See id.* ¶¶ 11, 64, 84–85. Petitioner does not direct us to any teaching in Birnboim that treatment with the "nucleic acid-preserving solution," standing alone, is sufficient to extract the nucleic acid from other components such that it is detectable by a nucleic acid test. Furthermore, there is neither any cogent argument nor testimony that Birnboim's treatment meets the "in one step" limitation of independent claims 1 or 31. *See* Pet.; Ex. 1002.

IPR2021-00851, Paper 13 at 15–16 (PTAB Nov. 18, 2021).

Similar reasoning applies here. That is, Birnboim's Examples 4–6, the evidence Petitioner relies on to meet the "detectably liberating nucleic acid" limitation, require other steps in addition to simply "contacting" a sample with the composition. *See* Ex. 1003 ¶¶ 116–122. Thus, we agree with Patent Owner that Petitioner has not shown Birnboim's teaching meets the requirement of claim 18.

Petitioner asserts that "there is nothing in Birnboim that suggests the liberated nucleic acids are not 'detectable' without further processing." Reply 18. That may well be the case; yet, Petitioner cites no evidence to support this assertion. We, thus, do not give weight to this mere attorney argument.

In sum, on the record before us, we find Petitioner has not met its burden of proving unpatentability of claim 18 by a preponderance of the evidence. Each of claims 19–23 depends, directly or indirectly, from claim 18. For the same reasons as explained above in addressing claim 18, we find Petitioner has not met its burden of proving unpatentability of claims 19–23 by a preponderance of the evidence either.

G. Alleged Obviousness over Birnboim and Mori

1. Claim 24

Independent claim 24 is similar to claim 1, and further requires that the recited mixture contain one or more surfactant and one or more short-chain alkanol. Claim 24 also lists specific compounds in five compound classes (chaotropes, detergents, chelators, buffers, and short-chain alkanols), from which constituents must be selected.

Petitioner asserts that claim 24 would have been obvious over the combination of Birnboim and Mori. Pet. 52–54. Petitioner relies on Birnboim for teaching specific compounds for chaotropes, detergents, buffers, chelators, and short-chain alkanols, pointing to its showing for claims 3, 4, 6, 7, and 9, respectively. Pet. 53 (citing Ex. 1002 ¶¶ 241–242).

Regarding surfactants, Petitioner contends that the ’467 patent “treats surfactants and defoaming agents as synonymous reagents.” *Id.* (citing Ex. 1001, 5:6–21, 6:64–67, 7:29–31; Ex. 1002 ¶ 243). Petitioner relies on Mori for teaching defoaming agents. *Id.* at 49–52 (citing Ex. 1011, 58, 59, 64). According to Petitioner, “a POSA would have been motivated to use Mori’s defoaming agent in Birnboim’s aqueous solution and would have had a reasonable expectation of success in doing so.” *Id.* (citing Ex. 1002 ¶¶ 230–239).

In its Response, Patent Owner repeats the arguments advanced in addressing claim 32, that is, Petitioner provides no reason to modify the chaotrope, reducing agent, and chelator in Birnboim's Example 3 together. PO Resp. 49–50. For the same reason as explained above, we do not agree with Patent Owner's argument. *See supra* Section V.E.4.

Patent Owner does not dispute the combination of Birnboim and Mori teaches or suggests each limitation of claim 24. After reviewing the record, we find persuasive Petitioner's mapping of each limitation of claim 24 and adopt it as our own. *See* Pet. 52–54.

In addition, we find Petitioner has met its burden in showing some reasoning for combining the teachings of Birnboim and Mori. Indeed, Birnboim teaches that, after the nucleic acid preserving composition is combined with the sample and introduced into a container, the container is "vigorously shaken" to place the nucleic acid into a "preserved state." Ex. 1003 ¶¶ 110, 113. Similarly, Mori teaches "homogenization treatment," including high-speed stirring and sonication, "[i]n the step of obtaining a sample solution containing nucleic acids from a sample by lysis of cell membrane and nuclear membrane to thereby solubilize nucleic acids." Ex. 1011, 59.

Recognizing that shaking causes foaming, Mori teaches "where cell membrane and nuclear membrane are dissolved . . . it is preferred that an antifoaming agent (defoaming agent) is contained in a sample solution containing nucleic acid." *Id.* at 64. In addition, Dr. Taylor testifies "[t]he use of defoaming agents to reduce bubbles and foaming in nucleic acid preserving solutions was well known in the prior art." Ex. 1002 ¶ 233 (citing Ex. 1012, Abstract, ¶¶ 1, 41).

For example, Moon explains that foaming occurs "during mechanical agitation, including mixing, transferring, movement through tubing, dispensing, etc." Ex. 1012 ¶ 41. According to Moon, "[f]oam and bubble formation can block or interfere with the detection or transfer of reagent" in, for example, PCR. *Id.* Moon teaches "[t]he presence of an antifoam agent in the reaction mixture prevents or reduces these effects, thereby allowing for increased accuracy of measuring of the contents of a mixture." *Id.*; *see also id.* ¶ 52 (teaching silicone-based defoaming agents for "improved performance in high foaming detergent compositions").

Moreover, as Petitioner points out, "[a] POSA would have also understood that ingredients such as detergents used to lyse cells and denature proteins may exacerbate foaming upon agitation." Pet. 51 (citing Ex. 1002 ¶ 235; Ex. 1013, 4.4.7; Ex. 1014, 20.2.6). Indeed, prior art Petitioner relies on teaches "[g]lycerol and Triton X-100 tend to cause foaming during sonication, thus reducing its effectiveness" (Ex. 1014, 20.2.6), and suggests "care should be taken to avoid foaming the lysate (which contains SDS) during sonication" (Ex. 1013, 4.4.7). Thus, we are persuaded that an ordinarily skilled artisan would have had a reason to add Mori's defoaming agent into Birnboim's composition.

And the ordinarily skilled artisan would have had a reasonable expectation of success in doing so, because Mori teaches, in a nucleic acid solubilizing composition, using a defoaming agent along with the same categories of ingredients in Birnboim: chaotropes, reducing agents, nuclease inhibitors, and buffers. Ex. 1011, 58, 63, 66; *see also* Ex. 1012 ¶¶ 41, 52, 67–90 (teaching using defoaming agents in similar compositions).

In sum, after reviewing the record, we determine Petitioner demonstrates by a preponderance of the evidence that the combination of Birnboim and Mori teaches or suggests all limitations of claim 24, and that an ordinarily skilled artisan would have had a reason to implement these teachings to arrive at the subject matter of claim 24 with a reasonable expectation of success. Thus, for the reasons discussed above, we determine Petitioner demonstrates by a preponderance of the evidence that claim 24 would have been obvious over Birnboim and Mori.

2. Claims 10, 11, 25, and 28

Petitioner asserts that claims 10, 11, 25, and 28 would have been obvious over the combination of Birnboim and Mori. Pet. 49–52, 55–58. Petitioner provides a detailed analysis, (1) showing that Birnboim teaches the additional limitations recited in these claims, and (2) arguing an ordinarily skilled artisan would have had a reason to combine or modify Birnboim's teachings to arrive at the claimed invention with a reasonable expectation of success. *Id.* (citing Ex. 1002 ¶¶ 173–175, 230–239, 249–258; Ex. 1003 ¶¶ 19, 49, 64, 66, 110, 113, 115; Ex. 1008 ¶ 63, claim 6; Ex. 1009, 3:60–65, 6:68–7:4, 7:25–29; Ex. 1011, 58, 59, 62–64, 66; Ex. 1012, Abstract, ¶¶ 1, 41, 52, 54, 67–90; Ex. 1013, 4.4.7; Ex. 1014, 20.2.6).

Patent Owner does not address these claims separately in its Response, and thus, has waived any argument for these challenged claims.

After reviewing the record, we agree with Petitioner's analyses and adopt them as our own. *See* Pet. 49–52, 55–58. Thus, we determine

Petitioner demonstrates by a preponderance of the evidence that Birnboim renders obvious claims 10, 11, 25, and 28.[20]

H. Alleged Obviousness over Birnboim and Das

Claim 12 depends from claim 2 and further recites that "the pathogens are influenza virus particles or influenza-infected cells, bacteria that causes tuberculosis or tuberculosis-infected cells." Petitioner asserts that claim 12 would have been obvious over the combination of Birnboim and Das. Pet. 59–62. Specifically, Petitioner argues that both Birnboim and Das teach compositions that preserve nucleic acids extracted from bacteria and viruses, and Das specifies that DNA is extracted from tuberculosis-causing mycobacteria. *Id.* at 59 (citing Ex. 1003 ¶ 27; Ex. 1008 ¶¶ 37–39). According to Petitioner, "a POSA would have been motivated to use Birnboim's composition in view of Das for the specific purpose of extracting and preserving a DNA in a sample suspected of containing tuberculosis-causing pathogens" (*id.* at 60 (citing Ex. 1002 ¶ 262)), and would have had a reasonable expectation of success when doing so (*id.* at 62 (citing Ex. 1002 ¶¶ 266, 267; Ex. 1008 ¶¶ 83, 89, 91–98)).

Patent Owner does not contest that Birnboim and Das teach "highly similar" compositions. PO Resp. 51 (citing Pet. 61–62). Instead, Patent Owner counters that "Das teaches multiple critical steps that are missing

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[20] We note that when addressing the challenge to claim 24, Patent Owner includes the language "its dependent claims," i.e., claims 25 and 28. *See* PO Resp. 49–50. To the extent Patent Owner has not waived its arguments regarding the patentability of claims 25 and 28, for the same reasons as explained above in addressing claim 24 (*see supra* Section V.G.1), we find Petitioner has demonstrated by a preponderance of the evidence that claims 25 and 28 would have been obvious over Birnboim and Mori.

from Birnboim." *Id.* (citing Ex. 2033 ¶¶ 66–69). In particular, Patent Owner argues that, unlike Birnboim, Das requires heating the specimen. *Id.* at 51–52 (citing Ex. 1008 ¶¶ 38, 39, 85). Das also requires, according to Patent Owner, a clarification step, for example, by mixing with a decontamination mix followed by centrifugation. *Id.* at 52 (citing Ex. 1008 ¶¶ 38, 52, 61). Thus, Patent Owner concludes that "a POSA would not simply apply Birnboim to bacteria that causes tuberculosis or tuberculosis-infected cells, and could not reasonably expect success in doing so." *Id.* at 51 (citing Ex. 2033 ¶¶ 66–69).

We do not agree that Das, read in context, requires heating the specimen. *See* Ex. 1008 ¶ 38. Indeed, Das teaches "[b]y heating specimen in modified lysis buffer even the toughest cells and objects like spores and baculovirus polyhedra are lysed easily." *Id.* Although heating renders Das's composition more effective against "the toughest cells and objects like spores," as explained above, spores are not within the scope of the recited "pathogens." *See supra* Section V.C.1.

Patent Owner also relies on Das's statement that "[m]ycobacterial cells are inactivated and lysed by heating the digested and decontaminated sample in modified lysis buffer at 85° C. for 20 min." PO Resp. 51–52 (citing Ex. 1008 ¶¶ 39, 85). But Das teaches using "a strong chaotropic agent," such as guanidinium isothiocyanate, "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." Ex. 1008 ¶ 38. In other words, the reagents in Das's composition perform, among others, qualitatively the same function with or without heating, i.e., inactivation and lysis. Thus, in view of

our construction of the term "kill pathogens," which only requires killing or inactivating *some* pathogens, we find that, even though it may help to better inactivate and lyse mycobacterial cells, heating is not required in Das.

We also do not agree that Das requires an additional clarification step. *See* PO Resp. 52 (citing Ex. 1008 ¶¶ 38, 52, 61). Das 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 "dirtier specimen like sputum." Ex. 1008 ¶ 38. Thus, Das does not require a clarification step, but merely teaches such a step may improve the quality of the DNA extracted from certain samples for certain later analysis. Moreover, Das does not mention a clarification step for detection/visualization techniques that do not involve PCR, such as the agarose/ethidium bromide gel electrophoresis in Birnboim's Example 4. *See* Ex. 1003 ¶ 117, Fig. 1.

Finally, we agree with Petitioner that, even if Das required heating and/or clarification, nothing in claim 12 would prohibit these steps. *See* Reply 22 (citing Ex. 1064, 240:6–12). In addition, the resulting "cleaner DNA preparation with improved yield" (*see* Ex. 1008 ¶ 39) would have provided additional reasoning to combine the teachings of Das and Birnboim.

In sum, after reviewing the record, we determine Petitioner demonstrates by a preponderance of the evidence that claim 12 would have been obvious over Birnboim and Das.

I. Alleged Obviousness over Birnboim, Mori, and Das

Claim 27 depends from claim 25 and further recites that "the pathogens are influenza virus particles or influenza-infected cells, bacteria

that causes tuberculosis or tuberculosis-infected cells." Petitioner contends claim 27 would have been obvious over Birnboim, Mori, and Das. Pet. 62–63 (citing Ex. 1002 ¶¶ 269–271). The parties rely on the same arguments as presented in addressing the grounds based on Birnboim and Mori, and Birnboim and Das. *Id.*; PO Resp. 54. For the same reasons explained above, we determine Petitioner demonstrates by a preponderance of the evidence that claim 27 would have been obvious over Birnboim, Mori, and Das. *See supra* Sections V.G., V.H.

J. Alleged Obviousness over Birnboim, Helftenbein, and Birnboim 2006

Claim 13 depends from claim 1 and recites that "the mixture further comprises added naked RNA or DNA present in an amount of about 1 pg/mL to 1 μg/mL."[21] Claim 14 depends from claim 13 and requires the method "further comprising detecting the presence or absence of the added naked DNA or RNA."

Petitioner argues the combination of Birnboim and Helftenbein renders claims 13 and 14 obvious. Pet. 63–65. Petitioner refers to Helftenbein for teaching the addition of an internal standard to its nucleic acid-stabilizing substance ("N-sS"). *Id.* at 63–64 (citing Ex. 1019, 2:60–63). According to Petitioner, Helftenbein teaches adding naked MS2-RNA as a positive control to the composition in Examples 5–8. *Id.* at 64 (citing Ex. 1019, 6:27–8:36, 8:64–9:37). Thus, Petitioner contends "[i]n view of Helftenbein, a POSA would have been motivated to use naked

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[21] The '467 patent defines "naked" nucleic acid as "released" or "lysed" nucleic acid. Ex. 1001, 6:41, 14:65, 16:1, 26:24. Based on this disclosure, Petitioner contends, and Patent Owner does not dispute, that "[t]he '467 patent equates nucleic acid in solution with 'naked' nucleic acid." Pet. 63 (citing Ex. 1001, 6:40–43, 14:64–15:2, 15:67–16:3).

carrier DNA or RNA as an internal positive control in Birnboim's composition with a reasonable expectation of success." *Id.* (citing Ex. 1002 ¶ 277).

Petitioner asserts that Birnboim 2006 teaches the use of a specific "Control DNA" in Example 7 as a positive control for the sequence being targeted in samples. *Id.* (citing Ex. 1023, 19–22 (Tables I-III)). The concentration of "Control DNA" in Example 7 ranges from 0.5 to 30 μg/mL, overlaps with that of "about 1 pg/mL to 1 μg/mL" recited in claim 13. *Id.* Thus, Petitioner argues "a POSA would have been motivated to use naked DNA or RNA present in an amount of about 1 pg/mL to 1 μg/mL in Birnboim's method with a reasonable expectation of success." *Id.* (citing Ex. 1002 ¶¶ 278–279).

Patent Owner disagrees. PO Resp. 55–56. Patent Owner argues neither Helftenbein nor Birnboim 2006 provides a motivation to modify Birnboim. *Id.* at 55. We are not persuaded by this argument.

In an obviousness analysis, we need not seek out "precise teachings" in the prior art; instead, we "can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). Moreover, Helftenbein teaches that adding internal control to the N-sS "permits the control of the whole method from the moment of sampling up to the detection of nucleic acids." Ex. 1019, 2:60–63. We find this explicit statement, in fact, amounts to the "precise teachings" and provides the reasoning for an ordinarily skilled artisan to modify Birnboim by adding internal control to the sample. *See* Reply 23–24.

Patent Owner further contends that "Helftenbein's Examples 5–8 disclose testing Helftenbein's 'serum' on separate samples of MS2-RNA as a control, *not including the MS2-RNA in the serum itself*." PO Resp. 55 (citing Ex. 1019, 6:27–9:37; Ex. 2033 ¶ 71). Thus, Patent Owner argues that the MS2-RNA "does not operate as an *internal* control." Sur-reply 21. In addition, Patent Owner asserts that the control DNA in Birnboim and Birnboim 2006 is "for the PCR assay, not for the collection, preservation, or extraction described in Birnboim Examples 3 and 4." PO Resp. 55–56 (citing Ex. 1003 ¶¶ 115, 121; Ex. 1023, 19–22; Ex. 2033 ¶¶ 72, 73). Thus, according to Patent Owner, neither Birnboim nor Birnboim 2006 teaches including naked DNA or RNA in "the mixture" of claim 1. *Id.* at 56. For the reasons explained below, we are not persuaded by these arguments either.

First, Patent Owner argues claims 13 and 14 require internal controls. *See* Sur-reply 20 (arguing Helftenbein does not teach an internal control "as per claims 13, 14"). Patent Owner is mistaken. Each of claims 13 and 14 only requires that the mixture further comprises "added naked RNA or DNA;" it does not mention an internal control. Petitioner argues that Helftenbein teaches "naked carrier DNA or RNA," and specifically "naked MS2-RNA." Pet. 63–64 (citing Ex. 1019, 2:60–63, 6:27–8:36, 8:64–9:37). Patent Owner does not dispute this assertion.

Second, Patent Owner appears to have misunderstood Helftenbein's teaching and/or Petitioner's argument. Petitioner relies on Helftenbein for teaching N-sS. *Id.* (citing Ex. 1019, 2:32–63). In Examples 5–8, Helftenbein teaches mixing N-sS with serum, and adding MS2-RNA as a control. Ex. 1019, 6:32–35, 6:52–56, 7:17–19, 8:16–18. In other words, serum is the sample, containing the nucleic acid to be extracted and stabilized.

Challenged claims 13 and 14 require the claimed mixture, not the sample, to further comprise naked RNA or DNA. Thus, the fact that the serum in Helftenbein does not include MS2-RNA is irrelevant.

Third, Petitioner relies on Helftenbein, and not Birnboim and Birnboim 2006, for teaching the addition of "naked RNA or DNA" to the nucleic acid-stabilizing substance. Pet. 63–64 (citing Ex. 1019, 2:60–63). Thus, we are satisfied with Petitioner's showing that the *combination* of Birnboim, Helftenbein, and Birnboim 2006 teaches including naked RNA or DNA in the composition for collecting nucleic acid, i.e., "the mixture" of claim 1.

In sum, we find Helftenbein teaches or suggests an internal positive control, and an ordinarily skilled artisan would have had a reason to include such an internal positive control in Birnboim's composition. We also find Birnboim 2006 teaches control DNA in a concentration range that overlaps with the one recited in claim 13. Patent Owner has not shown "the prior art teaches away from the claimed range, or the claimed range produces new and unexpected results." *See Ormco*, 463 F.3d at 1311. As a result, we determine Petitioner demonstrates by a preponderance of the evidence that claim 13 would have been obvious over Birnboim, Helftenbein, and Birnboim 2006.

For claim 14, Petitioner refers to Helftenbein's Examples 5–8 for teaching detecting the presence or absence of added naked positive control RNA through gel electrophoresis or PCR. *Id.* at 65 (citing Ex. 1019, 6:27–8:36). Given that Birnboim, in Examples 4–6, also teaches detecting the presence or absence of DNA in the contacted saliva sample through either gel electrophoresis or PCR, Petitioner continues, "a POSA would have

been motivated to detect the presence or absence of added naked DNA or RNA in Birnboim's method with a reasonable expectation of success." *Id.* (citing Ex. 1002 ¶¶ 281–282; Ex. 1003 ¶¶ 116–122). We agree with these contentions, sufficiently established by Petitioner, and Patent Owner does not dispute them. As a result, we determine Petitioner demonstrates by a preponderance of the evidence that claim 14 would have been obvious over Birnboim, Helftenbein, and Birnboim 2006.

K. Alleged Obviousness over Birnboim, Mori, and Helftenbein

Claim 26 depends from claim 25 and recites that "the mixture further contains naked RNA or DNA that has a predetermined nucleic acid sequence as an internal positive control that is detectable by PCR analysis." Petitioner contends that the combination of Birnboim, Mori, and Helftenbein renders claim 26 obvious. Pet. 65–66.

Specifically, Petitioner refers to Birnboim's Examples 5 and 6 for using a highly purified sample of DNA as an internal positive control. *Id.* at 65 (citing Ex. 1003 ¶¶ 119, 120). Similar to its arguments in challenging claims 13 and 14, Petitioner also refers to Helftenbein for teaching the addition of an internal standard to its nucleic acid-stabilizing substance ("N-sS"). *Id.* at 65–66 (citing Ex. 1019, 2:60–61). According to Petitioner, Helftenbein teaches adding naked MS2-RNA as a positive control to the composition in Examples 5–8, which has a known and therefore predetermined sequence. *Id.* at 66 (citing Ex. 1019, 6:27–8:36, 8:64–9:37). In addition, Petitioner argues that both Birnboim and Helftenbein teach using PCR to analyze and detect nucleic acids in a sample. *Id.* (citing Ex. 1003 ¶¶ 118, 119; Ex. 1019, 7:26–42).

Patent Owner relies on the same arguments as presented in addressing claims 13 and 14. PO Resp. 56. For the same reasons explained above, we do not agree with Patent Owner's arguments. *See supra* Section V.J.

In addition, as explained above, claims 13 and 14 do not require "internal controls." *See id.* Claim 26, however, does. Thus, we also address Patent Owner's argument that the MS2-RNA in Helftenbein's Examples 5–8 "does not operate as an ***internal*** control," an argument that was inapplicable to claims 13 and 14, but relevant here. *See* Sur-reply 21. As explained below, we do not agree with this argument.

According to the '467 patent, in certain embodiments, nucleic acids can be added to the claimed composition for a variety of purposes, including "as an internal positive control for downstream molecular processes and to track or monitor the fidelity of the nucleic acid preparation from sample collection to detection." Ex. 1001, 6:2–5. This is the only mention of "internal" positive control in the '467 patent.

Indeed, in explaining Figure 8A, which "depicts the real-time RT-PCR analysis of 'naked' influenza A avian H5 RNA template preserved in PrimeStore™ Solution after incubation in RNA/DNA nucleases," the '467 patent states "[r]eal-time RT-PCR Cycle threshold (CT) values of naked RNA preserved in PrimeStore with added nucleases . . . were similar to an equal quantity of template cRNA control . . . . Template cRNA reactions subjected to nuclease digestion without PrimeStore™ were almost completely degraded." Ex. 1001, 12:49–61. In other words, here, the '467 patent discloses an RNA control that is not part of the claimed composition.

Similarly, in explaining Figure 8C, the ’467 patent states “Lane 5 amplification of positive control RNA. Lane 5 (no amplification) is RNA without PrimeStore™.” *Id.* at 13:11–13. Putting aside the apparently contradictory statements regarding amplification of the RNA in lane 5, this description of Figure 8C suggests the “positive control RNA” therein also is not part of the claimed composition.

Thus, other than a general statement (*id.* at 6:2–5), the ’467 patent does not otherwise discuss including an “internal” positive control in the claimed composition. Instead, it only describes control DNA and RNA that are not part of the claimed composition. *See id.* at 12:49–61, 13:11–13. This reflects Patent Owner’s “own view of the ordinary skill in the art at the time it filed the application that led to the [’467] patent and it does so not by what the [’467] patent discloses but by what it *does not* disclose.” *Cf. Abbott Labs. v. Andrx Pharms., Inc.*, 452 F.3d 1331, 1341 (Fed. Cir. 2006).

With this understanding, we revisit Helftenbein, which teaches adding naked MS2-RNA as a positive control to the mixture of N-sS and serum. Ex. 1019, 6:48–8:36, 8:64–9:5. Considering Patent Owner’s own view of ordinary skill at the relevant time, as discussed above, we find that an ordinarily skilled artisan would have had a reason to include an internal positive control. This is further supported by Helftenbein, which teaches adding an “*internal* standard” to N-sS. *Id.* at 2:60–61 (emphasis added). The “internal standard” in Helftenbein serves the same purpose as the “internal positive control” required in challenged claim 16. *Compare* Ex. 1019, 2:61–63 (Helftenbein teaching the “internal standard” “permits the control of the whole method from the moment of sampling up to the detection of nucleic acids”), *with* Ex. 1001, 5:67–6:3 (the ’467 patent disclosing “an

internal positive control for downstream molecular processes and to track or monitor the fidelity of the nucleic acid preparation from sample collection to detection”).

Thus, we find Helftenbein teaches or suggests an internal positive control, and an ordinarily skilled artisan would have had a reason to include such an internal positive control in Birnboim’s composition.

For the remaining limitations of claim 26, Petitioner incorporates its analysis of claim 25, i.e., the combination of Birnboim and Mori renders claim 25 obvious. Pet. 66 (citing Ex. 1002 ¶¶ 285–286). Patent Owner relies on the same arguments as presented in addressing claim 24. PO Resp. 56. For the same reasons explained above, we find Petitioner’s argument more persuasive. *See supra* Section V.G.

In sum, for the same reasons explained above (*see supra* Sections V.G, V.J), as well as additional reasons explained in this Section, we determine Petitioner demonstrates by a preponderance of the evidence that claim 26 would have been obvious over Birnboim, Mori, and Helftenbein.

L. Alleged Obviousness over Birnboim, Mori, Helftenbein, and Birnboim 2006

Claim 40 depends from claim 31 and further recites

> the mixture further comprises one or more short-chain alkanols present in an amount from about 1% to about 25% (vol./vol.); one or more surfactants or defoaming agents present in an amount from about 0.0001% to about 0.3% (wt./vol.); and added naked RNA or DNA present in an amount of about 1 pg/mL to 1 μg/mL.

Ex. 1001, 37:3–9.

Petitioner points out that the additional limitations in claim 40 correspond to those recited in claims 8, 10, and 13. Pet. 67. Petitioner argues that Birnboim in combination with Mori and Helftenbein teaches each of those limitations. *Id.* Specifically, Petitioner relies on its arguments in challenging claim 8 (for short-chain alkanols), 10 and 24 (for surfactants or defoaming agents), and 13 (for naked RNA or DNA). *Id.* (citing Ex. 1002 ¶¶ 288–290).

Claim 41 depends from claim 40 and recites a list of specific short-chain alkanols and a list of specific surfactants or defoaming agents. The additional limitations in claim 41 correspond to those recited in claims 9 and 11. Claim 42 depends from claim 40 and requires "detecting the presence or absence of the added naked DNA or RNA." The additional limitations in claim 42 corresponds to that recited in claim 14. Petitioner relies on its arguments in challenging those respective claims. *Id.* at 67–68 (citing Ex. 1002 ¶¶ 292, 293, 295, 296).

Patent Owner does not respond to Petitioner's mapping of the short-chain alkanols and the surfactants or defoaming agents. It, however, repeats the same arguments addressing Petitioner's challenge of claims 13 and 14. *See* PO Resp. 57–58; Sur-reply 20–21. For the same reasons explained above (*see supra* Section V.J), we reject those arguments.

After reviewing the record, we agree with Petitioner's analyses. *See* Pet. 67–68. Thus, for the same reasons explained above (*see supra* Sections V.E, V.G, V.J), we determine Petitioner demonstrates by a preponderance of the evidence that claims 40–42 would have been obvious over Birnboim, Mori, Helftenbein, and Birnboim 2006.

M. Summary

After reviewing the entire record and weighing evidence offered by both parties, we determine that Petitioner has demonstrated by a preponderance of the evidence that claims 1–17 and 24–42 of the ’467 patent would have been obvious over the asserted prior art.[22] We find Petitioner, however, has not met its burden to show that claims 18–23 are unpatentable. Nonetheless, for the reasons set forth in the Sanctions Order, issued concurrently, we enter Adverse Judgment against Patent Owner as to all challenged original claims.

VI. REVISED CONTINGENT MOTION TO AMEND

Having determined that Petitioner has shown by a preponderance of the evidence that original claims 1–17 and 24–42 of the ’467 patent are unpatentable, we proceed to address Patent Owner’s Revised Contingent Motion to Amend.

A. 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

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[22] Petitioner also argues that Birnboim anticipates claims 1, 2, 4, 7, 8, 9, 17, 29, 31, and 34–39. Pet. 9–26, 28–32. Having determined that Petitioner has shown these claims would have been obvious over Birnboim, we do not address the anticipation ground. *See SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1359 (2018) (holding a petitioner “is entitled to a final written decision addressing all of the claims it has challenged”); *Bos. Sci. Scimed, Inc. v. Cook Grp. Inc.*, 809 F. App’x 984, 990 (Fed. Cir. 2020) (recognizing that the “Board need not address issues that are not necessary to the resolution of the proceeding” and, thus, agreeing that the Board has “discretion to decline to decide additional instituted grounds once the petitioner has prevailed on all its challenged claims”).

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 at 3–4 (PTAB Feb. 25, 2019) (precedential); *Bosch Auto. Serv. Sols. LLC v. Iancu*, 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).

B. Proposed Substitute Claims

Patent Owner proposes substitute claims 43–84 to replace original claims 1–42. Revised MTA 1, App. A. Specifically, Patent Owner proposes substitute claims 43, 66, 71, and 73 to replace original claims 1, 24, 29, and 31, 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.

In support of their respective positions regarding the Motion to Amend, Patent Owner relies on the Declarations of Dr. DeFilippi

(Exs. 2033, 2042); and Petitioner relies on the Declarations of Dr. Taylor (Exs. 1071, 1082) and Christopher M. Beausoleil (Ex. 1077).

C. Proposed Substitute Claims 60–65

Patent Owner proposes substitute claims 60–65 to replace original claims 18–23. Revised MTA, App. A. Because Petitioner has not shown by a preponderance of the evidence that claims 18–23 are unpatentable (*see supra* Section V.F), we need not address the patentability of proposed substitute claims 60–65. *See* Revised MTA 1 (Patent Owner asking the Board to consider the proposed substitute claims only if the corresponding original claim is found unpatentable). In any event, because we impose adverse judgment as sanctions against Patent Owner, we deny the Revised Motion to Amend in its entirety.

D. 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. Revised MTA 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. Revised MTA 11–24. 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." Revised MTA 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 id.* at App. 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 '467 patent issued from Patent Application No. 13/332,204 (Ex. 2022, "the '204 application"). Ex. 1001, code (21). Pointing to paragraphs of the '204 application, Patent Owner argues that "the proposed substitute claims are fully supported." Revised MTA 4–11.

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. Second MTA Opp. 18–20; MTA Sur-reply 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 VI.E.2.

Petitioner also argues that "[i]f PO argues that the newly-added limitation 'in one step' requires that the nucleic acids be detectable or detected by PCR without purification or extraction from the mixture comprising the composition and sample, then the claims would not satisfy the written description . . . requirement[]."[23] 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 VI.E.3.

After reviewing Patent Owner's identification (*see* Revised MTA 4–11), we are satisfied that, under proper claim construction (*see infra* Sections VI.E.2, VI.E.3), the '204 application provides sufficient written-description support for proposed substitute claims 43–59 and 66–84.

In sum, 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.

E. Additional Limitations of Proposed Substitute Claims

As explained above, Petitioner has shown by a preponderance of the evidence that the asserted prior art teaches each limitation of original claims 1–17 and 24–42. *See supra* Sections V.E, V.G–V.L. For the same reasons provided there, we find that the prior art asserted in the Petition challenging the original claims teaches the limitations of proposed substitute

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[23] Petitioner also argues that proposed substitute claim 71 is not enabled. Second MTA Opp. 22. A proper enablement analysis requires examination of various factors under *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). Petitioner has not done so. *See* Second MTA Opp. 22.

claims 43–59 and 66–84 that are identical to those of claims 1–17 and 24–42. We focus our discussion here on the additional limitations of proposed substitute claims 43–59 and 66–84.

1. Endogenous and Exogenous Nucleases

Each of proposed substitute claims 43, 71, and 73 requires the mixture to inactivate "endogenous and exogenous nucleases" or "endogenous and exogenous RNases and DNases." Patent Owner contends that Birnboim does not teach inactivating exogenous nucleases. Revised MTA 14. We disagree.

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 mucosa. Ex. 1003 ¶ 68. 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 teaches 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 nucleases." Second MTA Opp. 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." MTA Reply 2 (citing Second MTA Opp. 2). 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." *Id.* (citing Ex. 2042 ¶ 11; Ex. 2044).

As an initial matter, we note that Exhibit 2044, titled "Biofilms: Survival Mechanisms of Clinically Relevant Microorganisms," is a twenty-seven-page document. Yet, Patent Owner does not direct us to any specific disclosure that supports its argument.

With respect to the testimony Patent Owner relies on, Dr. DeFilippi testifies that

> [o]ne 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.[24] 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 3. As Petitioner points 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* MTA Sur-reply 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.* at 525:17–19 ("We are denaturing proteins, and the result of denaturing proteins would be destroying the activity of enzymes.").

Prior art, such as Birnboim, confirms 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

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[24] To the extent Dr. DeFilippi emphasizes "different types of biofilms" (Ex. 1096, 1067:2–10; Ex. 2042 ¶ 22), neither he, nor Patent Owner, sufficiently explains the relevance of biofilms to the proposed substitute claims at issue.

presence of guanidine, stringent precautions against adventitious[25] 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.”

Patent Owner emphasizes that, in Example 7, Birnboim added ribonuclease to digest and remove the majority of RNA present in the sample. Revised MTA 14. According to Patent Owner, this ribonuclease is an exogenous nuclease, and it is “clearly not inactivated.” *Id.* Therefore, 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 extra ribonuclease to digest RNA. *Id.* The ’467 patent, on the 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, 6:20–23 (emphasis added). Thus, the ’467 patent does not contemplate inactivating nucleases, such as the extra ribonuclease added in Birnboim Example 7, which is unrelated to the

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[25] Dr. DeFilippi appears to have misunderstood the term “adventitious.” *See* Ex. 1096, 985:22–986:1 (testifying that the term “‘adventitious’ means it takes advantage of the situation”). In fact, the term means “coming from another source and not inherent or innate.” *See* https://www.merriam-webster.com/dictionary/adventitious. Ex. 3011.

sample studied.[26] *See id.* at 9:8–9 (disclosing inactivating "exogenous or endogenous nucleases that may be ***present in, on, or about the sample itself***") (emphasis added).

In sum, Petitioner has shown by a preponderance of the evidence that Birnboim explicitly teaches that its compositions "inactivate endogenous and exogenous nucleases."

2. Entirely Non-Pathogenic

Each of proposed substitute claims 66, 71, and 73 recites "rendering a biological sample entirely non-pathogenic and safe for human handling." Patent Owner asserts paragraph 48 of the '204 application provide written description support for this additional limitation. Revised MTA 6, 8, 10.

Paragraph 48 states it is desirable that the "microbes, viruses, and/or pathogens . . . present in, on, or about the sample when collected . . . will be killed or sufficiently inactivated by one or more components of the composition to facilitate safe handling of the sample by the practitioner." Ex. 2022 ¶ 48. According to the '204 application, "[p]referably, 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." *Id.* Paragraph 48, however, does not explain what "entirely non-pathogenic" means. Nor does the Revised MTA. At the hearing, when inquired, Patent

[26] Were it otherwise, 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 the extra nucleases. Furthermore, the '467 patent does not teach how to inactivate an overwhelmingly large amount of added nucleases, and thus, would not enable the proposed substitute claims.

Owner asserted that the term means "zero pathogenic activity," so that the sample "could not infect someone, rendering it safe for handling." Tr. 134:19–135:14.

We look to the '467 patent Specification to interpret the limitations added in the Revised MTA. In Example 8, the '467 patent discloses "Killing of [Methicillin-resistant *Staphylococcus aureus*] MRSA (ATCC33592) in PrimeStore™ Solution." Ex. 1001, 27:6–10. 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 27:12–14, 28:1–3; *see also id.* at 29:5–7 (the same).

Similarly, Example 9 demonstrates that "the disclosed composition could quickly kill or inactiv[at]e microorganisms" in a chicken cloacal sample. *Id.* at 29:27–35. According to the '467 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 12:35–40. 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 '467 patent, we conclude that a sample is rendered "entirely non-pathogenic" when the treated sample forms no detectable colonies or plaques on agar plates.

That, however, does not resolve the issue completely 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 '467 patent. Petitioner argues that ABL test data

Second MTA Opp. 5 (citing Exs. 1201–1204; Ex. 1069, 272:13–273:7). This, Petitioner contends, demonstrates that the tested samples were rendered "entirely non-pathogenic." *Id.*

Patent Owner counters that data from the same set show Birnboim's composition did not inactivate two types of pathogens. Revised MTA 20 (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 "entirely non-pathogenic and safe for human handling." *Id.* (citing Ex. 2033 ¶ 12); *see also* MTA Reply 3 (citing Ex. 2019; Ex. 2033 ¶ 24) (the same).

Based on this record, and as explained below, we find Petitioner's argument more persuasive. Our conclusion is supported by other proposed substitute claims. For example, proposed substitute claim 59 recites "the biological sample contains viral particles, virally infected cells, bacteria, bacterially infected cells, fungal organisms, animal cells, *or* plant cells." In other words, a sample may contain a single type of pathogen, for example, influenza viruses or bacteria that cause tuberculosis. If, after contacted by a composition, such a sample forms no detectable plaques or colonies on an applicable plate assay, then the composition satisfies the requirement of rendering the sample entirely non-pathogenic.

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

[redacted]"[27] Second MTA Opp. 5 (citing Exs. 1201–1204; Ex. 1069, 272:13–273:7); *see also* Ex. 1069, 245:5–246:16 (Dr. Birkebak at ABL testifying [redacted]); 247:13–248:21 (similar testimony [redacted]). 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 teaches that its compositions inactivate the sample contacted and render the sample "entirely non-pathogenic and safe for human handling."

3. In One Step

Each of proposed substitute claims 43 and 71 recites the phrase "in one step" twice: once in the original language of claims 1 and 29, respectively; the other added in the proposed amendment. Proposed substitute claim 43 also recites "detecting the presence and identity of or absence of the pathogens in the biological sample;" and proposed substitute claim 71 further recites "PCR amplifying the nucleic acids, if present; and determining the presence or absence of the pathogens in the biological sample."

Although not explicitly presented, Petitioner argues that the newly "in one step" limitation does not require "the nucleic acids be detectable or

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

detected by PCR without purification or extraction from the mixture comprising the composition and sample." *See* Second MTA Opp. 20. For the reasons explained below, we agree with Petitioner's argument.

First, the structure of the proposed amended claims 43 and 71 shows that the added "in one step" does not include the detecting step in proposed amended claim 43, or the PCR amplification step in proposed amended claim 71. Indeed, after the added "in one step," each proposed amended claim recites three numbered parts, i.e., i), ii), and iii). Neither the detecting step nor the PCR amplification step has an assigned number. When pointing to written-description support, Patent Owner divides the "one step" with the three numbered parts from the detecting or the PCR amplification step. *See* Revised MTA 4, 9. By separating these limitations, Patent Owner signals that it does not consider the detecting or the PCR amplification step as part of the "one step."

Second, the '467 patent Specification shows the "in one step" limitation relates only to contacting the sample with the mixture prior to extraction, and does not include the detecting or PCR amplification step. According to the '467 patent,

> [t]he one-step formulations disclosed herein accomplish the following main functions: inactivation or killing of pathogens within the sample; lysis of cells and separation or release of nucleic acids from the cells; inactivation of endogenous or exogenous nucleases and other cellular enzymes to prevent degradation of the nucleic acids present in the sample; and facilitation of collection and handling of the sample at ambient temperatures, stabilization of the nucleic acids during subsequent transport and storage of the sample, and

> preservation/maintenance of the integrity of one or more polynucleotides contained with the liberated nucleic acids.

Ex. 1001, 3:33–43; *see also id.* at 1:32–37 (disclosing "a one-step composition 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").

The '467 patent discloses that the functions of denaturing proteins, inactivating nucleases, and killing pathogens recited in proposed amended claim 71 occur in one step, that is, by contacting the sample with the mixture. *See id.* at 3:67–4:2 ("In all embodiments, the one-step formulation is combined with the sample to initiate these functions."). "This is in contrast to previous technology in which inactivation did not necessarily occur, and lysis, stabilization, and preservation occurred in a succession of separate steps, each step typically using one or more distinct reagents and protocols that were separately added." *Id.* at 4:2–7.

The '467 patent makes clear, however, this "one step" does not include any "***subsequent*** isolation, detection, amplification, and/or molecular analysis," which occurs after the "one step" of contacting the sample with the claimed composition. *Id.* at 1:32–40 (emphasis added). Instead, one only obtains a population of polynucleotides at the end of the "one step:"

> The invention also provides a method for ***obtaining*** a population of polynucleotides from a sample suspected of containing nucleic acids. The method generally involves associating the sample with an amount of one of the disclosed compositions, under conditions effective to *obtain* a population of polynucleotides from the sample. The invention does not

> require separation of the population to "***obtain***" the sample, as later diagnosis may or may not need such separation.

Id. at 7:41–48 (emphases added).

Thus, intrinsic evidence supports our determination that the "in one step" limitation does not exclude additional steps between contacting the sample with the composition and detecting the nucleic acids. To the contrary, the '467 patent discloses that additional steps are necessary between preparing the preserved sample and subsequent analysis after the "one step." For example, according to the '467 patent,

> [t]he one-step formulation's preferably simultaneous inactivation of biological components containing nucleic acids, lysis and release of nucleic acids from cellular debris, stabilization, and preservation of nucleic acids reduces the chance for degradation of the RNA/DNA in the sample that may occur during lysis, or after lysis and before stabilization, which contributes to improved yield of the ***nucleic acids that are eventually extracted***.

Id. at 4:14–22 (emphasis added).

Third, extrinsic evidence, such as information about PrimeStore, Patent Owner's commercial product embodying the compositions disclosed in the '467 patent, also supports our determination. *See* Ex. 1001, 21:27–30, 22:14–17, 22:39–42 (stating the compositions of the '467 patent are alternatively referred to as "PrimeStore™ Solution," versions 1, 2, and 2.2). According to the product information sheet, "[s]amples collected in PrimeStore® MTM ***must be extracted*** using a commercially available extraction method such as silica spin columns or bead-based extraction systems." Ex. 1067 (emphasis added); *see also id.* ("6. Proceed with DNA/RNA extraction using a commercially available purification method.").

In sum, the "one step" recited in proposed substitute claims 43 and 71 only encompass the three numbered parts, and does not include the separate detecting or PCR amplification step. And Birnboim's compositions, upon contacting a sample suspected of containing pathogens, denature proteins, inactivate nucleases, kill pathogens, and do not degrade nucleic acid. *See supra* Sections V.E.1, VI.E.1, VI.E.2. Because these functions occur in one step, by contacting the sample with Birnboim's compositions, Birnboim teaches the "one step" limitation.

4. Without Further Separation

Proposed substitute claim 43 recites "the released nucleic acids are compatible with a nucleic acid test without further separation from the biological sample." This additional limitation was first presented in the original MTA. *See* original MTA 15–16.

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. First MTA Opp. 4 (citing Ex. 1003 ¶ 124). Petitioner points out that "[t]he target polynucleotide was not separated from the sample prior to running the samples on the agarose gel." *Id.* According to Petitioner,

> [t]o reduce the time and labor necessary to quickly and 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. This would obviate the need to conduct time-consuming separation after the sample has been contacted with the composition. Ex. 1071, ¶37.

Id. at 9.

In the Preliminary Guidance, we found Petitioner's argument persuasive. *See* PG 16. We explained that "[w]e do not view the addition of ribonuclease to the reaction vessel as causing separation from the sample, as recited in proposed substitute claim 43." *Id.*

In the Revised MTA, Patent Owner does not address Birnboim's Example 7 as it relates to the "no further separation" limitation.[28] *See* Revised MTA 20. In the MTA Reply, Patent Owner contends "[n]o such teaching is found in Birnboim" because "Birnboim's use of RNase in Ex[ample] 7 is a separation step used prior to DNA testing using gel electrophoresis that separates hydrolyzed RNA fragments from the intact DNA." MTA Reply 5 (citing Ex. 2042 ¶¶ 16, 39–40). We disagree.

Proposed substitute claim 43 requires the released nucleic acids "compatible with a nucleic acid test without further separation *from the biological sample*." It also recites "lysing a portion of cells in the biological sample to release nucleic acids," which makes clear that the sample is cells, and not merely the nucleic acids contained within.

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."

In sum, Petitioner has shown, by a preponderance of the evidence, that Birnboim teaches that the released nucleic acids are "compatible with a nucleic acid test without further separation from the biological sample."

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[28] Patent Owner only discusses Example 7 as it relates to another added limitation, i.e., inactivates "endogenous and exogenous nucleases." *See* Revised MTA 14, 19, 22.

F. Proposed Substitute Claim 43

Proposed substitute claim 43, which would replace claim 1, recites (with underlining representing addition):

> 43. A method for denaturing proteins, inactivating nucleases and killing pathogens in one step without degrading nucleic acids of a biological sample containing proteins, nucleases, and nucleic acids, and suspected to contain pathogens, comprising:
>
> in one step:
>
> i) providing a mixture containing one or more chaotropes, one or more detergents, one or more reducing agents, one or more chelators, and one or more buffers, together present in an amount sufficient to denature proteins, inactivate endogenous and exogenous nucleases, kill pathogens, and not degrade nucleic acids;
>
> ii) contacting the biological sample with the mixture which denatures proteins, inactivates endogenous and exogenous nucleases, kills pathogens, and does not degrade nucleic acids of the biological sample; and
>
> iii) lysing a portion of cells in the biological sample to release nucleic acids, wherein the mixture inactivates endogenous and exogenous RNases and DNases to prevent degradation of the released nucleic acids within the mixture, wherein the released nucleic acids are compatible with a nucleic acid test without further separation from the biological sample; and
>
> detecting the presence and identity of or absence of the pathogens in the biological sample.

As explained above, Petitioner has shown, by a preponderance of the evidence, that Birnboim renders claim 1 obvious. *See supra* Section V.E.1. We adopt that analysis for the identical limitations of proposed substitute claim 43. Also as explained above, Petitioner has shown, by a preponderance of the evidence, that Birnboim's compositions "inactivate endogenous and exogenous nucleases," and biologically inactivate the

sample contacted to render it "entirely non-pathogenic and safe for human handling." *See supra* Sections VI.E.1, VI.E.2. Furthermore, as explained above, Petitioner also has shown, by a preponderance of the evidence, that Birnboim teaches the "in one step" limitation and the "without further separation" limitation. *See supra* Sections VI.E.3, VI.E.4. Thus, Petitioner has shown, by a preponderance of the evidence, that Birnboim renders obvious proposed substitute claim 43.

G. Proposed Substitute Claim 66

Proposed substitute claim 66 would replace claim 24. It retains all limitations of claim 24, and adds the language "thereby rendering a biological sample entirely nonpathogenic and safe for human handling."

As explained above, Petitioner has shown, by a preponderance of the evidence, that the combination of Birnboim and Mori renders claim 24 obvious. *See supra* Section V.G.1. We adopt that analysis for the identical limitations of proposed substitute claim 66. Also as explained above, Petitioner has shown, by a preponderance of the evidence, that Birnboim's compositions biologically inactivate the sample contacted to render it "entirely non-pathogenic and safe for human handling." *See supra* Section VI.E.2. Thus, Petitioner has shown, by a preponderance of the evidence, that Birnboim renders obvious proposed substitute claim 66.

H. Proposed Substitute Claim 71

Proposed substitute claim 71, which would replace claim 29, recites (with underlining representing addition and strikethrough representing deletion):

> 71. A method for denaturing proteins, inactivating nucleases and killing pathogens thereby rendering a biological sample entirely nonpathogenic and safe for human handling in one step

> without degrading nucleic acid of the ~~a~~ biological sample containing proteins, nucleases, and nucleic acid comprising:
>
> in one step:
>
> i) providing a mixture containing one or more chaotropes, one or more detergents, one or more reducing agents, one or more chelators, and one or more buffers, together present in an amount sufficient to denature proteins, inactivate nucleases, kill pathogens, and not degrade nucleic acid;
>
> ii) providing the biological sample suspected to contain pathogens;
>
> iii) contacting the biological sample with the mixture which liberates nucleic acids of the pathogens such that they are detectable by ~~for~~ PCR analysis, wherein the mixture inactivates endogenous and exogenous RNases and DNases to prevent degradation of the liberated nucleic acids in the mixture;
>
> and PCR amplifying the nucleic acids, if present; and
>
> determining the presence or absence of the pathogens in the biological sample.

As explained above, Petitioner has shown, by a preponderance of the evidence, that Birnboim renders claim 29 obvious. *See supra* Section V.E.5. We adopt that analysis for the identical limitations of proposed substitute claim 71. Also as explained above, Petitioner has shown, by a preponderance of the evidence, that Birnboim's compositions "inactivate endogenous and exogenous nucleases," and biologically inactivate the sample contacted to render it "entirely non-pathogenic and safe for human handling." *See supra* Sections VI.E.1, VI.E.2. Furthermore, as explained above, Petitioner also has shown, by a preponderance of the evidence, that Birnboim teaches the "in one step" limitation. *See supra* Section VI.E.3. Thus, Petitioner has shown, by a preponderance of the evidence, that Birnboim renders obvious proposed substitute claim 71.

I. Proposed Substitute Claim 73

Proposed substitute claim 73 would replace claim 31. It retains all limitations of claim 31, and adds the language "thereby rendering a biological sample entirely nonpathogenic and safe for human handling" and "endogenous and exogenous" nucleases.

As explained above, Petitioner has shown, by a preponderance of the evidence, that Birnboim renders claim 31 obvious. *See supra* Section V.E.5. We adopt that analysis for the identical limitations of proposed substitute claim 73. Also as explained above, Petitioner has shown, by a preponderance of the evidence, that Birnboim's compositions inactivate endogenous and exogenous nucleases, and that Birnboim's compositions biologically inactivate the sample contacted to render it "entirely non-pathogenic and safe for human handling." *See supra* Sections VI.E.1, VI.E.2. Thus, Petitioner has shown, by a preponderance of the evidence, that Birnboim renders obvious proposed substitute claim 73.

J. Other Proposed Substitute Claims

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." Revised MTA 3. As explained above, we find Petitioner demonstrates by a preponderance of the evidence that original claims 1–17 and 24–42 would have been obvious over the asserted prior art. *See supra* Sections V.E, V.G–V.L. Also as explained above, we find Petitioner demonstrates by a preponderance of the evidence that proposed substitute claims 43, 66, 71, and 73 would have been obvious over the asserted prior art. *See supra* Sections VI.F–VI.I. Thus, we determine Petitioner has shown, by a

preponderance of the evidence, that the asserted prior art renders obvious proposed substitute claims 44–59, 67–70, 72, and 74–84.

K. Summary

In sum, Petitioner has shown, by a preponderance of the evidence, that the asserted prior art renders proposed substitute claims 43–59 and 66–84 obvious.

VII. MOTION TO EXCLUDE

Patent Owner filed a Motion to Exclude Evidence. Paper 83 (“MTE”). Specifically, Patent Owner moves to exclude Birnboim, the primary prior art reference relied on in the Petition. *Id.* at 1–2. Patent Owner also moves to exclude certain test results from ABL, the 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 4–5. Additionally, Patent Owner moves to exclude certain declarations of 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 2–4, 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 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 dismissed-in-part and denied-in-part.

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 contradicts 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 the

specification describes. Indeed, Patent Owner points to Paper 68, Petitioner's second MTA Opposition, 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 second MTA Opp. 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).

Because Petitioner relies on Birnboim to show 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, 1052, 1054, 1056–1058, 1060, 1083, 1085–1092, and 1095

Exhibits 1050, 1052, 1054, 1056–1058, 1060, 1083, 1085–1092, and 1095 are articles published in peer-reviewed journals. We do not rely on these exhibits in rendering this Decision. Thus, we dismiss this aspect of Patent Owner's Motion to Exclude as moot.

2. Exhibits 1008 and 1015

Patent Owner argues that Exhibits 1008 (Das) and 1015 (Chirgwin) "should be excluded to the extent that Petitioner relies on them for the truth of the 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, an article published in a scientific journal. *See* 37 C.F.R. § 42.61(c) (discussing the admissibility of "specification or drawing of a United States patent application or patent"). Thus, we deny Patent Owner's Motion to Exclude Exhibit 1015.

Although Rule § 42.61(c) does apply to Das, a published U.S. patent application, Patent Owner does not identify what "data" in Das Petitioner attempts to prove the truth of. Indeed, Patent Owner cites "Petition, 45, 62; Paper 40, 19; Paper 41, 2–3, 5–6" in support of its argument to exclude nine references, including Das. MTE 3. 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 Exhibit 1008. *See* 37 C.F.R. §§ 42.20(c), 42.62(a).

C. 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*. We do not rely on Exhibit 1068 in rendering this Decision. Thus, we dismiss this aspect of Patent Owner's Motion to Exclude Exhibit 1068 as moot.

D. Exhibits 1069, 1072, 1073, and 1200-1211[29]

Patent Owner engaged ABL to conduct biological testing in support of Patent Owner Response and its original 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 34, 2–3.

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 id.* at 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.*

[29] 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.

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 id.* at 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 44, 7–8[30] (objecting these Exhibits only "under FRE 401/402/403, needlessly cumulative evidence, little to no probative 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 43, 2 ("Exhibits 1205 and 1208 need not be sealed.").

Because Patent Owner fails to explain 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.

[30] Patent Owner does not include page numbers in Papers 43 and 44. We cite to the pages as if they were numbered properly.

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 the Patent Owner Response. Following our Order (Paper 34), 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'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 32 (making work product arguments PO seeks to preserve for appeal).

Paper 63 ("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 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 tests 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 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 Sanctions Order, the work-product doctrine is not absolute and generally allows discovery of "factual" or "non-opinion" work product. Sanctions Order 10 (citing *In re EchoStar Comms. Corp.*, 448 F.3d 1294, 1301 (Fed. Cir. 2006)); *see also id.* at 13 (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 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 VII.D.3), we deny Patent Owner's Motion to Exclude Exhibit 1069.

E. Exhibits 1071 and 1082

Exhibits 1071 and 1082 are Declarations of Petitioner's witness, Dr. Taylor. Dr. Taylor 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, 8. For the same reason explained above as related to Exhibits 1201–1204, 1206, and 1207–1211 (*see supra* Section VII.D.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, Dr. Taylor discusses Birnboim, Chirgwin, Das, and Goldrick, all of which are filed with the Petition. *See* Pet., Exhibit List. And Birnboim and Das were asserted, and Chirgwin was cited, in the Petition. *See id.* at 5, 8. Thus, it is unclear which paragraphs of Exhibit 1071 Patent Owner actually moves to exclude as irrelevant and prejudicial.

In any event, we do not rely on the allegedly “new prior art references” discussed in Exhibit 1071 in rendering this Decision, and all the obviousness grounds against the original challenged claims we discuss are properly asserted in the Petition. *See supra* Sections IV.C, V.E–V.L; *see also* Pet. 8.

Accordingly, we deny Patent Owner’s Motion to Exclude Exhibits 1071 and 1082.

VIII. MOTION TO SEAL

Patent Owner filed an unopposed Motion for entry of a Protective Order. Paper 39. 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 38). The Protective Order (Paper 38) is hereby entered. It shall govern the conduct of the proceeding unless otherwise modified.

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." Patent Trial and Appeal Board Consolidated Trial Practice Guide 19 (November 2019) ("TPG").[31] 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. *Id.* § 42.20(c).

From the Motion to Seal, we understand Patent Owner seeks to seal Exhibits 1201–1204, 1206, 1207, and 1210, which relate to the ABL test data Patent Owner originally withheld and is at issue in the Order on Sanctions. *See* Paper 43 ("Seal Mot."), 1–2. Patent Owner also seeks to seal deposition testimony of ABL employees (Exs. 1069, 1072, 1073) and "[o]ther" unidentified "potential exhibits." *Id.* at 2.

We understand from Petitioner's Opposition to the Motion to Seal that those other exhibits include Exhibits 1209 and 1211, which are additional

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[31] *Available at* https://www.uspto.gov/sites/default/files/documents/tpgnov.pdf?MURL=.

data relating to the originally withheld testing, and Exhibit 1071, which is Dr. Taylor's Second Declaration. *See* Opp. Mot. 6–15.

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." Seal Mot. 2.

Petitioner does not oppose the motion in principle, but argues Patent Owner provides insufficient detail or justification for the full scope of material it seeks to seal. Paper 51, 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. Petitioner provides a plan for how each item of the subject documents should be treated. *Id.* at 6–15.

In its Reply, Patent Owner contends that Petitioner is trying to "force more details into the public record before PO can appeal this issue." Seal Reply 2. Patent Owner, also for the first time, identifies the particular material sought to be sealed. *Id.* at 2–5. Specifically, Patent Owner seeks to seal the entirety of Exhibits 1202–1204, 1206, 1207, 1209, and 1210, and seal portions of Exhibits 1069, 1071–1073, 1201, and 1211. *Id.*

Patent Owner seeks to seal Exhibit 1071, one of the Declarations of Dr. Taylor, because he discusses Exhibits 1202–1204, 1206, 1207, 1210,

and 1211, as well as “consulting testing PO asserts as its protected work product.” Seal Reply 4. Similarly, Patent Owner seeks to seal portions of Exhibits 1069, 1072, and 1073, the three ABL employees’ deposition transcripts. *Id.* at 4–5. According to Patent Owner, although the reopened depositions were “taken precisely to allow Petitioner to ask about the information PO contends is subject to work product immunity,” “PO limited its redactions to testimony regarding that consulting testing.” *Id.* at 4–5.

As explained above in connection with our decision on the Motion to Exclude, the work-product doctrine is not designed to protect factual information in Exhibits 1201–1204, 1206, 1207, and 1209–1211. *See supra* Section VII.D.3. As such, Patent Owner’s reasoning for sealing Exhibits 1069 and 1071–1073 is not persuasive either. Thus, Patent Owner’s Motion to Seal 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, and Exhibits 1069, 1071–1073, 1201–1204, 1206, 1207, 1209–1211 will remain sealed until the completion of all appeals. 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.

We also note that 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." Seal Reply 2–3. There, Patent Owner identifies Petitioner's Reply (Paper 40), the first MTA Opposition (Paper 41), and the Motion for Sanctions (Paper 57).[32] 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 51) as well as Patent Owner's Reply in Support of the Motion to Seal (Paper 63), 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,[33] 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

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[32] Petitioner filed a redacted version of the Reply (Paper 46), the first MTA Opposition (Paper 45), and the Motion for Sanctions (Paper 61).
[33] We 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.

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 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.

IX. CONCLUSION[34]

On the merits, after reviewing the entire record and weighing evidence offered by both parties, we determine that Petitioner has demonstrated by a preponderance of the evidence that claims 1–17 and 24–42 of the ’467 patent would have been obvious. We find Petitioner, however, has not met its burden to show that claims 18–23 are unpatentable. Nonetheless, for the reasons set forth in the Sanctions Order, issued concurrently, we enter Adverse Judgment against Patent Owner as to all challenged original claims.

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[34] 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).

In summary:

Claim(s)	**35 U.S.C. §**	**Reference(s)**	**Claims Shown Unpatentable**	**Claims Not Shown Unpatentable But Deemed Unpatentable**[35]
1, 2, 4, 7, 17–20, 22, 23, 29, 31, 34–39	102(b)[36]	Birnboim		18–20, 22, 23
1–9, 15–23, 29–39	103(a)	Birnboim	1–9, 15–17, 29–39	18–23
10, 11, 24, 25, 28	103(a)	Birnboim, Mori	10, 11, 24, 25, 28	
12	103(a)	Birnboim, Das	12	
27	103(a)	Birnboim, Mori, Das	27	
13, 14	103(a)	Birnboim, Helftenbein, Birnboim 2006	13, 14	
26	103(a)	Birnboim, Mori, Helftenbein	26	
40–42	103(a)	Birnboim, Mori, Helftenbein, Birnboim 2006	40–42	
Overall Outcome			1–17, 24–42	18–23

[35] As explained above, we determine that Petitioner has not met its burden to show that claims 18–23 are unpatentable. *See supra* Section V.F. Nonetheless, for the reasons set forth in the Sanctions Order, issued concurrently, we enter Adverse Judgment against Patent Owner as to all challenged original claims. Thus, we deem claims 18–23 unpatentable.

[36] As explained above, because we determine that Petitioner has shown claims 1, 2, 4, 7, 17, 29, 31, and 34–39 would have been obvious over Birnboim, we do not address whether Birnboim anticipates these claims. *See supra* Section V.M. n.22.

We also determine that Petitioner has demonstrated by a preponderance of the evidence that proposed substitute claims 43–59 and 66–84 are unpatentable under 35 U.S.C. § 103 as obvious over the asserted prior art. We do not reach the merits of proposed substitute claims 60–65. In addition, for the reasons set forth in the Sanctions Order, issued concurrently, we deny Patent Owner's Revised Motion to Amend.

Revised Motion to Amend Outcome	**Claims**
Original Claims Cancelled by Amendment	
Substitute Claims Proposed in the Amendment	43–84
Substitute Claims: Motion to Amend Granted	
Substitute Claims: Motion to Amend Denied	43–59, 66–84
Substitute Claims: Not Reached	60–65

X. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that all challenged claims (claims 1–42) of the '467 patent are *deemed unpatentable* based on Adverse Judgment under 37 C.F.R. § 42.12 for the reasons set forth in the Sanctions Order (Paper 109), issued concurrently, and *will be cancelled*;

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 the Sanctions Order;

FURTHER ORDERED that Petitioner has demonstrated by a preponderance of the evidence that claims 1–17 and 24–42 of the '467 patent are unpatentable under 35 U.S.C. § 103 based on the grounds set forth in the Petition;

FURTHER ORDERED that Patent Owner's Motion to Exclude Exhibits 1003, 1008, 1015, 1069, 1071, 1082, and 1201–1211 is *denied*;

FURTHER ORDERED that Patent Owner's Motion to Exclude Exhibits 1050, 1052, 1054, 1056–1058, 1060, 1068, 1072, 1073, 1083, 1085–1092, 1095, and 1200 is *dismissed*;

FURTHER ORDERED that the Protective Order (Paper 38) is hereby *entered*;

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 1069, 1071–1073, 1201–1204, 1206, 1207, and 1209–1211 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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