

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

10X GENOMICS, INC.,
Petitioner

v.

BRUKER SPATIAL BIOLOGY, INC.,
Patent Owner

Case IPR2023-01300
U.S. Patent No. 11,473,142

PETITIONER'S REPLY TO PATENT OWNER RESPONSE

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PETITIONER’S UPDATED EXHIBIT LIST

Exhibit No.	Description
1001	<i>Intentionally Left Blank</i>
1002	<i>Intentionally Left Blank</i>
1003	<i>Curriculum Vitae</i> of Paul Spellman, Ph.D.
1004	File History of U.S. Patent No. 11,377,689
1005	International Patent Application Publication No. WO 2017/019456 A2 to So et al., published February 2, 2017 (“So456”)
1006	International Patent Application Publication No. WO 2021/133849 A1 to Chell et al., published July 1, 2021 (“Chell”)
1007	“Explore Illumina sequencing technology,” Illumina, Inc., accessible at https://www.illumina.com/science/technology/nextgeneration-sequencing/plan-experiments/paired-end-vs-singleread.html
1008	<i>Intentionally Left Blank</i>
1009	U.S. Patent Application No. 16/272,487, filed February 11, 2019
1010	<i>Intentionally Left Blank</i>
1011	<i>Intentionally Left Blank</i>
1012	File History of U.S. Patent Application No. 16/272,487
1013	Merritt, <i>et al.</i> , “Multiplex digital spatial profiling of proteins and RNA in fixed tissue,” <i>Nature Biotechnology</i> 38:586-599 (May 2020)
1014	File History of U.S. Patent No. 11,473,142
1015	“Visium Spatial Gene Expression Reagent Kits,” 10x Genomics, Inc., Document No. CG000239, Rev. F, 2021

Exhibit No.	Description
1016	Stahl <i>et al.</i> , “Visualization and analysis of gene expression in tissue selections by spatial transcriptomics,” <i>Science</i> 353(6294):78-82 (July 1, 2016), with attached Supplementary Materials
1017	International Patent Application Publication No. WO 2012/140224 A1 to Frisen <i>et al.</i> , published October 18, 2012
1018	Spatial Transcriptomics Workflow, accessible at https://spatialtranscriptomics.com/workflow/
1019	Kivioja <i>et al.</i> , “Counting absolute numbers of molecules using unique molecular identifiers,” <i>Nature Methods</i> 9(1):72-76 (January 2012), with attached Supplementary Information
1020	<i>Intentionally Left Blank</i>
1021	<i>Intentionally Left Blank</i>
1022	NanoString Technologies, Inc.’s Initial Infringement Contentions with Attachment A and Exhibit 1, <i>10x Genomics, Inc. et al. v. NanoString Technologies, Inc.</i> , Case No. 1:22-cv-01375 (D. Del.), filed November 23, 2022
1023	Scheduling Order, <i>NanoString Technologies, Inc. v. 10x Genomics, Inc.</i> , Case No. 1:22-cv-01375 (D. Del.), filed April 13, 2023
1024	Joint Claim Construction Statement with Exhibits A through C, <i>NanoString Technologies, Inc. v. 10x Genomics, Inc.</i> , Case No. 1:22-cv-01375 (D. Del.), filed August 4, 2023
1025	Duncan <i>et al.</i> , “A method for detecting single mRNA molecules in <i>Arabidopsis thaliana</i> ,” <i>Plant Methods</i> 12:13 (2016)
1026	Lieben, L., “Spatial transcriptomics in plants,” <i>Nature Reviews Genetics</i> 18:394 (2017)

Exhibit No.	Description
1027	Jemt <i>et al.</i> , “An automated approach to prepare tissue-derived spatially barcoded RNA-sequencing libraries,” <i>Scientific Reports</i> 6:37137 (2016)
1028	Asp <i>et al.</i> , “Spatial detection of fetal marker genes expressed at low level in adult human heart tissue,” <i>Scientific Reports</i> 7:12941 (2017)
1029	“Interim Procedure for Discretionary Denials in AIA Post-Grant Proceedings with Parallel District Court Litigation,” United States Patent and Trademark Office Memorandum, June 21, 2022
1030	Fantini <i>et al.</i> , “Assessment of antibody library diversity through next generation sequencing and technical error compensation,” <i>PLOS One</i> 12(5):e0177574 (2017)
1031-1037	<i>Intentionally Left Blank</i>
1038	Complaint, NanoString Technologies, Inc. v. 10x Genomics, Inc., Case No. 1:22-cv-01375 (D. Del.), filed October 20, 2022
1039	5’ Amino Modifier C6, Integrated DNA Technologies
1040	Devor <i>et al.</i> , “Strategies for Attaching Oligonucleotides to Solid Supports,” Integrated DNA Technologies, 2005
1041	Ambardar <i>et al.</i> , “High Throughput Sequencing: An Overview of Sequencing Chemistry,” <i>Indian Journal of Microbiology</i> , 56(4):394-404 (October-December 2016)
1042	U.S. Patent No. 10,329,600 to Fu <i>et al.</i> , issued June 25, 2019
1043	U.S. Patent No. 11,473,142 to Beechem <i>et al.</i> , issued October 18, 2022 (“142 patent”)
1044	Declaration of Paul Spellman, Ph.D.

Exhibit No.	Description
1045	Onodera, K., “Selection for 3'-End Triplets for Polymerase Chain Reaction Primers,” <i>Methods in Molecular Biology</i> , 402:61-74 (2007)
1046	Tian <i>et al.</i> , “A large-scale analysis of mRNA polyadenylation of human and mouse genes,” <i>Nucleic Acids Research</i> , 33(1):201-212 (2012)
1047	CodeLink Activated Slides User Guide, SurModics, Inc.
1048	Khodakov <i>et al.</i> , “Recent developments in nucleic acid identification using solid-phase enzymatic assays,” <i>Microchem Acta</i> , 181(13-14):1633-1646 (2014)
1049	European Patent Application Publication No. EP 1114859 A1 to Ota <i>et al.</i> , published July 11, 2001
1050	Mercier <i>et al.</i> , “Solid Phase DNA Amplication: A Simple Monte Carlo Lattice Model,” <i>Biophysical Journal</i> , 85:2075-2086 (October 2003)
1051	<i>Intentionally Left Blank</i>
1052	Memorandum Opinion and Order, <i>NanoString Technologies, Inc. v. 10x Genomics Inc.</i> , Case No. 1:22-cv-01375 (D. Del.), February 1, 2024
1053	Motion of 10x Genomics, Inc. for Entry of an Order (i) Modifying the Automatic Stay with Respect to the 653 Action and the IPR Proceedings and (ii) Granting Related Relief, <i>In re: Nanostring Technologies, Inc., et al.</i> , Case No. 24-10160 (Bankr. D. Del.), February 22, 2024

Exhibit No.	Description
1054	Order (A) Approving Asset Purchase Agreement, (B) Approving the Sale of the Debtors' Assets Free and Clear of Liens, Claims, Interests, and Encumbrances, (C) Approving the Assumption and Assignment of Certain Executory Contracts and Unexpired Leases, and (D) Granting Related Relief, <i>In re: Nanostring Technologies, Inc., et al.</i> , Case No. 24-10160 (Bankr. D. Del.), April 19, 2024
1055	Second Declaration of Paul Spellman, Ph.D.
1056	Deposition Transcript of David Sherman, Ph.D. (January 30, 2025)
1057	Asp <i>et al.</i> , “Spatial detection of fetal marker genes expressed at low level in adult human heart tissue,” <i>Nature Scientific Reports</i> , 7:12941 (2017)
1058	Lieben, L., “Spatial transcriptomics in plants,” <i>Nature Reviews Genetics</i> (2017)

TABLE OF AUTHORITIES

Cases

<i>Allergan, Inc. v. Sandoz Inc.</i> , 726 F.3d 1286 (Fed. Cir. 2013)	16
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<i>Par Pharm. v. TWI Pharms., Inc.</i> , 773 F.3d 1186 (Fed. Cir. 2014)	16, 18
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I. INTRODUCTION

The Petition's Grounds are based on Bruker's initial infringement contentions, e.g., interpreting claim 1's synthesizing step as a single synthesis reaction. In pre-institution briefing, Bruker presented a new infringement interpretation in which claim 1's synthesizing step encompasses multiple synthesis reactions. In its Institution Decision, the Board adopted Bruker's multi-step synthesis construction and still found a reasonable likelihood that Stahl and So-456 each anticipates claim 1. As shown below, the challenged claims are unpatentable under either construction.

II. STAHL ANTICIPATES CLAIMS 1-4 AND 6-13 (GROUND 1)

A. Stahl teaches the claimed synthesizing steps according to Bruker's infringement contentions

Under Bruker's infringement contentions, Stahl teaches claim 1(c) and 1(d). Pet., 26-29; EX1044, ¶¶107-115; EX1022, 18-20, 22; EX1055, ¶¶29-44. It is undisputed that each of claim 1(c) and 1(d) “*requires performing a synthesis reaction to generate DNA products,*” and “the synthesis reaction [] *requir[es]* (1) the collected oligonucleotides to be used as templates and (2) the location-identifying sequences to be incorporated into the DNA products.”¹ POR, 22; EX2008, ¶35; EX1056, 26:8-27:7. It is also undisputed that a *single* synthesis

¹ Emphasis has been added throughout unless otherwise indicated.

reaction meets both the template and incorporation requirements, as Dr. Sherman testified that “[a] *single event* provides that synthesis of that product” and “there’s *a reaction* and it synthesizes the product in *a single event*.” EX1056, 28:6-24; *see also*, Pet., 26-29; POR, 22; EX2008, ¶¶35; EX1055, ¶¶29-31.

Consistent with this interpretation, the Petition demonstrated that Stahl discloses the claimed synthesizing steps at least because Stahl’s method includes a reverse transcription reaction for synthesizing first-strand cDNAs using the collected mRNAs as templates, and the resulting DNA products comprise location-identifying sequences—all in a single event. Pet., 26-29; EX1044, ¶¶107-115; EX1016, FIGs. 1-2, S2, 78-79, Suppl. Materials 4-5. Bruker’s infringement contentions similarly cite Visium FF’s “Step 1 Permeabilization & Reverse Transcription” that “produces spatially barcoded, full-length cDNA from poly-adenylated mRNA on the slide” by a reverse transcription reaction (a single event). EX1022, 18-22; EX1055, ¶¶32-37.

Bruker’s POR attempts to avoid anticipation by construing claim 1’s incorporation requirement to mean “*synthesis of each nucleotide* of the location-identifying sequence *as it becomes part of the ‘DNA products.’*” POR, 32; *id.* (“the incorporation ... must be *part of the synthesis reaction* ...”); *id.*, 33, 35. According to Bruker, Stahl’s first-strand cDNA synthesis does not meet claim 1’s synthesizing steps because the “location-identifying sequence is not synthesized.”

Id., 36. Bruker relies on the 142 patent’s Figure 7 for its construction, but Figure 7’s embodiment uses a pair of ligated nucleic acid probes as the template for amplification, *not* the collected “identifier oligonucleotide[s],” as required by claim 1. POR, 34; EX1043, FIG. 7, 25:19-33; EX1055, ¶¶41. Moreover, Bruker’s IPR construction is at odds with both its district court infringement interpretation, which cites Visium FF’s first-strand cDNA synthesis to meet the claimed incorporation requirement, and Dr. Sherman’s “single event” interpretation. EX1022, 18-19; EX1056, 28:6-24; EX1055, ¶¶38-44. Bruker cannot have it both ways. *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1351 (Fed. Cir. 2001) (“A patent may not, like a nose of wax, be twisted one way to avoid anticipation and another to find infringement.”) (internal citations omitted)).

B. Stahl teaches the claimed synthesizing steps under the Board’s constructions

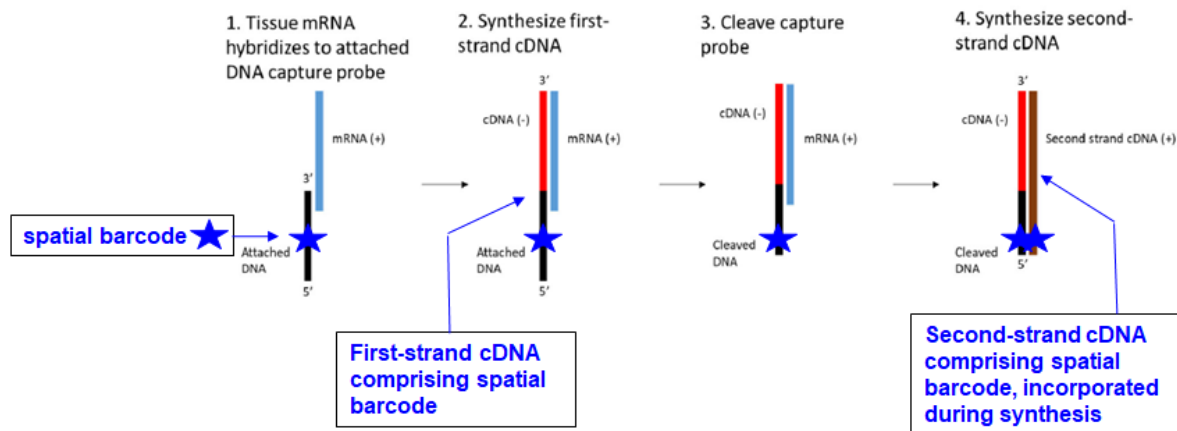
After the Petition was filed, Bruker argued in its pre-institution sur-reply that the synthesizing step is *not* a single event, but instead encompasses *multiple steps* as Visium FF’s “steps 1 [first-strand cDNA synthesis] and 2 [second-strand cDNA synthesis] *together* perform the claimed synthesis reaction.” Paper 17, 4 (emphasis in original); EX1022, 18-20; DOI, 18 (“Patent Owner argues that its infringement contentions for the synthesis reaction ‘specifically refer to both [the accused product’s] steps 1 and 2.’”). At Institution, the Board similarly construed “synthesizing DNA products” as encompassing a multi-step process, “consistent

with the Specification's disclosure [and] with Patent Owner's infringement contentions, where Patent Owner identifies 'synthesizing DNA products' as covering a *multi-step* amplification process resulting in a DNA product containing location-identifying nucleic acid sequences." DOI, 21-22.

Bruker argues that the Board's construction is flawed because it relied on "almost exclusively a single passage" from the specification and purportedly reads limitations into the claim. POR, 17-19. But the specification has far more than a single passage supporting the Board's multi-step construction, as it repeatedly refers to amplification reactions as part of the process for synthesizing DNA products. *See e.g.*, EX1043, 1:44-67, 2:1-25, 2:26-54, 3:24-47, 3:48-4:9, 4:34-5:2, 5:3-37, 5:44-6:8, 6:9-43, 6:44-7:9, 7:10-44, 8:18-52, 8:53-9:23, 9:24-58, 9:59-10:29, 11:1-25, 11:26-52, 12:29-57, 12:58-13:8, Examples 1-6; EX1055, ¶¶5-17. And while Bruker argues against equating "synthesizing" with "amplifying" (POR, 18), it is clear from the specification and Bruker's infringement interpretations that "synthesizing" in claim 1 *includes* amplifying. *Id.*; EX1022, 32-33. This is also evident from the language of claim 5, which specifies that synthesizing comprises a specific type of amplification (solid-phase). EX1043, 148:37-41; EX1055, ¶12. And as Dr. Spellman explains, in templated-synthesis reactions, the first-strand synthesis *is* a type of amplification. EX1055, ¶13.

Applying the multi-step construction, the Board concluded that Stahl teaches

“synthesizing DNA products” because Stahl “teaches a two-step method of creating cDNA with identifying nucleic acids by reverse transcription, followed by generation of a second strand cDNA that incorporates a primer necessary to sequence the strand.” DOI, 23; EX1055, ¶¶45-52. Stahl’s multi-step synthesis reactions are evident in Bruker’s own schematic of Stahl’s workflow:



EX1055, ¶48 (annotated in blue); POR, 29, 35; EX2008, ¶¶46, 55.

In the above schematic, Stahl’s step 2 (synthesizing first-strand cDNAs comprising a spatial barcode, using the collected mRNAs as templates) and step 4 (second-strand cDNA synthesis using the first-strand cDNAs as templates, wherein the reverse complement of the spatial barcode of the first-strand cDNA is incorporated into the second-strand cDNA) are akin to Visium FF’s steps 1 and 2, and “together” these steps in Stahl satisfy the claimed synthesizing steps under Bruker’s stated litigation position and the Board’s construction. EX1055, ¶¶48-52; Paper 17, 4; EX1022, 18-20; DOI, 23; EX1016, Suppl. Materials, 6; EX1056, 43:11-25; Pet., 26-31.

Contrary to Bruker's assertion, 10x is not precluded from arguing that Stahl's second-strand cDNA synthesis satisfies claim 1's incorporation requirement. POR, 36-37. As explained in *Axonics, Inc. v. Medtronic, Inc.*, an IPR petitioner "is entitled under the APA to respond to new claim construction arguments made by a patent owner or adopted by the Board *sua sponte*." 75 F.4th 1374, 1382 (Fed. Cir. 2023); *see also* 37 C.F.R. § 42.23(b).

C. Stahl teaches the claimed sequencing step according to Bruker's infringement contentions

The Petition demonstrated that Stahl's method includes claim 1(e) under Bruker's infringement contentions. Pet., 29-31; EX1044, ¶¶116-121; EX1022, 22-24; EX1043, 147:54-61; EX1055, ¶¶53-70. In litigation, Bruker alleged that Visium FF infringes the claimed sequencing step because in Visium FF, "[l]ibraries are ... generated from the cDNA and sequenced," citing Visium FF's Step 4 ("Library Construction") and Step 5 ("Sequencing"). EX1022, 23; Pet., 29-31; EX1044, ¶¶116-121. Visium FF's Step 4 uses the second-strand cDNAs (which themselves were generated *downstream* from the first-strand cDNAs) to construct a library by adding sequencing adapters and amplifying the library; and Step 5 sequences the library via Illumina paired-end sequencing. EX1022, 23; EX1015, 17-18; EX1055, ¶¶55, 65-66. Thus, under Bruker's litigation interpretation, claim 1(e) encompasses sequencing molecules that are not the first- or second-strand cDNA molecules per se, because the sequenced molecules also

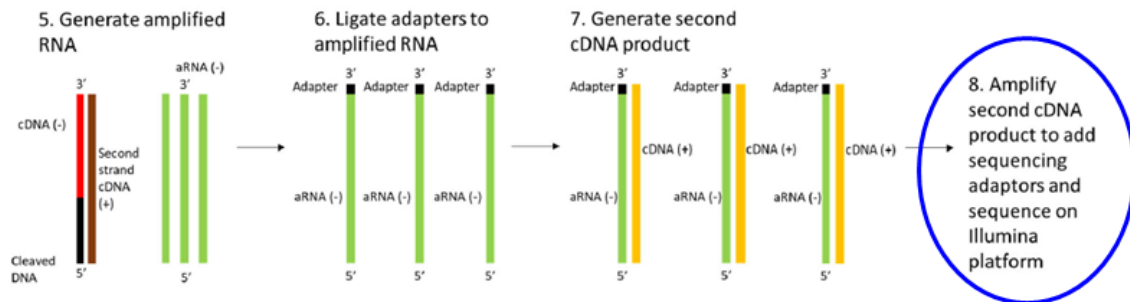
contain adapter and index sequences. *Id.*

The Petition showed that Stahl’s sequencing is akin to that in Visium FF: Stahl teaches sequencing a library using “paired-end sequencing” on the “Illumina NextSeq platform,” where the library was constructed from the amplified copies of second-strand cDNAs, which themselves were generated downstream from the first-strand cDNAs. EX1016, Suppl. Materials, 6-7; Pet., 30; EX1044, ¶¶117-118.

Bruker argues that Stahl’s method does not satisfy claim 1(e) because Stahl’s method sequences a molecule that is not the first-strand cDNA, but rather a “second cDNA product [that] possesses a different sequence.” POR, 30; *id.*, 29. However, Stahl’s method—like Visium FF—sequences a library of molecules that are “different” from the first-strand cDNAs in that they comprise additional adapter and index sequences not present in the first-strand cDNAs. EX1022, 23 (referring to adding adapters and indexes by “via End Repair, A-tailing, Adaptor Ligation, and PCR.”); EX1055, ¶¶55-61. Bruker’s argument also belies the 142 patent’s specification, which consistently discloses sequencing a *downstream amplified library* generated from the DNA products synthesized using the collected oligonucleotides as templates, and not sequencing the original “DNA products.” *See e.g.*, EX1043, Examples 1-6; EX1055, ¶¶62-64.

Bruker’s portrayal of Stahl’s “deliberate effort” to perform “stranded RNA sequencing” is a strawman argument because Stahl’s sequencing library included

molecules comprising the sequence of the captured mRNAs (sense (+) strand) *and* molecules comprising the complementary sequence (antisense (-) strand). POR, 30-31; EX1055, ¶¶58-60. Bruker admits that Stahl's "cDNA products" (the orange molecules in Bruker's schematic) are amplified to generate a sequencing library for Illumina "paired-end sequencing." EX2008, ¶46; POR, 29, 35; EX1056, 56:22-57:19; EX1016, Suppl. Materials, 7. *See* EX1055, ¶¶58-59 (annotations added):



Dr. Spellman testified the same during his cross-examination. EX2009, 75:16-76:8.

As Dr. Spellman explains, a library generated for Illumina paired-end sequencing includes molecules comprising sequences of both sense (+) *and* antisense (-) strands. EX1055, ¶¶60-61. Bruker conveniently minimizes amplification in step 8 of its schematic (circled above), and omits mention of paired-end sequencing entirely. When asked if Stahl's amplification generates both sense and antisense strands for sequencing, Dr. Sherman testified, "I don't know." EX1056, 56:9-17; *id.*, 65:19-66:4 ("I can't say one way or the other.").

Bruker also mischaracterizes the Petition as exclusively relying on Stahl's Cy3-labeled cDNAs ("red bars") as the "DNA products." POR, 24-28. Quite the

contrary, the Petition clearly identified the “red bars” in Stahl’s Figure 1A as *representative depictions of cDNA synthesis*, not as the claimed DNA products. *See* Pet., 26 (“Stahl’s Figure 1A *depicts cDNA synthesis* as red bars.”); *id.* (“Stahl provides a figure *depicting* ‘[s]patially localized *cDNA synthesis*,’ which shows ‘*cDNA synthesis* with Cy3-labeled nucleotides.”); *id.*, 27 (“This is also *depicted* in Stahl’s Figure 1A ... *cDNA synthesis, shown as red bars.*”). Dr. Spellman confirmed this at deposition. EX2009, 58:15-22. By comparison, when referring to the claimed “DNA products,” the Petition relied on Stahl’s *full-length* DNA products comprising the synthesized cDNA *and* the spatial barcode. *See* Pet., 29 (“Stahl’s synthesis reaction produces *cDNA products comprising the spatial barcode of the capture probe.*”); *id.* (referring to Stahl’s “*barcoded cDNA.*”). And for sequencing, the Petition cited Stahl’s description of synthesizing first-strand cDNAs from “samples intended for sequencing.” Pet., 26 (citing EX1016, Suppl. Materials, 4-5); EX1044, ¶¶105-106. The Petition also referred to Stahl’s Figure 2B and Supplemental Materials pages 6-7, which disclose methods and results for *sequencing* cDNAs without Cy3-nucleotides. Pet., 31; EX1044, ¶¶119-120; EX1055, ¶¶67-70.

D. Stahl teaches the claimed sequencing step under the Board’s constructions

Stahl’s disclosures also satisfy the sequencing step under the Board’s and Bruker’s IPR constructions. DOI, 28; POR, 16; EX1055, ¶¶71-73. The Board

construed the sequencing step as “locating the specific target analyte within the tissue sample by correlating the DNA product using the location-identifying nucleic acid sequences.” DOI, 28. Bruker argues that the Board’s construction “obviates” the requirement for sequencing, and proposes adding a wherein clause to the Board’s construction: “wherein the sequence of the DNA product and the sequence of the location identifying nucleic acid sequences are determined via sequencing.” POR, 16. The Board’s construction, however, requires that the target analyte is located “*using the location-identifying nucleic acid sequences,*” which are of course determined *by sequencing*. DOI, 28; EX1055, ¶¶18-24. Regardless, both the Board’s and Bruker’s IPR constructions encompass sequencing molecules that are different from the first-strand (and second-strand) cDNAs due to, e.g., addition of adapters and index sequences. EX1055, ¶¶18-24.

As explained above, under the Board’s construction of “synthesizing DNA products,” Stahl’s first-strand synthesis and second-strand synthesis *together* generate the claimed DNA products (the second-strand cDNAs). *See* Section II.B. And both the Board’s and Bruker’s constructions encompass sequencing a library of molecules that are not identical to the first- or second-strand cDNAs due to added adapter and index sequences. *See* Section II.C. Stahl teaches the claimed sequencing step under these constructions because Stahl teaches sequencing a library of molecules generated from the amplified copies of the second-strand

cDNAs, determining the sequences of the DNA products and their spatial barcodes, and further correlating the spatial barcodes with the DNA product to identify their spatial location. EX1055, ¶¶71-73; EX1016, 78, 81, Suppl. Materials, 6-7, FIGs. 2, 3, S4, S10A-10C; EX1044, ¶¶117-120; Pet., 29-31; *Axonics*, 75 F.4th at 1381-82; 37 C.F.R. § 42.23(b).

E. Stahl teaches amplifying a library using the DNA products as templates (claim 7)

Under Bruker's infringement contentions, Stahl teaches claim 7's amplifying a library using the DNA products as templates. Pet., 37; EX1044, ¶¶141-142; EX1016, Suppl. Materials, 6-7; EX1055, ¶¶74-79. According to Bruker, Visium FF practices claim 7 based on Visium FF's step 3 (amplifying the second-strand cDNAs) and step 4 (preparing a sequencing library). EX1022, 35-36; EX1055, ¶74. Stahl's method includes a multi-step amplification of second-strand cDNAs (synthesized from the first-strand cDNAs as templates) and generation of a "cDNA library [] for sequencing." EX1016, Suppl. Materials, 6-7; Pet., 37; EX1044, ¶¶141-142; EX1055, ¶¶75-76.

Bruker argues that these reactions in Stahl do not use the first-strand cDNA products as templates and thus do not satisfy claim 7. POR, 38-39. This argument contradicts Bruker's infringement contentions for claim 7, which rely on Visium FF's second-strand cDNA amplification (step 3) and subsequent library preparation (step 4)—neither of which use the first-strand cDNAs as templates for

amplification. EX1022, 35-36; EX1055, ¶77.

Stahl’s multi-step amplification and cDNA library generation also anticipates claim 7 under the Board’s construction of “synthesizing DNA products.” DOI, 22. Under the Board’s construction, “DNA products” are *not* limited to “the first cDNA strand – and only this strand.” DOI, 22. Thus, the synthesized “DNA products” include Stahl’s second-strand cDNAs, which Stahl discloses using as templates in the multi-step process for generating a sequencing library. EX1016, Suppl. Materials, 6-7; EX1044, ¶¶141-142; EX1055, ¶¶78-79; *Axonics*, 75 F.4th at 1382; 37 C.F.R. § 42.23(b).

III. CLAIMS 1-13 ARE OBVIOUS OVER STAHL, AND CLAIM 5 IS FURTHER OBVIOUS OVER STAHL AND FRISEN (GROUNDS 2-3)

A. Claims 1-4 and 6-13

As the Petition demonstrated, even if Stahl were found not to anticipate claims 1-4 and 6-13, Stahl certainly suggests practicing them and provides motivation to do so with a reasonable expectation of success. Pet., 44-49; EX1044, ¶¶160-178. Bruker’s only rebuttal is that the Petition allegedly “provides no reason why a POSA would have been motivated to modify Stahl’s method to meet the claimed methods.” POR, 40. Bruker misses the point. Because Stahl discloses all the claim limitations under Bruker’s infringement contentions, no further modifications are needed for a POSA to arrive at the claimed methods. EX1055, ¶¶80-84; *Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1373 (Fed. Cir. 2019)

(noting that because “[a single reference] alone disclosed every element of [the challenged claims],” “the Board had no obligation to find a motivation to combine [the prior art].”); *see also Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983) (“[A] disclosure that anticipates under § 102 also renders the claim invalid under § 103, for anticipation is the epitome of obviousness.” (internal quotations omitted)). Tellingly, Bruker never identifies any claim limitations actually missing from Stahl, instead only quibbling over “*Petitioner’s identified DNA products.*” POR, 2-3.

B. Claim 5

The Petition demonstrated that a POSA would have been motivated to modify Stahl with a reasonable expectation of successfully performing the second-strand synthesis on Stahl’s array (solid-phase) for several reasons, including improved “sensitivity, selectivity, and scalability,” reduced “undesirable primer interactions,” and improved parallelization for high-throughput systems. Pet., 45-49 (Ground 2), 49-56 (Ground 3); EX1044, ¶¶165-196. These motivations and expectations were evident in view of Stahl and the general knowledge in the art (Ground 2) and in view of Stahl and Frisen (Ground 3). Pet., 45-56; EX1044, ¶¶165-196; EX1055, ¶¶85-121.

In response, Bruker *first* argues that the Petition’s discussion of solid-phase second-strand cDNA synthesis fails to show modification of “Petitioner’s

identified DNA products” (first-strand cDNAs). POR, 41-42. This argument fails for the same reasons discussed above for claim 1’s synthesizing steps (c) and (d). *See* Section II.A-B. Stahl teaches claim 1’s synthesizing steps under both Bruker’s infringement contentions and the Board’s constructions. Bruker’s argument to the contrary for claim 5 is meritless, as it is for claim 1.

Second, Bruker challenges reasonable expectation of success, alleging that the Petition provides “no specifics how Stahl can be modified.” POR, 42. Here, Bruker ignores claim 5’s open-ended term “*comprises*,” which requires only that claim 1(c) and 1(d) *comprise* performing “a solid-phase amplification reaction.” EX1043, 148:37-41; EX1044, ¶¶166-167; Pet, 45-46; EX1055, ¶¶88-89. Moreover, solid-phase synthesis reactions, including for amplification, were well-known and routine in the art, particularly in high-throughput molecular bioanalytical methods like Stahl’s. Pet., 48-49, 55-56; EX1044, ¶¶175-177. Dr. Spellman further provided ample evidence of solid-phase amplification approaches that would have guided a POSA’s routine modifications of Stahl. *See id.* (citing EX1005, EX1017, EX1042, EX1049). Such modifications were well within the skillset of a POSA. EX1055, ¶¶90-93; *see KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007) (“[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or

her skill.”); *id.*, 416 (“The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.”). Indeed, as Bruker concedes, “Frisen suggests that synthesis of the second-strand cDNA and amplification of the double-stranded cDNA can occur in solid-phase.” POR, 47; *see also*, EX1017, 12:9-11, 38:20-23, 38:27-32, 39:5-6, 40:13-41:21, 42:28-43:7, 42:28-43:7, 103:12-19; EX1044, ¶175. And Stahl’s method already includes a similar solid-phase reaction for first-strand cDNA synthesis. EX1044, ¶175; EX1016, 78-79, Figs. 1-2, Suppl. Materials, 4-5.

Bruker’s technical arguments against a reasonable expectation of success also fail. POR, 42-44; EX1055, ¶¶94-102. Initially, Dr. Sherman provides scant underlying support for his opinions, entitling them little or no weight. *See e.g.*, EX2008, ¶¶74-85; 37 C.F.R. §42.65(a). Notwithstanding Dr. Sherman’s unsupported opinions, Bruker argues that a POSA modifying Stahl would encounter “issues,” because solid-phase amplification (i) is less efficient than solution-phase; (ii) creates spatial constraints on RNA polymerase; and (iii) uses different DNA polymerases compared to solution-phase. POR, 42-43. These so-called “issues,” alone or together, were not a concern to a POSA. EX1055, ¶¶94-102.

Claim 5 does not require any particular solid-phase amplification efficiency. EX1055, ¶99; EX1056, 32:1-1. Thus, the pertinent question is not about

expectations for solid-phase amplification *efficiency*; rather, the question is whether a POSA would “have a reasonable expectation of success of developing *the claimed invention*.” *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013); *see also Par Pharm. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1198 (Fed. Cir. 2014) (“The reasonable expectation of success ... does not necessitate an absolute certainty for success.”).

Bruker’s spatial constraints argument erroneously assumes that Stahl’s *RNA amplification* must occur in solid phase. POR, 43 (“generation of amplified RNA would be significantly affected if the involved cDNA molecules were in solid phase.”). As Dr. Spellman explains, in modifying Stahl, the POSA skips the cleavage step and the first-strand cDNAs remain bound to the array while the second-strand cDNAs are synthesized on the array using the first-strand cDNAs as templates. Pet., 47; EX1044, ¶172 (“perform the second-strand cDNA synthesis and/or library amplification on [array]”); EX2009, 91:8-20; EX1055, ¶¶100-102. This solid-phase second-strand cDNA synthesis satisfies claim 5’s solid-phase amplification under Bruker’s infringement contentions. EX1022, 33; EX1044, ¶¶167-168; EX1055, ¶¶100-102. The POSA would have known that in Stahl’s modified method, the second-strand cDNAs could be released from the array to perform RNA amplification in solution (as already taught in Stahl) or maintained on the array to perform RNA amplification. EX1055, ¶¶100-102; EX1044, ¶172.

These assay design choices and optimizations were well within the skillset of a POSA. *Id.* As were simple modifications to extend Stahl's capture probe length if the RNA polymerase truly required more physical space for on-array RNA amplification. EX1055, ¶102; EX1056, 21:7-10. These were not "significant optimization[s]," as Dr. Sherman alleges; this was routine. EX2008, ¶77; EX1055, ¶¶100-102.

Bruker's argument regarding different types of polymerases ignores the level of skill in the art. POR, 43, 5-6. Bruker itself acknowledges the high skill level of a POSA, who understands amplification and sequencing methodologies. POR, 5-6. As Dr. Spellman explains, a variety of polymerase enzymes were well known in the art and selection of optimal enzymes for a particular use (e.g., solid-phase amplification) was routine. EX1055, ¶¶96-98.

Third, Bruker attempts to nitpick motivation for solid-phase amplification, while ignoring fundamental tenants of obviousness law. POR, 44-46. Bruker alleges that Frisen's 2012 publication (before Stahl's 2016 publication) would have deterred a POSA from modifying Stahl with Frisen's solid-phase second-strand cDNA synthesis. POR, 44-45, 48. However, for obviousness, "evidence of a motivation to combine need not be found in the prior art references themselves, but rather may be found in the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved." *DyStar Textilfarben*

GmbH & Co. v. CH Patrick Co., 464 F.3d 1356, 1366 (Fed. Cir. 2006) (internal quotations omitted). As Dr. Spellman explained at deposition, a POSA would have had “a large number of reasons” to modify Stahl’s workflow, e.g., “spatially restrict individual ... molecules” or “as simple as wanting to skip the user enzyme [i.e., cleavage] step, for example.” EX2009, 93:14-20; EX1055, ¶¶103-104, 114-121.

Bruker also argues that improved sensitivity and selectivity of solid-phase amplification “is uncertain” because the art only suggests that it “may” occur. POR, 45 (quoting EX1048, 11). Obviousness, however, does not require “an absolute certainty for success.” *Par Pharm.*, 773 F.3d at 1198. The art’s teaching that solid-phase amplification “may” improve sensitivity and selectivity would have been enough motivation to modify Stahl’s method and reasonably expect it to work. EX1055, ¶¶105-106. Indeed, the same reference that Bruker quotes explicitly states that “[a] large variety of enzymatic reactions have been *shown to be successfully performed on microarrays*” and “*progress has been made* in the implementation of these techniques.” EX1048, 11; EX1044, ¶¶172-173, 188-190; EX1055, ¶106. Similarly, Frisen’s disclosure that solid-phase second-strand cDNA synthesis is “optional” simply would not have deterred a POSA. POR, 47; EX1055, ¶¶105-106; *Intel Corp. v. Qualcomm Inc.*, 21 F.4th 784, 800 (Fed. Cir. 2021) (“[i]t’s not necessary to show that a combination is the *best* option, only that

it be a *suitable* option.”) (emphasis in original)).

Bruker further alleges there were “known drawbacks of solid-phase amplification,” such as “electrostatic forces, the finite number of primers, polymerase and nucleotide availability, sterile molecules, and DNA stiffness.” POR, 45 (citing EX2013, 40-41). Bruker relies on a 2005 publication which announced solid-phase amplification as a “*new method* to amplify DNA.” EX2013, Abstract; EX1055, ¶¶107-109. Moreover, Bruker’s exhibit characterizes these aspects *not* as “drawbacks” (Bruker’s term), but merely as “effect[s]” that “can play an important role” in solid-phase amplification. EX2013, 40; EX1055, ¶¶107-109. Bruker’s other criticisms of solid-phase amplification rely on EX1050’s discussion of *colony* amplification, not second-strand cDNA synthesis. POR, 49; EX1055, ¶¶110. And even if considered “drawbacks,” the art already provided solutions by 2018 as evidenced in the numerous examples and methods for performing solid-phase amplification. EX1044, ¶175 (citing EX1005; EX1017; EX1042; EX1049); EX1055, ¶¶107-109.

Bruker also argues against motivation by alleging that any benefit from a solid-phase reaction “is already accrued by the first-strand cDNA synthesis.” POR, 46. The benefits from solid-phase synthesis of Stahl’s first-strand cDNAs (retaining spatial information of the target mRNAs) and second-strand cDNAs (e.g., scalability) are different and non-interchangeable. EX1055, ¶¶111-112.

In sum, a POSA would have recognized solution-phase and solid-phase amplification as “a finite number of identified, predictable solutions,” providing the POSA with a “good reason to pursue the known options within his or her technical grasp.” *KSR*, 550 U.S. at 421.

IV. SO-456 ANTICIPATES CLAIMS 1-13 (GROUND 4)

A. So-456 teaches the claimed synthesizing steps according to Bruker’s infringement contentions

Under Bruker’s infringement contentions, So-456 discloses claim 1’s synthesizing steps at least because So-456 discloses synthesizing first-strand cDNAs using the collected mRNAs as templates, and the resulting first-strand cDNAs comprise location-identifying sequences. Pet., 61-64; EX1044, ¶¶209-215; EX1022, 18-22; EX1055, ¶¶122-127.

Bruker argues that So-456’s first-strand cDNA synthesis does not meet claim 1’s synthesizing steps for two reasons: (i) similar to Stahl, So-456’s location-identifying sequences are present in the capture probes and not “synthesized”; and (ii) So-456’s method uses two location-identifying sequences, only one of which is incorporated in the first-strand cDNA. POR, 52-55. Bruker’s first argument fails for the same reasons discussed above for Stahl. *See* Section II.A. That is, Bruker’s argument conflicts with its infringement contentions, which refer to Visium FF’s *first-strand cDNA synthesis* for the synthesizing steps. EX1022, 18-19; EX1055, ¶¶128-130; *See* Section II.A.

Bruker's second argument ignores claim 1's plain language, which only requires that "*at least one* nucleic acid sequence that identifies the first [and second] location of the tissue sample" be incorporated into the DNA products. EX1043, 147:42-53; EX1055, ¶¶131-132. By Bruker's own admission, Stahl's first-strand cDNA synthesis incorporates *at least one* location-identifying sequence because the first-strand cDNAs comprise "spatial address region 2325a," which Bruker admits is "a unique spatial address for the X dimension." POR, 52-53; EX1005, ¶318, FIG. 25B; EX1044, ¶¶214-215. Thus, at a minimum, So-456's spatial address region 2325a incorporated into the first-strand cDNAs identifies the *location in the x-dimension* of the tissue sample and satisfies this claim element. EX1055, ¶¶131-132.

B. So-456 teaches the claimed synthesizing steps under the Board's construction

Similar to Stahl, the Board found that So-456 teaches "synthesizing DNA products" under its construction, because So-456 "teaches a two-step method of creating cDNA with identifying nucleic acids by reverse transcription, followed by generation of a second strand cDNA that incorporates a primer necessary to sequence the strand." DOI, 22, 40-41.

Indeed, So-456's method includes synthesizing first-strand cDNAs comprising a spatial barcode by using the collected mRNAs as templates (e.g., Figure 25A, step 2415), and then synthesizing second-strand cDNAs using the

first-strand cDNAs as templates, wherein the spatial barcode present in the first-strand cDNAs is “incorporated” into the second-strand cDNA during synthesis (e.g., Figure 25B, step 2425). EX1005, FIG. 25-A-B, ¶¶314-318; EX1044, ¶¶209-215; EX1055, ¶¶133-139. Thus, So-456’s steps 2415 and 2425 together satisfy each of the claimed synthesizing steps under the Board’s construction. These steps in So-456 are also akin to Visium FF’s steps 1 and 2, which Bruker argued “together” satisfy the claimed synthesizing steps. EX1055, ¶¶140-142; Paper 17, 4; EX1022, 18-20; DOI, 40-41; *Axonics*, 75 F.4th at 1382.

C. So-456 teaches conditions that release oligonucleotides

The Petition demonstrated that So-456 expressly and inherently teaches claim 1’s conditions that release oligonucleotides from a tissue sample, under Bruker’s infringement contentions. *See* Pet., 60-61; EX1022, 11-14, 18; EX1044, ¶¶207-208; EX1005, ¶¶152, 154, 155, 308, 315. Bruker argues that the disclosures in So-456 relate to “nothing more than sectioning the tissue and placing it on a capture array.” POR, 58. This is false. EX1055, ¶¶143-153.

As the Petition explained, So-456 expressly teaches that “a tissue sample is prepared for analysis” *before* “the target nucleic acid in the tissue section is transferred onto an array.” Pet., 60; EX1005, ¶¶152, 154; *see also id.*, ¶308 (“mRNA molecules are *captured* onto the array”), ¶315 (“mRNA molecule 2510 in a tissue sample is *captured* on capture probe.”); EX1055, ¶¶143-146. These

disclosures in So-456 are express teachings of conditions that *release the target nucleic acid* from the tissue, and not merely sectioning and placing a tissue on the array as Bruker alleges. EX1055, ¶¶147-150. So-456 identifies sectioning only as an “embodiment[]” of such treatment conditions. EX1005, ¶152; Pet., 60-61; EX1055, ¶147. Dr. Sherman’s argument that the “claimed ‘conditions’ would have been different from prior methods” (EX2008, ¶109) is misleading because the claims are not limited to any specific type of condition or type of tissue sample. EX1055, ¶¶151. All claim 1 requires is *any* condition that releases the first and second plurality of oligonucleotides. *Id.*, ¶¶146-151

So-456 also inherently teaches the claimed conditions, as noted in the Petition: “So-456 also discloses that the ‘target nucleic acid’ (mRNA) ‘diffuse[s] from the tissue’ onto the array, *further confirming that the tissue sample was treated* to create a condition to ‘release’ the mRNA from the tissue onto the array.” Pet., 60 (citing EX1005, ¶155; EX1044, ¶¶206-207). By Bruker’s own admission, “it would be *impossible*” to analyze the nucleic acids in a tissue sample “without first treating the sample so that the sample nucleic acids are released.” POR, 57-58. Bruker conveniently ignores So-456’s teaching in ¶[0155] that the “target nucleic acid” (mRNA) “*diffuse[s] from the tissue*” onto the array. EX1005, ¶155; EX1044, ¶¶207-208; EX1055, ¶¶149-150; Pet., 60. Bruker’s argument that “inherency was not invoked in the Petition” (POR, 60) is baseless, as there is no requirement to

“couch [arguments] specifically in terms of inherency.” *Ty Inc. v. Softbelly’s, Inc.*, IPR2020-00689, Paper 43, 24 (P.T.A.B. Sept. 10, 2021).

D. So-456 teaches solid-phase amplification under Bruker’s infringement contentions (claim 5)

The Petition showed that, under Bruker’s infringement contentions, So-456 anticipates claim 5, because So-456 expressly discloses solid-phase second-strand cDNA synthesis using the first-strand cDNA products as templates. Pet., 68-71; FIG. 25B. EX1005, FIG. 25B, ¶318; EX1044, ¶¶230-235.

Bruker wrongly argues that “Petitioner must show how synthesis of the first-strand cDNA is performed in So-456 using a solid-phase amplification reaction.” POR, 60. As discussed above, claim 5’s open-ended term “comprises” requires only that claim 1 steps (c) and (d) *comprise* performing “a solid-phase amplification reaction.” EX1043, 148:37-41; EX1044, ¶230; Pet., 68-69. So-456’s solid-phase second-strand synthesis takes place after the first-strand cDNA synthesis and before the sequencing step (i.e., as part of the synthesis step), and thus satisfies the plain language of claim 5 and is consistent with Bruker’s infringement contentions. *Id.* Moreover, Bruker’s IPR position is inconsistent with its infringement contentions, which rely on Visium FF’s *first-strand synthesis* to meet claim 1’s synthesizing steps but Visium FF’s *second-strand synthesis* to meet claim 5’s solid-phase amplification step. EX1022, 18-19, 32-33; EX1055, ¶¶154-156; *see supra*, Sections II.A-B, IV.A-B.

So-456 also anticipates claim 5 under the Board’s construction of “synthesizing DNA products,” which are *not* limited to “the first cDNA strand – and only this strand.” DOI, 22, 40-41; *see* Sections II.B, IV.B. Thus, the synthesized “DNA products” under the Board’s construction include So-456’s second-strand cDNAs generated by solid-phase amplification—just like Visium FF’s “second strand synthesis” in Step 2 identified in Bruker’s infringement contentions. EX1005, FIG. 25A-B; EX1044, ¶¶230-235; EX1022, 18-19; EX1055, ¶¶157-158; *Axonics*, 75 F.4th at 1382.

E. So-456 teaches amplifying a library using the DNA products as templates (claim 7)

The Petition showed that, under Bruker’s infringement contentions, So-456 teaches amplifying a library using the DNA products as templates. Pet., 71-72; EX1044, ¶¶238-239; EX1005, ¶¶310, 317-318, FIGs. 24, 25B. According to Bruker, Visium FF practices claim 7 based on Visium FF’s step 3 (amplifying the second-strand cDNAs) and step 4 (preparing a sequencing library). Section II.E; EX1022, 35-36; EX1055, ¶¶159-163. So-456’s method includes amplification of second-strand cDNAs (which used the first-strand cDNAs as templates) to “generate a sequencing library,” consistent with Bruker’s infringement position. EX1005, ¶313; EX1044, ¶¶238-239; EX1055, ¶¶159-163.

Bruker argues that So-456’s amplification reactions do not satisfy claim 7 because these reactions use as templates the second-strand cDNAs, which are

“different strands” from the first-strand cDNAs (“Petitioner’s identified ‘DNA products’”) and have sequences “inversely complementary” to the first-strands cDNAs with additional sequences. POR, 61-62. Bruker’s litigation position again belies its IPR argument, because Bruker’s infringement contentions for claim 7 identify Visium FF’s second-strand cDNA amplification (step 3) and subsequent library preparation (step 4), both of which use as templates the second-strand cDNAs, which are different from Bruker’s identified DNA products for claim 1’s synthesis steps and have sequences “inversely complementary” to the first-strands cDNAs with additional sequences. EX1022, 35-36; EX1055, ¶¶164-165.

So-456 also anticipates claim 7 under the Board’s construction of “synthesizing DNA products.” DOI, 22, 40-41. Under that construction, the synthesized “DNA products” include So-456’s second-strand cDNAs, which So-456 teaches using as templates in the subsequent amplification reactions to generate a sequencing library. EX1005, ¶313, FIG. 25A-B; EX1044, ¶¶238-239; EX1055, ¶¶166-167; *Axonics*, 75 F.4th at 1382.

V. CLAIMS 1-13 ARE OBVIOUS OVER SO-456 (GROUND 5)

Even if So-456 were found not to anticipate claims 1-13, So-456 suggests practicing them and provides motivation to do so with a reasonable expectation of success. Pet., 77-79; EX1044, ¶¶253-256. Bruker’s rebuttal is that the Petition does not “address why the missing elements discussed for Ground 4 would have been

obvious,” and that the Petition “provided no specific modifications of So-456.”

POR, 63. As discussed above, “anticipation is the epitome of obviousness.”

Connell, 722 F.2d at 1548. Because So-456 teaches all the claim limitations under both Bruker’s infringement contentions and the Board’s and Bruker’s IPR constructions, there are no missing elements, and a POSA needed no modifications to arrive at the claimed methods. EX1055, ¶¶168-170; *Realtime Data*, 912 F.3d at 1373; *Connell*, 722 F.2d at 1548.

VI. CONCLUSION

The Petition showed by a preponderance of the evidence that all of the challenged claims are unpatentable. Bruker’s POR fails to show otherwise.

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CERTIFICATE OF WORD COUNT (37 C.F.R. § 42.24(d))

1. This Petitioner's Reply complies with the type-volume limitation of 5,600 words, comprising 5,538 words, excluding the parts exempted by 37 C.F.R. § 42.24(c).

2. This Petitioner's Reply complies with the general format requirements of 37 C.F.R. § 42.6(a) and has been prepared using Microsoft® Word 2016 in 14-point Times New Roman font.

Respectfully submitted,

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CERTIFICATE OF SERVICE (37 C.F.R. § 42.6(e))

I certify that the above-captioned **PETITIONER'S REPLY TO PATENT OWNER RESPONSE** and associated Exhibits 1055-1058 were served in their entireties upon the Patent Owner on February 12, 2025, upon the following parties via email:

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