

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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10X GENOMINCS, INC.,  
Petitioner,

v.

BIO-RAD LABORATORIES, INC.,  
Patent Owner.

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IPR2020-00089  
Patent 9,896,722 B2

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Before CHRISTOPHER M. KAISER, KIMBERLY McGRAW, and  
ELIZABETH M. ROESEL, *Administrative Patent Judges*.

McGRAW, *Administrative Patent Judge*.

JUDGMENT  
Final Written Decision  
Determining Some Challenged Claims Unpatentable  
*35 U.S.C. § 318(a)*

## I. INTRODUCTION

In this *inter partes* review, instituted pursuant to 35 U.S.C. § 314, 10X Genomics, Inc. (“Petitioner”) challenges claims 1–7 and 10–17 of U.S. Patent No. 9,896,722 B2 (Ex. 1001, “the ’722 patent”), owned by Bio-Rad Laboratories, Inc. (“Patent Owner”). This Final Written Decision is entered pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons discussed below, Petitioner has not shown by a preponderance of the evidence that claims 15–17 of the ’722 patent are unpatentable but has shown by a preponderance of the evidence that claims 1–7 and 10–14 are unpatentable.

### A. Procedural History

Petitioner filed a Petition for *inter partes* review of claims 1–7 and 10–17 of the ’722 patent. Paper 2 (“Pet.”). Patent Owner filed a Preliminary Response. Paper 7. Applying the standard set forth in 35 U.S.C. § 314(a), which requires demonstration of a reasonable likelihood that Petitioner would prevail with respect to at least one challenged claim, we instituted an *inter partes* review of all challenged claims on all asserted grounds. Paper 8 (“Inst. Dec.”).

Following institution, Patent Owner filed a Patent Owner Response (Paper 26, “PO Resp.”), Petitioner filed a Reply (Paper 29, “Pet. Reply”), and Patent Owner filed a Sur-reply (Paper 31, “PO Sur-reply”). An oral hearing was held on January 27, 2021, and a copy of the hearing transcript has been entered into the record. Paper 38 (“Tr.”)

### B. Real Parties-in-Interest

Petitioner identifies 10X Genomics, Inc. as the real party-in-interest. Pet. 70. Patent Owner identifies Bio-Rad Laboratories, Inc. as the real

party-in-interest. Paper 24, 1 (Bio-Rad Laboratories, Inc.’s Updated Mandatory Notices, “Mandatory Notices”).

*C. Related Matters*

There are three related proceedings before the Board involving the parties. IPR2020-00088 also involves the ’722 patent, and IPR2020-00086 and IPR2020-00087 involve related U.S. Patent No. 9,562,837 B2 (“the ’837 patent”), to which the ’722 patent claims priority as a continuation-in-part. Ex. 1001, code (63). The January 27, 2021, oral hearing transcript pertains to all four cases. Final written decisions are issued in the three related proceedings concurrently with this Decision.

The parties also identify *Bio-Rad Laboratories, Inc. v. 10X Genomics, Inc.*, Case No. 1:18-cv-01679-RGA (D. Del. Oct. 25, 2018) as a related matter. Pet. 70; Paper 24, 1.

*D. The ’722 Patent*

The ’722 patent is titled “System for Handling Microfluidic Droplets” and issued on February 20, 2018. Ex. 1001, codes (45), (54). The ’722 patent was filed on January 25, 2017, and claims priority to Application No. 11/803,104 (“the ’104 application”), which was filed on May 11, 2007 and issued as the ’837 patent. *Id.* at codes (22), (63). The ’722 patent also claims priority to a number of provisional applications, the earliest of which (Provisional Application Nos. 60/799,833 and 60/799,834) were filed on May 11, 2006. *Id.* at code (60).

The ’722 patent discloses an assembly that includes a droplet formation module and a chamber. *Id.* at code (57); 3:11–12, 3:36–37, 52:47–48, 53:30–31. The droplet formation module is configured to form droplets surrounded by an immiscible fluid. *Id.* at code (57); 3:12–20, 52:47–57. The chamber is configured to receive droplets and immiscible

fluid and has an outlet configured to receive substantially only droplets. *Id.* at code (57), 3:37–48, 53:31–34. According to the '722 Patent, the assembly is “particularly useful for reducing potential contamination associated with sample handling.” *Id.* at 52:36–38.

Figure 38 of the '722 Patent is reproduced below:

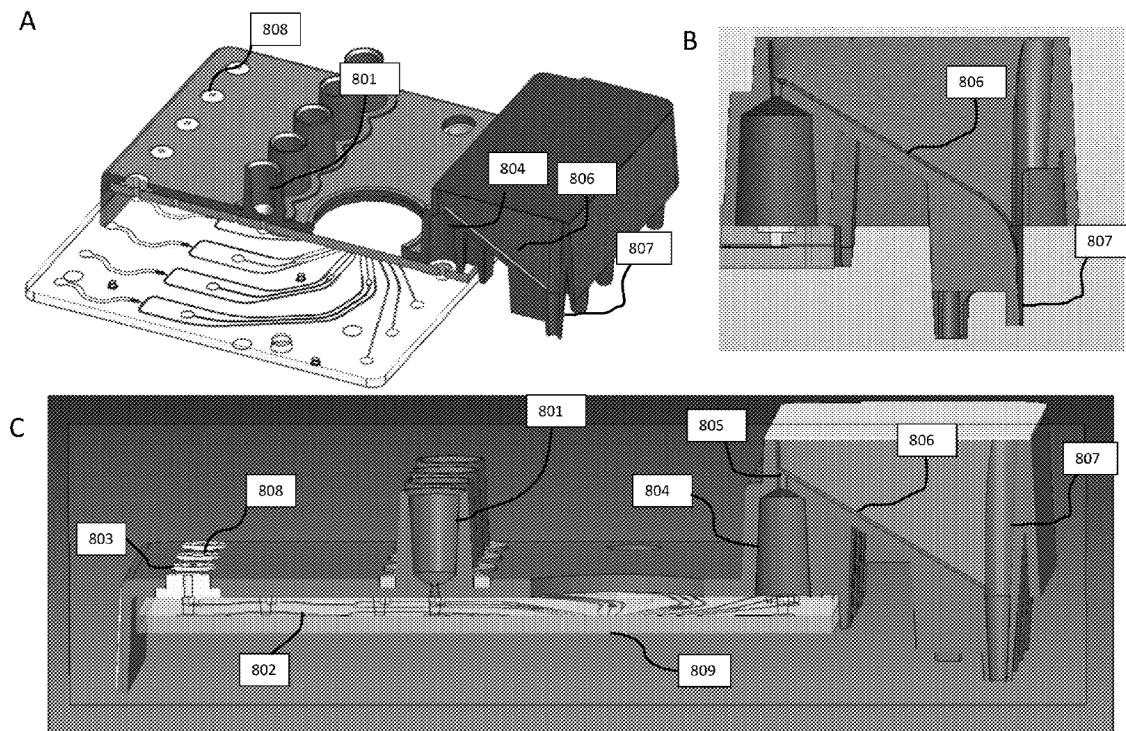


FIG. 38

Figure 38 shows a microfluidic assembly that includes a droplet formation module and a chamber. Ex. 1001, 8:22–23, 53:47–48, 54:4–7, 54:43–50. The droplet formation module includes sample input 801, channel 802, and oil input 803. *Id.* at 54:4–7. The assembly includes chamber 804 equipped with outlet 805, which is connected to slide 806, which is in turn connected to output nozzle or exit port 807. *Id.* at 54:43–50, 54:56–66, 55:3–5. The assembly also includes reagent input 808 and coalescence module 809. *Id.* at 54:13–15, 54:28–31.

An aqueous sample solution is introduced through sample input 801, and oil is introduced through oil input 803. Ex. 1001, 53:57–59, 54:1–2. The oil and aqueous solution meet at a junction in channel 802 such that the aqueous solution is segmented by the oil, thereby forming droplets. *Id.* at 54:2–4. “As the oil containing the droplets moves along the assembly through the channel 802, the oil and droplets begin to enter the chamber 804.” *Id.* at 54:46–48. “Due to the difference in their respective densities, the oil and droplets separate from each other in the chamber 804.” *Id.* at 54:48–50. Droplets exit chamber 804 into outlet 805 “leaving a large part of the oil behind.” *Id.* at 54:50–53. Droplets exiting chamber 804 through outlet 805 enter slide 806 and travel through the slide and nozzle 807, which leads to a vessel or container for collecting the droplets. *Id.* at 54:60–55:1.

*E. Illustrative Claims*

Among the claims challenged by Petitioner, claims 1 and 14 are independent. Claim 1 is illustrative of the claimed subject and is reproduced below, with paragraph breaks adjusted and bracketed numbers added to correspond with Petitioner’s identification of claim elements:

1. [1.0] A method of reducing contamination associated with sample handling, comprising:
  - [1.1] providing an aqueous fluid comprising a sample through a sample inlet;
  - [1.2] providing an immiscible fluid flowing through a main channel that is in fluidic communication with the sample inlet, wherein the main channel is in a horizontal plane;
  - [1.3] partitioning the aqueous fluid with the immiscible fluid to form a plurality of droplets in the main channel, wherein at least one droplet comprises a sample;
  - [1.4] flowing the droplets toward a downstream separation chamber that is in fluidic communication with the main channel,

[1.5] wherein the separation chamber has a wider cross-section than the main channel cross-section and [1.6] the separation chamber is disposed perpendicular to the main channel; and

[1.7] separating the plurality of droplets from the immiscible fluid in the separation chamber based on the different densities of the droplets and the immiscible fluid.

Ex. 1001, 88:2–22.

Claim 14 is identical to claim 1, except that the preamble of claim 14 recites “reducing sample loss” instead of “reducing contamination” as in claim 1, and claim 14 omits the recitation of “wherein at least one droplet comprises a sample” as recited in claim element 1.3. *Compare* Ex. 1001, 88:2–22, *with id.* at 88:52–89:3.

#### *F. Testimonial Evidence*

In support of its unpatentability contentions, Petitioner relies on a Declaration by Richard B. Fair, Ph.D. (Ex. 1008) and a Responsive Declaration of Richard B. Fair, Ph.D. (Ex. 1074) filed with the Reply. Petitioner also filed a document titled “Cross-Reference Corrections” identifying corrections to Exhibit 1008. Ex. 1083. Patent Owner cross-examined Dr. Fair and filed a transcript of the deposition as Exhibit 2017.

Patent Owner relies on a Declaration of Shelly Anna, Ph.D. Ex. 2016. Petitioner cross-examined Dr. Anna and filed a transcript of the deposition as Exhibit 1075.

#### *G. Prior Art and Asserted Grounds*

Petitioner asserts that claims 1–7 and 10–17 would have been unpatentable on the following grounds (Pet. 20):

| Claim(s)<br>Challenged | 35 U.S.C. § <sup>1</sup> | Reference(s)/Basis                                    |
|------------------------|--------------------------|-------------------------------------------------------|
| 1–3, 10, 11, 14        | 102                      | Thorsen <sup>2</sup>                                  |
| 1–4, 10, 11, 14        | 103                      | Thorsen                                               |
| 1–7, 10–17             | 103                      | Thorsen, Ismagilov 119 <sup>3</sup>                   |
| 1–7, 10–17             | 103                      | Thorsen, Ismagilov 119,<br>Ismagilov 091 <sup>4</sup> |

## II. ANALYSIS

### A. Legal Standards

“In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.” *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify “with particularity . . . the evidence that supports the grounds for the challenge to each claim”)); *see also* 37 C.F.R. § 42.104(b) (2019) (requiring a petition for *inter partes* review to identify how the challenged claim is to be construed and where each element of the claim is found in the prior art patents or printed publications relied upon).

A claim is anticipated under 35 U.S.C. § 102 only if “each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegaal Bros. v. Union Oil Co.*,

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<sup>1</sup> We do not need to determine whether or not the AIA applies to the ’722 Patent because, as discussed below, Petitioner’s asserted references are prior art to the ’722 Patent under either the AIA or pre-AIA version of § 102.

<sup>2</sup> Ex. 1003, T. Thorsen, *Microfluidic Technologies for High-Throughput Screening Applications* (2003) (“Thorsen”).

<sup>3</sup> Ex.1005, Ismagilov et al., US 2006/0094119 A1, pub. May 4, 2006 (“Ismagilov 119”).

<sup>4</sup> Ex. 1004, Ismagilov et al., US 7,129,091 B2, issued Oct. 31, 2006 (“Ismagilov 091”).

814 F.2d 628, 631 (Fed. Cir. 1987). A claim is unpatentable under 35 U.S.C. § 103 if “the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and when in evidence (4) objective evidence of nonobviousness, i.e., secondary considerations. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

Additionally, the obviousness inquiry typically requires an analysis of “whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue.” *KSR*, 550 U.S. at 418 (*citing In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2016) (requiring “articulated reasoning with some rational underpinning to support the legal conclusion of obviousness”)). Furthermore, Petitioner does not satisfy its burden of proving obviousness by employing “mere conclusory statements,” but “must instead articulate specific reasoning, based on evidence of record, to support the legal conclusion of obviousness.” *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016).

*B. Level of Ordinary Skill in the Art*

Relying on Dr. Fair’s testimony, Petitioner asserts that a person of ordinary skill in the art (“POSA”) would have had “a PhD in chemistry, biochemistry, mechanical or electrical engineering, or a related discipline with one year of experience related to systems for handling microfluidic droplets,” “a Bachelor of Science in such fields with four years of such

experience,” or an equivalent level of education and practical experience. Pet. 3; Ex. 1008 ¶ 40. Petitioner and Dr. Fair assert that a “POSA would have knowledge of scientific literature concerning droplets (including emulsions), and systems and methods for handling them (including both their formation and handling downstream of formation), their applications, and chemistry, components, and reactions that occur within them.” Pet. 3; Ex. 1008 ¶ 40. In addition, Petitioner and Dr. Fair assert that a “POSA may have worked on a multidisciplinary team and drawn on his or her own skills along with certain specialized skills of others; and a chemist, engineer, and biologist may have been part of the team.” Pet. 3; Ex. 1008 ¶ 40.

Relying on Dr. Anna’s testimony, Patent Owner asserts that a POSA “would have had at least the equivalent of a Bachelor’s degree in engineering, physics, or chemistry and two years of academic, research, or industry experience related to fluid mechanics, fluid dynamics, or microfluidics.” PO Resp. 15 (citing Ex. 2016 ¶¶ 71–73). In addition, Patent Owner asserts that “[a]dditional training or study could substitute for work experience and additional work experience or training could substitute for formal education.” PO Resp. 15; Ex. 2016 ¶ 71.

Both sides’ declarants represent that their opinions would not change based on their opponent’s articulation of the level of ordinary skill in the art. Ex. 1074 ¶ 13; Ex. 2016 ¶ 73.

We find that Patent Owner’s definition of a POSA is consistent with the scope and content of the ’722 Patent and the asserted prior art. In addition, we find that Patent Owner’s definition of a POSA is consistent with the legal standard for obviousness, which is to be determined from the viewpoint of a person of ordinary, not extraordinary, skill. *Stewart-Warner Corp. v. City of Pontiac, Mich.*, 767 F.2d 1563, 1570 (Fed. Cir. 1985)

(section 103 is not concerned with the actual skill of the inventors—whose skill may be extraordinary—but rather with the level of ordinary skill in the art).

In contrast, Dr. Fair’s opinion about the level of ordinary skill in the art is based on his own experience working in the field and “working with others in this field who consistently had that level of education and/or experience and worked with a multidisciplinary team.” Ex. 1074 ¶ 10.

Dr. Fair considers himself “an expert in the art of biomedical microfluidics and related applications, including handling microfluidic droplets.”

Ex. 1008 ¶ 42. We find that Petitioner and Dr. Fair have defined a POSA based on the level of skill possessed by Dr. Fair and others like him who are experts in the field. Ex. 1008 ¶¶ 40–42; Ex. 1074 ¶¶ 9, 10. In our view, the level of skill in the art proposed by Petitioner and Dr. Fair is more akin to extraordinary, rather than ordinary skill in the art.

For these reasons, we apply Patent Owner’s definition of a POSA. We also apply a portion of Petitioner’s definition, namely that a POSA “would have knowledge of scientific literature concerning droplets (including emulsions), and systems and methods for handling them (including both their formation and handling downstream of formation), their applications, and chemistry, components, and reactions that occur within them.” Pet. 3; Ex. 1008 ¶ 40. This portion is undisputed by Patent Owner and is consistent with the ’722 Patent and the asserted prior art, as summarized below.

In any event, our determinations regarding Petitioner’s challenges do not turn on the differences between Petitioner’s and Patent Owner’s definitions of a POSA, and our conclusion would be the same under either party’s definition.

*C. Claim Construction*

For petitions for *inter partes* review filed on or after November 13, 2018, such as here, we apply the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b), following the standard articulated in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc). 37 C.F.R. § 42.100(b); 83 Fed. Reg. 51,340, 51,340–41, 51,343 (Oct. 11, 2018). In applying this standard, we generally give claim terms their ordinary and customary meaning, as would be understood by a person of ordinary skill in the art, at the time of the invention and in the context of the entire patent disclosure. *Phillips*, 415 F.3d at 1312–13.

Petitioner proposes constructions for the phrases: (1) “main channel” (claims 1, 14), (2) “providing an immiscible fluid flowing through a main channel that is in fluidic communication with the sample inlet” (claims 1, 14); (3) “separation chamber” (claims 1, 14); (4) “sample” (claims 1, 14), and (5) “continuous phase carrier fluid” (claims 15–16) that are based on Patent Owner’s expected claim constructions in view of Patent Owner’s infringement contentions in the related district court action. *See* Pet. 18–19 (citing Ex. 1008 ¶¶ 77–80; Ex. 1026, 26).

In our Institution Decision, we addressed the construction of “separation chamber” and determined that no other claim term required express construction. Dec. Inst. 9. For the reasons set forth below, we maintain our construction of separation chamber. We also address the construction of the term “sample.”

*1. “separation chamber” (Claims 1, 14)*

Claim 1 recites that the claimed method comprises “flowing the droplets toward a downstream separation chamber.” Ex. 1001, 88:13–14.

Claim 1 further recites “separating the plurality of droplets from the immiscible fluid in the separation chamber based on the different densities of the droplets and the immiscible fluid.” *Id.* at 88:20–22. Claim 14 recites similar limitations. *Id.* at 88:62–63, 89:1–3.

Petitioner contends that “separation chamber” should be construed as “[b]road enough to encompass an open well,” asserting that this construction is in accordance with the construction proposed by Patent Owner in its infringement contentions in the co-pending district court litigation. Pet. 19 (citing Ex. 1026 (Bio-Rad’s Patent Infringement Contentions, Case No. 1:18-cv-01679), 13–22; Ex. 1052 (Complaint for Patent Infringement, Case No. 1:18-cv-01679), 24–28).

Patent Owner responds that “separation chamber” should be construed as a “chamber sized to accommodate multiple droplets and an immiscible fluid in separated form,” which is the same construction Patent Owner proffered in district court. PO Resp. 18; Ex. 2032-corrected (Joint Claim Construction Chart filed in district court), 8.

Petitioner does not dispute Patent Owner’s construction. *See* Pet. Reply 2 (stating Patent Owner’s construction of “separation chamber” is broad enough to include Thorsen’s incubation chamber and outlet wells).

We find that the Specification supports Patent Owner’s construction for “separation chamber.” The Specification discloses that partitioned portions, i.e. droplets, and immiscible fluid flow into a chamber, where the partitioned portions sink, float, or are displaced from the chamber as a result of a difference in density between the partitioned portions and the immiscible fluid. Ex. 1001, 2:45–50, 3:37–46. Patent Owner’s construction is further supported by the Specification’s description of a “chamber . . . configured to receive droplets and an immiscible fluid from the droplet

formation module,” where “the immiscible fluid displaces the droplet from the chamber into the outlet due to the difference in density.” *Id.*

at 53:31–37. Patent Owner’s construction is also consistent with the Specification’s disclosure that “the chamber can include any vessel suitable for holding droplets, for example, test tubes, vials, beakers, jars, and PCR tubes.” *Id.* at 53:44–47.

Accordingly, we adopt Patent Owner’s proposed, undisputed construction of “separation chamber” as a “chamber sized to accommodate multiple droplets and an immiscible fluid in separated form.”

2. “sample” (*Claims 1, 14*)

Petitioner asserts that a sample includes “a compound, composition, and/or mixture of interest, from any suitable source(s).” Pet. 31. Patent Owner responds that a sample is a “fluid containing molecules, cells, small molecules (organic or inorganic) or particles.” PO Resp. 15; *see also* Ex. 1001, 26:48–50 (describing a fluid “containing a sample such as molecules, cells, small molecules (organic or inorganic) or particles”).

We need not construe the term “sample” as Petitioner has sufficiently shown that the cited art teaches a “sample” under either party’s proposed construction.

We determine that no other claim term requires express construction for purposes of resolving any issue in dispute. *See Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (“only those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy”); *see also Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (applying *Vivid Techs.* in the context of *inter partes* review).

*D. Overview of the Asserted References*

We summarize the relevant disclosures of Petitioner's asserted references below.

*1. Thorsen (Ex. 1003)*

Thorsen is a Ph.D. dissertation. Ex. 1003, 6.<sup>5</sup> Petitioner asserts that Thorsen is prior art to the '722 Patent under § 102(a)(1) and pre-AIA § 102(a) and (b) "because it is a printed publication that was available to the public more than one year before the earliest date of application for the 722 Patent." Pet. 13; *see also* Ex. 1003 (Decl. of Shirley Katherine Johnson), ¶ 7. Patent Owner does not contest the prior art status of Thorsen.

Thorsen relates to the design and development of microfluidic devices for high-throughput screening applications. Ex. 1003, 6, 10. Thorsen describes the "development of a two-phase microfluidic device," including "crossflow-based dynamic formation of picoliter-sized water droplets in a continuously flowing oil-surfactant stream." *Id.* at 10.

In one design described in Chapter 4, Thorsen uses a "serpentine outlet channel" (i.e., a "serpentine outlet") to slow down droplets in a microfluidic device. *Id.* at 115 (stating the length and width of the serpentine outlet channels were varied to create a long outlet path that served as an incubation chamber for the encapsulated enzyme and substrate"). In another design described in Chapter 3, Thorsen replaces the serpentine output channel with a large, high cavity (i.e., an "incubation chamber") to slow down droplets in a microfluidic device. *Id.* at 99.

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<sup>5</sup> We cite to Exhibit 1003 using the page numbers added by Petitioner in the lower right corner of each page.

a) *Chapter 3*

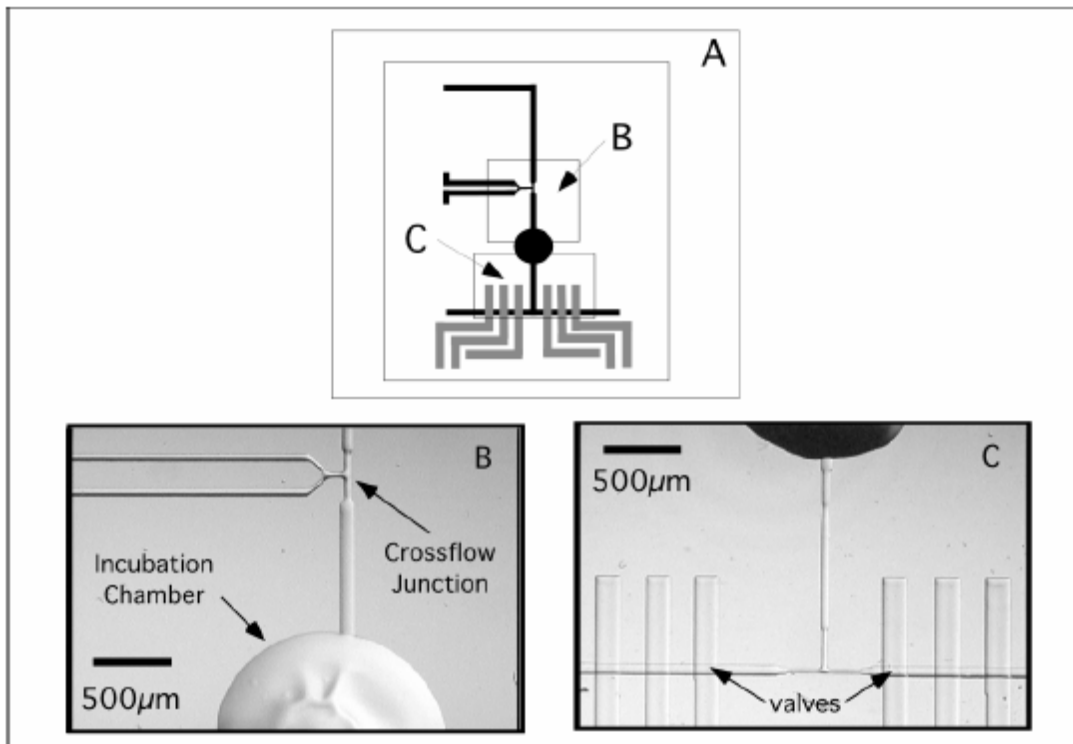
Thorsen Chapter 3 discusses microfluidic crossflow as a droplet formation technology. Ex. 1003, 52. Thorsen reviews the channel architecture and theory of existing microfluidic crossflow devices, including those having a serpentine channel to incubate the contents of the droplets. *Id.* at 62–89. Thorsen reports that he developed “integrated elastomeric valves” for gating microfluidic flow and sorting droplets. *Id.* at 53, 89, 97, 104 (“we successfully demonstrated droplet sorting via elastomeric valves in the silicone microfluidic devices”).

Thorsen Chapter 3 describes the design and fabrication of microfluidic device prototypes including a large cavity “incubation chamber” as follows:

Multilayer soft lithography techniques were used to fabricate a two-layer Dow Corning Sylgard 184 crossflow device with integrated valves for droplet sorting. . . . A significant design modification was added to the device to accommodate chemical screening reactions where incubations of several minutes to a few hours are optimal (Figure 3.28A). The serpentine output channel at the crossflow junction was replaced with a large (~500  $\mu\text{m}$ ) high cavity to slow down the droplets and create an on-chip incubation chamber (Figure 3.28B). . . . A control layer of valves was added for sorting droplets at the T-junction intersection at the end of the chip (Figure 3.28C).

Ex. 1003, 99, 101.

Figure 3.28 of Thorsen is reproduced below:



Ex. 1003, 101. Thorsen Figure 3.28 shows a microfluidic chip design, including: (A) a schematic of a silicone crossflow device with an incubation cavity, where black represents the flow layer and grey represents the control layer; (B) a high resolution image of an actual chip showing a crossflow junction and an incubation chamber; and (C) a high resolution of a sorting junction in a chip showing valve structures. *Id.*

Thorsen describes the steps for fabricating the Sylgard 184 crossflow devices, stating that after “the two-layer crossflow devices were cured, they were released from the mold, processed, and sealed channel side down on the coated coverslips.” *Id.*

Thorsen describes testing the crossflow devices having an incubation chamber as follows:

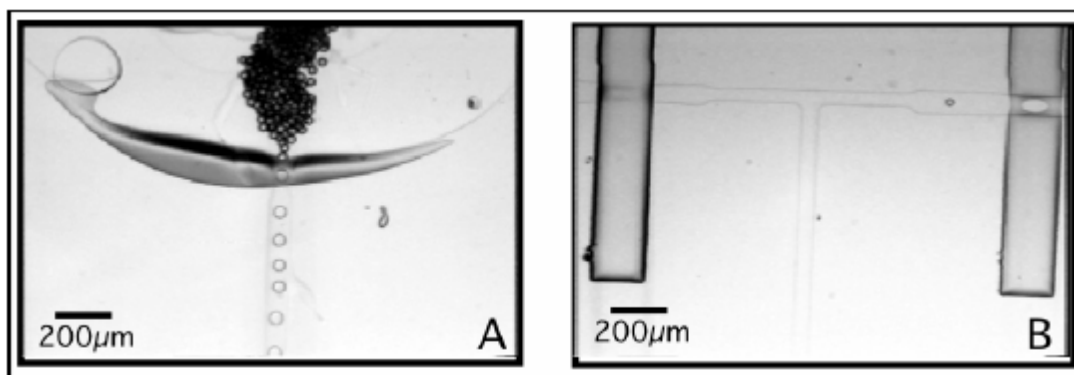
Droplets were generated in the Sylgard 184 crossflow devices using mineral oil/1% Span 80 for the continuous phase

and dH<sub>2</sub>O for the disperse phase. Water and oil streams were balanced at the crossflow junction at ~12/15 psi water/oil-surfactant (w/o-s). Water droplet formation was initiated by increasing the water pressure to 12.5–13.0 psi. Generated water droplets entered the “incubation” cavity, where they encountered a sharp drop in flow velocity (Figure 3.29A). After ~1 hour, the droplets had passed entirely through the cavity and re-entered the narrow (~60 μm wide) outlet channel, where they flowed toward the T-junction for valve-based sorting.

Initial sorting was performed by manually switching the valves while observing the droplets under 20x magnification. The elastomeric valves were actuated using pressurized air controlled by an external solenoid valve. When ~13–15 psi of air pressure was applied to the selected control channel, the interfacial membrane between the two channel layers (Figure 3.28C) was deflected down, closing the underlying flow channel. Manual valve switching rates of several Hz were carried out without any observable mechanical breakdown. The valves efficiently sorted the droplets at the T-junction (Figure 3.29B).

*Id.* at 102–103.

Figure 3.29 of Thorsen is reproduced below:



*Id.* at 103. Thorsen Figure 3.29 shows: (A) water droplets entering the incubation cavity of a Sylgard 184 device; and (B) sorting of droplets using elastomeric valves. *Id.*

Thorsen also describes the development of a fluorescence-activated droplet sorter using his Sylgard 184 microfluidic chip having a microcavity and elastomeric valves. Ex. 1003, 104–111. Thorsen discloses that, “[a]s a functional demonstration of the device, the fluorescence-activated droplet sorter was used to sort 2–3  $\mu\text{m}$  diameter droplets filled with either green . . . or red . . . fluorescent dyes.” *Id.* at 109. Thorsen describes using the microcavity crossflow device to generate red and green droplets. *Id.* at 109–110. Thorsen states: “The formed droplets entered the microcavity, where they slowed down and formed a mixed cluster of droplets.” *Id.* at 110. Thorsen discloses that, to sort the droplets, a detection region was set up downstream of the microcavity and upstream of a T-junction near the device outlets. *Id.* at 110–111. Responsive to fluorescence emission detection, the valves were actuated to sort the red and green droplets toward the respective outlet channels. *Id.* at 110.

Thorsen describes the results of his sorting experiment as follows:

Sorting efficiency was measured both by looking at the PMT [photomultiplier tube] output values of the output material in the collection wells. As droplets formed a large aggregate in the output wells, PMT readings were not especially useful as neighbor droplets washed out the signal from improperly sorted droplets. Visual inspection of the output wells was carried under a 40x objective . . . on an inverted microscope . . . equipped with a mercury lamp. The wells were rapidly scanned using both green . . . and red . . . filter sets to look for improperly sorted droplets. Of the thousands of sorted droplets in each well, only a small fraction ( $\sim 1\text{--}2\%$ ) were of the wrong dye type.

*Id.* at 111.

*b) Chapter 4*

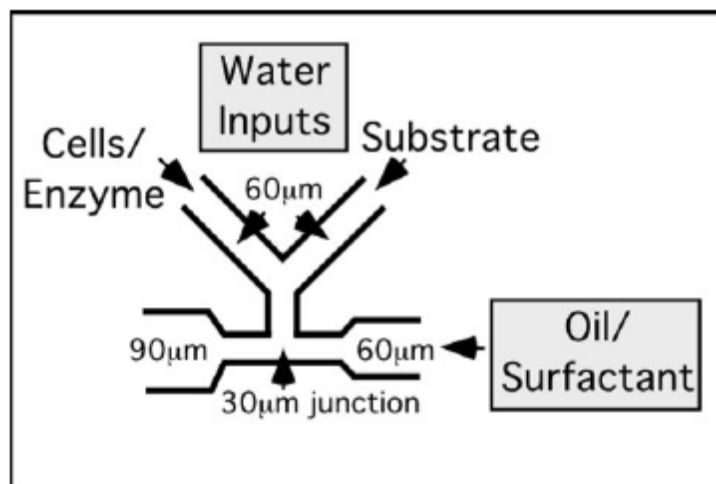
Thorsen Chapter 4 discusses biochemical screening applications for microfluidic crossflow devices. Ex. 1003, 113. In particular, Thorsen

Chapter 4 describes the development and characterization of a model enzyme system in reverse vesicles generated by microfluidic crossflow using a serpentine channel design to act as an incubation chamber for encapsulated enzyme and substrate. *Id.* at 114. Thorsen describes the microfluidic crossflow device for measuring enzyme activity at the single cell level as follows:

Cells [i.e., *Escherichia coli* (“*E. coli*”)] expressing a recombinant enzyme [i.e., p-nitrobenzyl (pNB) esterase (“pNB esterase”)] and the appropriate substrate are injected into separate water channels that meet at the crossflow junction (Figure 4.1). As soon as the two water streams merge, they are immediately encapsulated into a droplet in the oil-surfactant stream. As the droplets flow down the channel toward the outlet, the substrate is converted to a detectable fluorescent product.

*Id.* at 114.

Figure 4.1 of Thorsen is reproduced below:



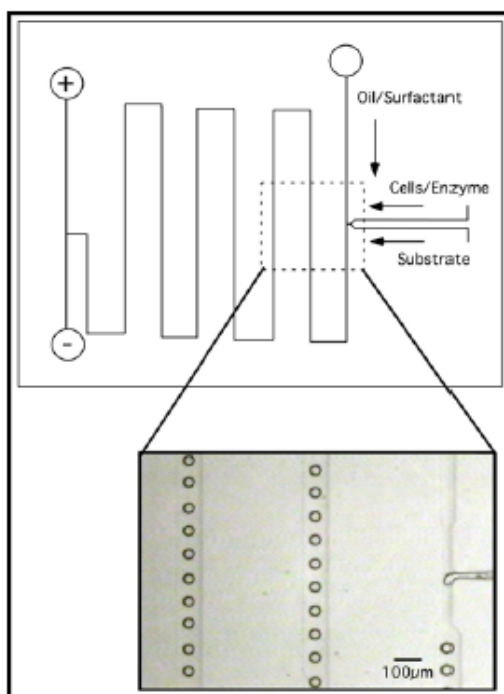
*Id.* at 115. Thorsen Figure 4.1 shows a microfluidic channel layout in a microfluidic crossflow device for single cell catalysis measurements. *Id.*

Thorsen Chapter 4 describes the preparation and testing of microfluidic crossflow devices using a serpentine output channel as follows:

Several crossflow patterns were designed with serpentine outlet channels. The length and width of the channel where the droplets emerge from the crossflow junction were varied to create a long outlet path that served as an incubation chamber for the encapsulated enzyme and substrate. Single-layer devices were fabricated in Sylgard 184 from the photoresist molds of the patterns. With a 90  $\mu\text{m}$  wide x 10  $\mu\text{m}$  high output channel ~8 cm in length, formed droplets required ~20 minutes to reach the output well. Given adequate spacing between the monodisperse droplets at the crossflow junction, water droplets in mineral oil/2% Span 80 (13.0/15.0 psi w/o-s) traveled as a perfectly coherent stream from the crossflow junction to the outlet well (Figure 4.2). At higher relative water pressures, the generated droplets collided in the output channels, forming aggregates.

Ex. 1003, 115.

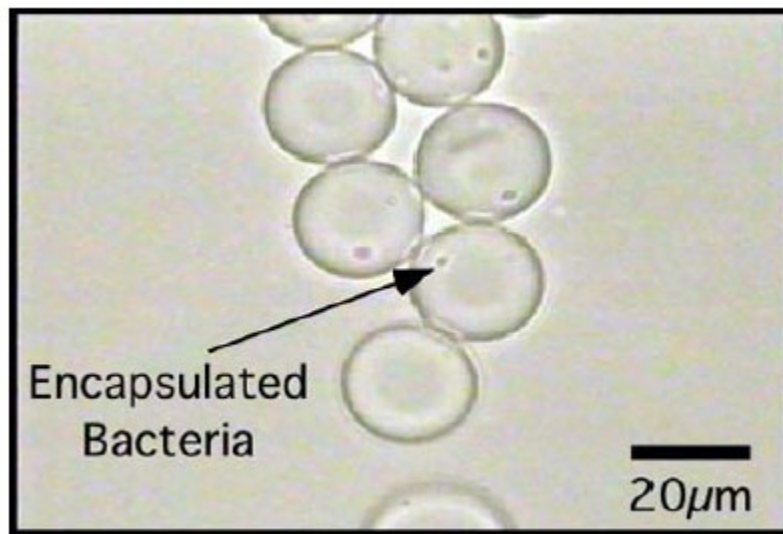
Figure 4.2 of Thorsen is reproduced below:



Ex. 1003, 116. Thorsen Figure 4.2 shows a serpentine channel design for a biochemical screening chip. *Id.* According to Thorsen, “[m]onodisperse water droplets in mineral oil/2% Span 80 retain a coherent pattern as they flow towards the device outlet.” *Id.*

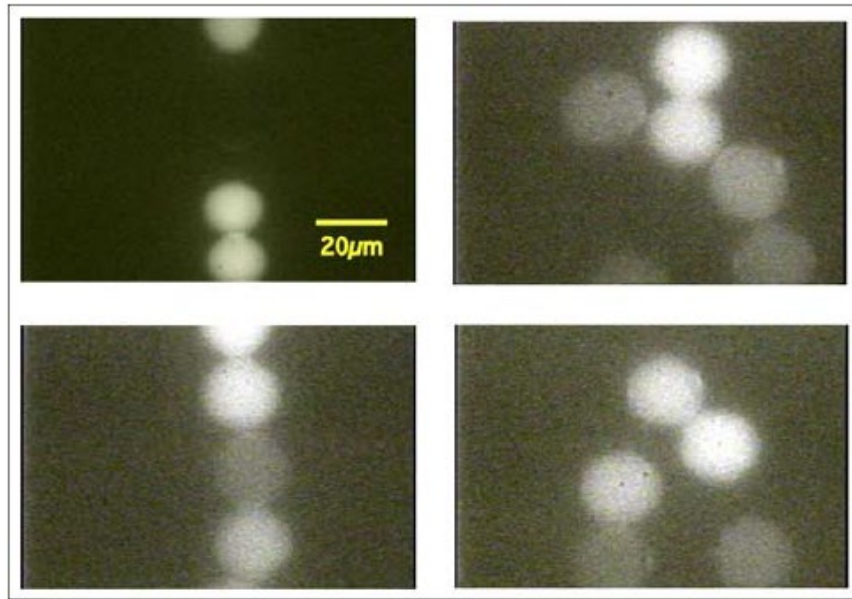
Thorsen describes cross flow experiments using devices fabricated from Sylgard 184. *Id.* at 118. An oil stream was balanced against two separate aqueous inputs (containing washed *E. coli* cells and substrate respectively) as previously described for the two-color droplet sorting experiment in Chapter 3. *Id.*

Figure 4.4 of Thorsen is reproduced below.



Ex. 1004, 119. Thorsen Figure 4.4 shows *E. coli* bacteria cells encapsulated in droplets generated by microfluidic crossflow. *Id.* Thorsen states that although the crossflow assay was unreliable, “a few good examples of catalysis inside the formed droplets were still acquired” as shown in Figure 4.5. *Id.* Thorsen further states that droplets were visualized for fluorescent product approximately 10 minutes after encapsulation, after they had flowed through 4–5 loops of the wide serpentine outlet channel. *Id.*

Figure 4.5 of Thorsen is reproduced below.



Ex. 1004, 120. Thorsen Figure 4.5 depicts monodisperse droplets containing *E. coli* expressing recombinant pNB esterase and fluorescein diacetate substrate. *Id.* The active *E. coli* cells took on a bright fluorescent green coloration as they accumulated fluorescein product during catalysis, making it easy to visually confirm their presence in droplets. *Id.* at 119.

2. *Ismagilov 091 (Ex. 1004)*

Ismagilov 091 is asserted as prior art to the '722 Patent under 35 U.S.C. § 102(a)(2) and pre-AIA § 102(e) as of its May 9, 2003 filing date and under § 102(a)(1) and pre-AIA § 102(a) as of its December 8, 2005 publication date. Pet. 16. Petitioner contends that Ismagilov 091 is prior art under pre-AIA § 102(b), if the challenged claims are not entitled to their earliest asserted priority date. *Id.*

Patent Owner does not contest the prior art status of Ismagilov 091. We do not need to address Petitioner's contention under pre-AIA § 102(b) because Patent Owner does not attempt to show a date of invention earlier

than Ismagilov's 091's filing date or publication date. We find that Ismagilov 091 is prior art to the '722 patent regardless of whether the AIA applies to the patent.

Ismagilov 091 discloses microfabricated substrates and methods of conducting reactions in droplets ("plugs") in a flow of carrier fluid in a substrate. Ex. 1004, code (57).

Ismagilov 091 discloses that "[p]lugs' . . . are formed in a substrate when a stream of at least one plug-fluid is introduced into the flow of a carrier-fluid in which it is substantially immiscible." Ex. 1004, 9:20–23. According to Ismagilov 091, the "plugs" may be in the form of "an aqueous plug-fluid . . . surrounded by a non-polar or hydrophobic fluid such as an oil." *Id.* at 9:39–44. Ismagilov 091 discloses that an "inlet port" is "an area of a substrate that receives plug-fluids," and "[t]he inlet port can be in fluid communication with a channel." *Id.* at 8:41–42, 8:46–47. According to Ismagilov 091, a "channel" includes "microchannels." *Id.* at 7:46–48. Ismagilov 091 discloses that an "outlet port" is "an area of a substrate that collects or dispenses the plug-fluid, carrier-fluid, plugs or reaction product." *Id.* at 9:5–8.

In a section headed, "Channels and Devices," Ismagilov 091 discloses a device that "includes one or more substrates comprising a first channel comprising an inlet separated from an outlet." Ex. 1004, 14:20–23. According to Ismagilov 091,

The device may have one or more outlet ports or inlet ports. Each of the outlet and inlet ports may also communicate with a well or reservoir. The inlet and outlet ports may be in fluid communication with the channels or reservoirs that they are connecting or may contain one or more valves.

*Id.* at 14:36–40. In this section, Ismagilov 091 also discloses that “a plug-forming region generally comprises a junction between a plug-fluid inlet and a channel containing the carrier-fluid such that plugs form.” *Id.* at 14:44–45.

In a section headed, “Fabrication of Channels, Substrates, and Devices,” Ismagilov 091 discusses methods for fabricating microfluidic devices, including a polymer casting method. Ex. 1004, 16:1–7, 16:23–41. According to this method, a negative image of the channels is etched into a crystalline silicon wafer, and the wafer is used as a mold for casting the channels from polydimethylsiloxane (PDMS). *Id.* at 16:23–28. In this method, the silicon wafer mold is placed in the bottom of a Petri dish, uncured PDMS is poured onto the mold, and the PDMS then cured and removed from the mold. *Id.* at 16:30–35. Ismagilov 091 discloses that “[h]oles may be cut into the PDMS using, for example, a tool such as a cork borer or a syringe needle.” *Id.* at 16:35–36. According to Ismagilov 091, the PDMS channels are treated with hydrochloric acid to render the surface hydrophilic. *Id.* at 16:37–38. Ismagilov 091 discloses that the PDMS channels can be “placed onto a microscope cover slip (or any other suitable flat surface), which can be used to form the base/floor or top of the channels.” *Id.* at 16:38–41.

Ismagilov 091 also discloses that “[a] substrate containing the fabricated flow channels and other components is preferably covered and sealed, preferably with a transparent cover, e.g., thin glass or quartz, although other clear or opaque cover materials may be used.” Ex. 1004, 16:60–64. According to Ismagilov 091, the substrate can include “[a] variety of channels for sample flow” as well as “manifolds (a region consisting of several channels that lead to or from a common channel).” *Id.* at 17:10–11, 17:18–20. Such manifolds can “route[] the flow of solution to

an outlet.” *Id.* at 17:23–27. Ismagilov 091 discloses that “[t]he outlet can be adapted for receiving, for example, a segment of tubing or a sample tube, such as a standard 1.5 ml centrifuge tube. Collection can also be done using micropipettes.” *Id.* at 17:27–30.

Figure 3A of Ismagilov 091 is reproduced below.

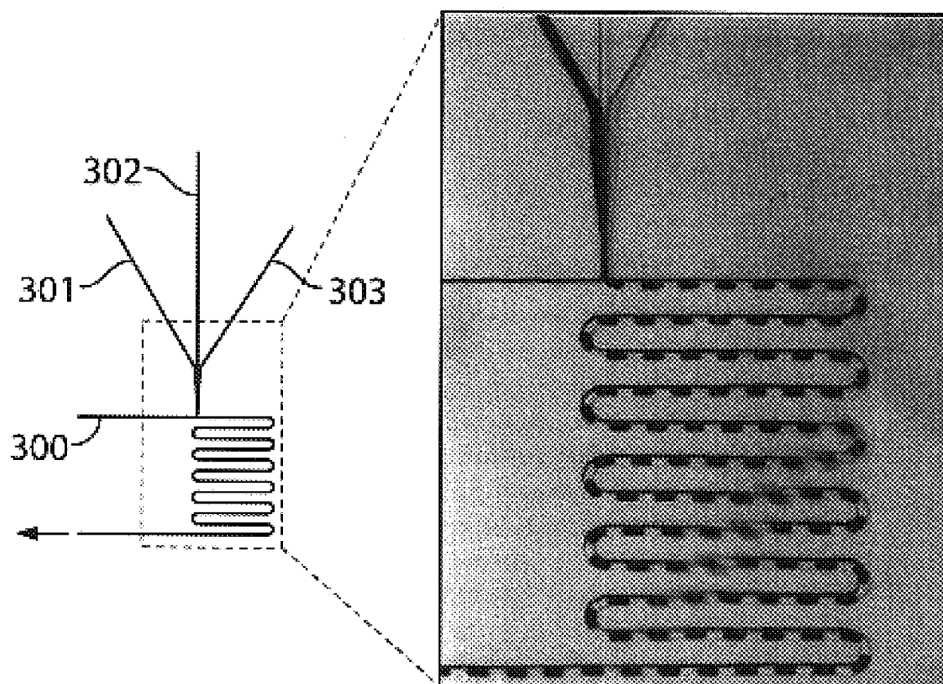


**FIG. 3A**

Ismagilov 091 Figure 3A shows a photograph (right side) and a schematic diagram (left side) depicting a stream of plugs formed from an aqueous plug-fluid and an oil (carrier-fluid) in curved serpentine channels. Ex. 1004, 4:6–10, 18:24–26, Fig. 3A. According to Ismagilov 091, the carrier-fluid is introduced into inlet port 300 of a substrate, and three aqueous plug-fluids are introduced in separate inlet ports 301, 302, and 303. *Id.* at 18:31–33.

Ismagilov 091 discloses that “[p]lug-fluids may comprise a solvent and optionally, a reactant” and that “[s]uitable carrier-fluids include oils, preferably fluorinated oils.” Ex. 1004, 20:10–11, 20:37–38. According to

Ismagilov 091, “[t]he carrier-fluid or plug-fluid, or both may contain additives, such as agents that reduce surface tensions (e.g., surfactants).” *Id.* at 20:45–47.

3. *Ismagilov 119 (Ex. 1005)*

Ismagilov 119 is asserted as prior art to the ’722 Patent under 35 U.S.C. § 102(a)(2) and pre-AIA § 102(e) as of its March 16, 2005 filing date and under § 102(a)(1) and pre-AIA § 102(a) as of its May 4, 2006 publication date. Pet. 17. Patent Owner does not contest the prior art status of Ismagilov 119. We find that Ismagilov 091 is prior art to the ’722 patent regardless of whether the AIA applies to the patent.

Ismagilov 119 incorporates Ismagilov 091 by reference. Ex. 1005 ¶ 30. Like Ismagilov 091, Ismagilov 119 also discloses a microfluidic system and refers to droplets as “plugs.” *Id.* ¶ 22, Fig. 13b (showing “aqueous droplets, or plugs” being formed at the junction between “channel a” through which an aqueous stream is pumped and “channel b” through which a carrier fluid is pumped).

Ismagilov 119 discloses that “the use of fluorinated carrier fluid can provide protection of plugs and control of the surface chemistry.” Ex. 1005 ¶ 9. Ismagilov 119 discloses that, if centrifugation is used as a force for bringing two plugs into contact, then “preferably the carrier fluids and the plug fluids have different densities, as is the case when aqueous plug fluids and fluorinated carrier fluids are used.” *Id.* ¶ 14.

Ismagilov 119 discloses that “it is desirable add a surfactant into the carrier fluid . . . to control the surface tension and the wetting properties of the carrier fluid.” Ex. 1005 ¶ 94. For example, Ismagilov 119 discloses “perfluorooctanol as the surfactant when fluorinated fluids were used as carrier fluids.” *Id.* According to Ismagilov 119, “fluorous-soluble

surfactants can be used to control non-specific protein adsorption at a fluorinated carrier-aqueous interface.” *Id.* Ismagilov 119 provides an example of a fluorosoluble surfactant that “arranges itself at the fluorinated carrier-aqueous interface during plug formation and presents a monolayer of oligoethylene glycol groups.” *Id.*

*E. Asserted Anticipation of Claims 1–3, 10, 11, and 14 by Thorsen*

Petitioner contends that Thorsen anticipates claims 1–3, 10, 11, and 14. *See* Pet. 21, 28–60, 64–65. Patent Owner responds that Thorsen does not disclose (1) a “separation chamber,” a “separation chamber [that] is disposed perpendicular to the main channel,” or “separating the plurality of droplets from the immiscible fluid in the separation chamber based on the different densities of the droplets and the immiscible fluid” as recited in each of the independent claims, (2) “collecting the separated droplets” as recited in claim 2, and (3) “wherein the separated droplets are collected in a vessel” as recited in claim 3. *See, e.g.*, PO Resp. 25–27, 35.

For the reasons stated below, we conclude that Petitioner has shown by a preponderance of the evidence that Thorsen anticipates claims 1, 2, 10, 11, and 14 but has not shown that Thorsen anticipates claim 3.

*1. Claim 1*

*a) [1.0] A method of reducing contamination associated with sample handling, comprising:*

Petitioner contends, and Patent Owner does not dispute, that Thorsen discloses the preamble of claim 1 (a “method of reducing contamination associated with sample handling, comprising”) by describing the screening of cell populations by physically separating cells to allow the assay of a single colony or cell and by encapsulating cells and substrate in vesicles like liposomes or reverse micelles. Pet. 28 (citing Ex. 1003, 54–55).

We are persuaded by Petitioner's undisputed contentions and find that Thorsen discloses the preamble of claim 1.<sup>6</sup>

b) [1.1] providing an aqueous fluid comprising a sample through a sample inlet;

Petitioner contends that Thorsen discloses the subject matter recited in claim limitation 1.1. Pet. 29–34. In particular, Petitioner contends Thorsen's crossflow junction—which is used in Thorsen's microfluidic devices having an either incubation chamber system as disclosed in Chapter 3 or the serpentine channel system disclosed in Chapter 4—and is depicted in Figure 3.28, comprises a sample inlet through which an aqueous solution comprising a sample is provided. Pet. 29–30, 32–33 (citing *inter alia* Ex. 1003, Figs. 3.28, 4.1, 4.2).

Petitioner states that Thorsen describes using the crossflow junction to provide water droplets in mineral oil and therefore discloses providing an aqueous (water-based fluid) through a sample inlet. Pet. 30–31 (citing Ex. 1003, 102, 114–116. Figs. 3.29, 4.1, 4.2). Petitioner contends a POSA would understand Thorsen to “expressly disclose” using its incubation chamber system to perform chemical screening of samples of interest because Thorsen states that its system is used for “chemical screening” and that chemical screening includes the screening of a sample, such as a compound, composition, and/or mixture of interest from any suitable source. Pet. 31–32 (citing Ex. 1003, 10, 21, 26, 99; Ex. 1008 ¶¶ 103–105).

Petitioner also points to Thorsen's disclosure of “Water inputs” that include “‘Cells / Enzyme’ of interest” (i.e., *Escherichia coli* (“*E. coli*”) and

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<sup>6</sup> Because we find that Thorsen discloses the subject matter recited in the preamble of claim 1, we need not, and do not, determine if the preamble should be construed as limiting.

recombinant p-nitrobenzyl esterase (“pNB esterase”)) as a sample in an aqueous solution, along with a “substrate,” in a chemical screening assay in the microfluidic device having a serpentine channel system described in Chapter 4. Pet. 32–33 (citing Ex. 1003, 114–120, Figs. 4.1, 4.2); *see also* Ex. 1003, 114 (describing a model enzyme system in reverse vesicles generated by microfluidic cross flow using an enzyme (pNB esterase) expressed in a cell (*E. coli*)).

Petitioner also states Thorsen describes using the incubation chamber system described in Chapter 3 for an assay to sort red and green droplets containing samples of red (R-phycoerythrin) fluorescent dye or green fluorescein dye. Pet. 34 (citing Ex. 1003, 109–112).

Patent Owner does not dispute that Thorsen provides an aqueous fluid through a sample inlet. *See generally* PO Resp. Patent Owner, however, contends that that Thorsen does not disclose or suggest providing an aqueous fluid *comprising a sample* through the inlet. *See, e.g.*, PO Resp. 23–25, 43–44.

In particular, Patent Owner contends that Thorsen does not disclose using cells or enzymes as samples because the experiments disclosed in Chapter 4 using cells/enzymes reported problems with the adhesion of cells to the channel walls. *Id.* at 23. Patent Owner points to Thorsen’s statement of problems with “flow balance,” “cell adhesions to PDMS” and “substrate autohydrolysis [sic].” PO Resp. 9 (citing Ex. 1003, 120–127; Ex. 2016 ¶¶ 36–40). Patent Owner also points to Thorsen’s statements that “[w]orking on the development of a microfluidic crossflow assay emphasized the difficult dynamic integration process between biochemical and micromechanical systems” and “that the problems he experienced

ultimately ‘plagued the assays’ and that ‘further research in this area’ was needed.” *Id.* at 9–10 (quoting Ex. 1003, 127).

Patent Owner similarly contends that a POSA would not understand Thorsen to disclose use of the incubation chamber disclosed in Chapter 3 to perform chemical screening because the channel walls of Thorsen’s incubation chamber system were made from the same material as the serpentine channel system and “Thorsen reported problems with the adhesion of cells to the channel walls in his only attempt to use an actual sample, *i.e.*, his use of pNB esterase in the serpentine channel system of Chapter 4).” PO Resp. 23–24 (citing Ex. 2016 ¶ 111); *see also id.* at 39–40 (asserting Thorsen’s Chapters 3 and 4 do not describe a single system and that even they do describe a single system, the system is not enabled).

Patent Owner also contends that the red and green dyes (*i.e.*, fluorescein and R-phycoerythrin) disclosed in Thorsen Chapter 3 are not samples themselves. PO Resp. 24–25 (citing Ex. 2016 ¶ 112).

We have reviewed the parties’ evidence and arguments and determine Petitioner has shown persuasively that Thorsen discloses the subject matter recited in claim limitation 1.1, notwithstanding Patent Owner’s arguments to the contrary.

For example, we determine that Petitioner has shown persuasively that the green (fluorescein) and red (R-phycoerythrin) fluorescent dyes disclosed in Thorsen Chapter 3 are “samples” under either party’s definition of the term sample. Patent Owner contends that although “fluorescein and R-phycoerythrin complexes may be used to indicate the presence of certain bacteria or antibodies, they are not ‘samples’ themselves within the meaning of the ’722 claims.” PO Resp. 24–25 (citing Ex. 2016 ¶112). We disagree with Patent Owner. The green and red fluorescent dyes are each compounds

and thus satisfy Petitioner's definition of "sample" (i.e., "a sample, such as a compound, composition, and/or mixture of interest, from any suitable source"). The dyes are also molecules and thus satisfy Patent Owner's definition of "sample" (i.e., fluid containing "molecules, cells, small molecules (organic or inorganic) or particles").

We also agree with Petitioner that Thorsen's microfluidic devices, including the microfluidic device having the incubation chamber disclosed in chapter 3, is intended for chemical screening of samples. Pet. 31. Thorsen states that in "this thesis, I present . . . microfluidic devices for high-throughput screening applications, such as mutant enzyme libraries expressed in prokaryotic hosts...", 21 ("...thousands of single cells or small molecules such as DNA or proteins can be individually compartmentalized and examined"). We further agree that a POSA would understand that Thorsen's incubation chamber system is not limited to using only the materials used in the disclosed experiments (i.e., water and oil or the red and green fluorescent dyes). Pet. 32. Thorsen's chapter 3 states that the incubation chamber is a design modification "to accommodate chemical screening reactions where incubation of several minutes to a few hours are optimal (Figure 3.28A)" (Ex. 1003, 99), thus indicating that the incubation chamber is intended for use with chemical screening reactions and samples besides that used in the disclosed experiments. We are persuaded by Petitioner's argument and Dr. Fair's testimony that a POSA would understand this statement to expressly disclose use of samples in screening reactions where incubation intended to be used with this system is not limited to water droplets in oil or to only samples having green and red fluorescent dyes. Pet. 31–34; Ex. 1008 ¶¶ 103–107.

As discussed in more detail below, we also agree with Petitioner that Thorsen discloses use of samples comprising *E. coli* cells and pNB esterase enzymes in the experiments disclosed in Chapter 4. We disagree with Patent Owner argument that the *E. coli* cells and pNB esterase enzyme are not “samples.” Patent Owner directs us to Thorsen’s reported problems “with the adhesion of cells to the channel walls” in the experiments involving “use of pNB esterase in the serpentine channel system of Chapter 4.” PO Resp. 23–24; *see also id.* at 43–44 (discussing Thorsen’s cell adhesion problem in the context of obviousness). Patent Owner also points to Thorsen’s disclosure of problems that “plagued the assays” including problems with “flow balance,” “cell adhesions to PDMS,” and “substrate hydrolysis.” *Id.* at 9–10 (citing Ex. 1003, 120–127; Ex. 2016 ¶¶ 36–40); *see also id.* at 41–42 (asserting that the devices disclosed in Thorsen’s Chapters 3 and 4 are not enabled due to problems that “plagued the assays” including difficulty seeing micro-sized bacterial cells at low concentrations thus making it difficult to balance the aqueous inputs at the crossflow junction and bacterial cell adhesion to the walls of the microchannels prior to encapsulation (citing Ex. 1003, 121; Ex. 2016 ¶ 152)); *see also* PO Sur-reply 15 n.1 (stating Thorsen states in Chapter 4 that the devices failed when he used a solution of pNB esterase and citing PO Resp. 41).

Although Thorsen identifies problems with the crossflow assay described in Chapter 4 and states the assay was unreliable due to the problems that “quickly made the fabricated devices non-functional” (*see* Ex. 1003, 119), Thorsen also states that, in spite of the problems, a “few good examples of catalysis inside the formed droplets were still acquired” (Ex. 1003, 120).

As such, even though Thorsen identifies issues with cell adhesion in the crossflow assay of Chapter 4, Thorsen also discloses successful results using the assay. *See Celeritas Techs. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1361 (Fed. Cir.1998) (stating a “reference is no less anticipatory if, after disclosing the invention, the reference then disparages it”); *Ramusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005) (stating “proof of efficacy is not required in order for a reference to be enabled for purposes of anticipation”). Thus, Thorsen discloses the successful use samples, including *E. coli* cells and pNB esterase in the serpentine channel system of chapter 4.

In particular, we find Thorsen describes an experiment in which it was possible to visualize droplets containing *E. coli* bacterial cells for fluorescent product for approximately 10 minutes after encapsulation after they had flowed through 4–5 loops of the wide serpentine output channel. Ex. 1003, 119. Thorsen further explains that the “active cells took on a bright fluorescent green coloration as they accumulated fluorescein product during catalysis, making it easy to visually confirm their presence in droplets under a 60x/1.4 NA oil immersion objective.” *Id.* Additionally, Thorsen provides photographs of *E. coli* bacterial cells successfully encapsulated in droplets that were generated by microfluidic crossflow (Ex. 1003, Fig. 4.4) and as well as images of monodisperse droplets containing *E. coli* expressing recombinant pNB esterase and fluorescein diacetate substrate, thus illustrating “a few good examples of catalysis inside the formed droplets” (Ex. 1003, 119, Fig. 4.5). Thus, we disagree with Patent Owner that Thorsen does not enable the use of cells (i.e., *E. coli*) and enzymes (i.e., pNB esterase) as samples.

Therefore, we determine that Petitioner has sufficiently shown that Thorsen's chapters 3 and 4 each disclose providing an aqueous fluid sample through a sample inlet as recited in claim element 1.1. We also agree with Petitioner that, for purposes of anticipation, a POSA would understand that Thorsen discloses using samples, such as molecules, DNA, proteins, and cells, in the microfluidic device having an incubation chamber of Chapter 3.

*c) [1.2] providing an immiscible fluid flowing through a main channel that is in fluidic communication with the sample inlet, wherein the main channel is in a horizontal plane*

Petitioner contends, and Patent Owner does not dispute, that Thorsen discloses the subject matter of claim element 1.2 by disclosing an immiscible fluid (e.g., mineral oil) flowing through a main channel (e.g., the channels shown in Ex. 1003, Fig. 3.28, Box B) that is in fluidic communication with the sample inlet (shown in Ex. 1003, Fig. 3.28, Box B). Pet. 41–42 (citing Ex. 1003, 73–74, 76, Figs. 3.28, 3.29, 4.2, 4.4, 4.5).

Petitioner further contends, and Patent Owner does not dispute, that Thorsen's main channel is in a horizontal plane. Pet. 42–43 (citing Ex. 1003, 96–97, 103, 111, Figs. 3.28, 3.29, 4.2, 4.4, 4.5; Ex. 1008 ¶ 123; Ex. 1006 ¶¶ 31, 196–196, Fig. 8).

We agree with Petitioner's undisputed contentions and find that Thorsen discloses the subject matter recited in claim element 1.2.

*d) [1.3] partitioning the aqueous fluid with the immiscible fluid to form a plurality of droplets in the main channel, wherein at least one droplet comprises a sample*

Petitioner asserts that Thorsen discloses using a cross flow junction to form droplets in the main channel by partitioning aqueous fluid with an immiscible oil fluid and that at least one of the droplets in the main channel comprises a sample. Pet. 43–44 (citing Ex. 1003, 62, 73–74, 99–103, 109–

111, 113–116, Figs. 3.28, 3.29, 4.1, 4.2, 4.4). Other than contending Thorsen does not disclose a “sample,” Patent Owner does not dispute that Thorsen discloses the subject matter recited in claim element 1.3.

We disagree with Patent Owner’s argument that Thorsen does not disclose a “sample” for the reasons stated above in Section I.E.1.b. We are persuaded by Petitioner’s contentions and find that Thorsen Chapters 3 and 4 each disclose the subject matter recited in claim element 1.3.

- e) *[1.4] flowing the droplets toward a downstream separation chamber that is in fluidic communication with the main channel,*

Petitioner asserts that Thorsen discloses flowing droplets toward the incubation chamber in Chapter 3 and discloses flowing droplets to outlet wells that are found in both the microfluidic device having an incubation chamber disclosed in Chapter 3 and the microfluidic device having a serpentine channel as disclosed in Chapter 4, and that the incubation chamber and the outlet wells are each independently “a downstream separation chamber that is in fluidic communication with the main channel” as recited in claim element 1.4. Pet. 44–47.

Patent Owner responds that neither Thorsen’s incubation chamber nor outlet wells are separation chambers because Petitioner has not sufficiently shown that droplets and oil will necessarily separate based on their different densities inside the incubation chamber or the outlet wells. *See, e.g.,* PO Resp. 25–33.

We disagree with Patent Owner’s argument because it is based upon a claim construction of “separation chamber” that we did not adopt. As noted above, we adopted Patent Owner’s proposed construction of “separation

chamber” as a “chamber sized to accommodate multiple droplets and an immiscible fluid in separated form.”

Petitioner has provided sufficient evidence that both Thorsen’s incubation chamber and outlet wells are “separation chambers” because both constitute a chamber sized to accommodate multiple droplets and an immiscible fluid in separated form.<sup>7</sup>

Petitioner persuasively shows that Thorsen’s incubation chamber is sufficiently sized to accommodate multiple droplets and immiscible fluid in separated form. For example, Petitioner points to Figure 3.29A of Thorsen, which depicts multiple droplets in mineral oil entering and accumulating in Thorsen’s incubation chamber. Pet. 46; Ex. 1003, Fig. 3.29A; *see also* Ex. 1003, 99 (stating that Thorsen’s incubation chamber has a “large (~500  $\mu\text{m}$ ) high cavity”), 110 (stating “thousands” of red and green droplets were formed and that the formed droplets entered the microcavity, where they slowed down and formed a mixed cluster of droplets).

Petitioner also persuasively shows that Thorsen’s outlet wells are sufficiently sized to accommodate multiple droplets and immiscible fluid in separated form. For example, Petitioner also points to Thorsen’s disclosure that water droplets in mineral oil collected in Thorsen’s outlet wells. Pet. 46–47 (citing Ex. 1003, 91–92, 95–97, Figs, 4.1, 4.2); *see also* Ex. 1003, 111 (stating that thousands of droplets in mineral oil collected in Thorsen’s outlet wells).

Thus, for the foregoing reasons, we agree with Petitioner that Thorsen discloses the subject matter recited in claim element 1.4.

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<sup>7</sup> Whether both Thorsen’s incubation chamber and outlet wells disclose “separating” droplets as required by claim element 1.7 is addressed below.

*f) [1.5] wherein the separation chamber has a wider cross-section than the main channel cross-section and [1.6] the separation chamber is disposed perpendicular to the main channel; and*

Petitioner contends that both Thorsen's incubation chamber and outlet wells are each separation chambers that have a wider cross section than the main channel cross-section, as required by claim element 1.5 and that Thorsen's incubation chamber and outlet wells are each disposed perpendicular to the main channel, as required by claim element 1.6.

We are persuaded by Petitioner's contentions. For example, we are persuaded by Petitioner's argument and evidence that Thorsen's incubation chamber (separation chamber) has diameter of approximately of 200  $\mu\text{m}$  and a height of approximately 500  $\mu\text{m}$  and, therefore, has a wider cross-section than, and is disposed perpendicular to, Thorsen's main channel, which has a cross-section of approximately 100  $\mu\text{m}$ . *See, e.g.*, Pet. 50–52 (citing Ex. 1003, 16, 44, 84, 80, 99, 103, Figs. 3.28, 3.29, 4.1; Ex. 1008 ¶¶ 139–143).

We are also persuaded by Petitioner's argument that Thorsen's outlet wells (separation chamber) have a wider cross-section than, and are disposed perpendicular to, Thorsen's main channel. Pet. 50–53 (citing Ex. 1003, 91–92, 95–97, 109–111, 115, Figs. 3.28, 3.29, 4.1, 4.2; Ex. 1008 ¶¶ 145–149). For example, Petitioner persuasively shows that Thorsen's outlet wells have a wider cross-section than the main channel because the main channel is wide enough to accommodate only one droplet, while the outlet well is large enough to accommodate thousands of droplets. *See, e.g.*, Pet. 51 (citing Ex. 1003, 109–111, 115, Fig. 4.2). We are also persuaded by Petitioner's argument, supported by the undisputed declaration testimony of Dr. Fair, that Thorsen's outlet wells, which have an open top, must extend up and out

of the plane of the main channel in order for the chip to not leak droplets out of the bottom when the channels are closed with a glass cover slip.

Pet. 52–53 (citing Ex. 1003, 79–83); Ex. 1008 ¶¶ 147–149.

Patent Owner responds that Thorsen’s outlet wells are not disposed perpendicular to the main channel because Thorsen does not disclose the design or dimensions of the open structures and because there are well structure designs that are not perpendicular to a main channel. PO Resp. 33–34 (citing Ex. 2016 ¶¶ 132–135; Ex. 2017, 69:2–18).

We disagree with Patent Owner’s argument. We are persuaded by Petitioner’s argument that Thorsen’s outlet wells were fabricated by punching through multiple layers of the microchip (i.e., the thick upper layer of PDMS and the thin lower layer of PDMS), whereas the main channel is only patterned only along the thin bottom layer. Pet. Reply 14; Ex. 1003, 98–102, Fig. 3.27. Patent Owner admits that Thorsen fabricated the openings (i.e., outlet wells) in the devices by punching holes in the microchip itself at the channel ends, as was standard practice at the time. PO Resp. 2. Thus, because the outlet well was formed by punching through the thick upper layer on top through to the thin lower layer where the channel is located, we find the outlet well extends perpendicular to the channel formed on the bottom layer of the microchip.

Thus, we find Thorsen’s incubation chamber and outlet wells satisfy the subject matter recited in claim elements 1.5 and 1.6.

g) *[1.7] separating the plurality of droplets from the immiscible fluid in the separation chamber based on the different densities of the droplets and the immiscible fluid.*

Petitioner contends that Thorsen discloses separating droplets as required by claim element 1.7 in both Thorsen's incubation chamber and in its outlet wells. Pet. 55–56. Patent Owner opposes. PO Resp. 25–33, 35.

We are persuaded by Petitioner's contentions.

*(1) separating droplets in an incubation chamber*

Petitioner argues that Thorsen discloses separating a plurality of droplets from immiscible fluid in its *incubation chamber* based on the different densities of the droplets and immiscible fluid. Pet. 55 (citing Ex. 1003, 76, 80–84, 100–103, 119, Figs. 3.28, 3.29).

We are persuaded by Petitioner's contentions. Thorsen discloses aqueous droplets in mineral oil, which is less dense than water. We are persuaded by Petitioner's arguments that, because the droplets and oil are of different densities, Thorsen's droplets will sink relative to the less dense mineral oil based on their density, and that this is depicted in Thorsen Figure 3.29. Pet. 55; *see also* Ex. 1008 ¶ 51 (describing the different densities of water and mineral oil). In particular, Petitioner persuasively shows that Figure 3.29 of Thorsen discloses aqueous droplets, which are more dense than the surrounding mineral oil (an immiscible fluid), that have entered and settled to the bottom of the Thorsen's incubation chamber based on density. Pet. 55 (citing Ex. 1003, 76, 80–84, 100–103, 119, Figs. 3.28, 3.29); *see also* Pet. 52 (stating Figure 3.29 shows the droplets in the incubation chamber sinking down against the microscope slide floor). Therefore, Petitioner persuasively shows that Thorsen discloses separating the plurality of droplets (aqueous droplets) from the immiscible fluid

(mineral oil) in the separation chamber (incubation chamber) based on the different densities of the droplets and the immiscible fluid.

Patent Owner makes a number of arguments to support its contention that there is no separation of droplets in Thorsen's incubation chamber. PO Resp. 25–28. These arguments are not persuasive.

First, Patent Owner contends that because there is a steady state flow of droplets into the incubation chamber that is the same as the flow out of droplets out of the chamber, there is no separation of oil from the droplets. *Id.* at 26 (citing Ex. 2016 ¶¶ 117–121). We disagree with Patent Owner because Petitioner has provided persuasive evidence that droplets separate out from the oil and settle onto the bottom of the incubation chamber while *in the incubation chamber*. Indeed, even Patent Owner admits that Figure 3.29 “shows a ‘clump’ of droplets at the bottom of the chamber.” *Id.* at 27; *see also id.* (stating that not all of the droplets are resting on the bottom of the incubation chamber as there are multiple layers of droplets); *see also* Ex. 2016 ¶ 121 (stating that Figure 3.29 does not show “*all* [droplets] resting on the bottom,” but not disputing that the figure shows *some* droplets resting on the bottom (emphasis added)). Thus, Petitioner has sufficiently shown that Thorsen discloses separating droplets from immiscible fluid based on density in the incubation chamber by disclosing that the water droplets settled in clumps in the bottom of the incubation chamber before the droplets flow out of the incubation chamber.

To the extent Patent Owner contends that Thorsen does not disclose separating droplets because oil remains mixed in between the droplets, we disagree. *See* PO Sur-reply 6 (stating “there can be no separation when oil remains mixed in between the droplets while in the incubation chamber”). As described above, Petitioner has sufficiently shown that Thorsen discloses

separating aqueous droplets from the immiscible mineral oil fluid in its incubation chamber based on the different densities of the droplets and the oil by disclosing that the water droplets have settled to the bottom of the incubation chamber.

Second, Patent Owner contends that the '722 patent explains that the “purpose of the separation chamber is to separate droplets from the immiscible fluid so that they may be collected” and that “[s]uch collection cannot occur in the incubation chamber.” PO Resp. 26–27 (citing Ex. 2016 ¶¶ 117–121). This argument is not persuasive because we construed a “separation chamber” to mean a “chamber sized to accommodate multiple droplets and an immiscible fluid in separated form.” Claim 1 does not require collection of droplets, let alone that any collection of droplets occur within the separation chamber.

Third, Patent Owner contends that Thorsen teaches that different oils may be used in its devices and that if the selected oil has the same density as water, the droplets will not settle to the bottom, but rather “will be mixed with the oil as they are dispersed throughout the incubation chamber.” *Id.* (citing Ex. 2016 ¶¶ 117–121). This argument is not persuasive as it ignores Thorsen’s disclosure of mineral oil, which is denser than water, and that water droplets settled to the bottom of the incubation chamber as shown in Figure 3.29.

Therefore, Petitioner persuasively shows that Thorsen discloses separating the plurality of droplets (aqueous droplets) from the immiscible fluid (mineral oil) in the separation chamber (incubation chamber) based on the different densities of the droplets and the immiscible fluid.

(2) *separating droplets in outlet wells*

Petitioner also contends Thorsen discloses separating droplets in its outlet wells as required by claim element 1.7<sup>8</sup> because Thorsen “discloses an outlet well that has a volume sufficient for the droplets to move relative to the oil phase such that the denser droplets will sink to the bottom of the outlet well while the less dense mineral oil floats to the top.” Pet. 55–56 (citing Ex. 1003, 90–92, 96, Figs. 4.2; Ex. 1008 ¶¶ 156–159).

We are persuaded by Petitioner’s contentions. In particular, Petitioner persuasively shows that Thorsen’s outlet wells have a volume sufficient to accumulate “thousands” of droplets. Pet. 55 (citing Ex. 1003, 90–92, 96, Fig. 4.2). We are also persuaded by Petitioner’s argument, supported by the persuasive testimony of Dr. Fair, that this volume is sufficient for the droplets to move relative to the oil phase such that the denser droplets will sink to the bottom of the outlet well while the less dense mineral oil will float to the top. Pet. 56 (citing Ex. 1008 ¶¶ 156–159; Ex. 1026, 21–22).

Patent Owner makes a number of arguments to support its contention that there is no separation of droplets in Thorsen’s outlet wells. PO Resp. 28–33. These arguments are not persuasive.

First, Patent Owner contends that Petitioner’s argument that Thorsen’s outlet wells are separation chambers is undermined by Petitioner’s own expert who testified during deposition that he was not asserting that outlet wells were separation chambers. PO Resp. 28–29 (citing Ex. 2017, 80:19–81:22; Ex. 2016 ¶¶ 123).

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<sup>8</sup> Petitioner’s argument that Thorsen discloses using its outlet wells for *collecting* separated droplets as required by claim 2 is addressed below in Section II.E.2.

We disagree with this argument because we are persuaded by Petitioner's argument that the cited portion of Dr. Fair's testimony is directed to his opinion as to whether Thorsen's device discloses a "separation chamber" under a construction of that term that requires the separation chamber to be "substantially enclosed," a construction that is not asserted in the present proceeding. Pet. Reply 10–11; *see also* Ex. 2017, 77:2–5 (Dr. Fair asked if Thorsen discloses a separation chamber "using the 10X construction of separation chamber where the chamber has to be substantially enclosed"); *see also* Ex. 2017, 81:19–82:3 (Dr. Fair providing testimony that Thorsen's incubation chamber "meets 10X's claim construction"). As such, we disagree with Patent Owner that Dr. Fair testified during his deposition that he was not asserting that outlet wells were separation chambers.

Second, Patent Owner contends that Thorsen does not expressly disclose separating droplets from immiscible fluid in its outlet wells and, as such, Petitioner's argument is based on inherency. PO Resp. 29. Patent Owner contends that Thorsen's outlet wells cannot serve as an anticipatory reference because Thorsen states that "different oils may be used, including oils with the same or substantially similar densities as water." PO Resp. 29 (citing Ex. 2016 ¶ 124). We disagree with this argument because it ignores Thorsen's disclosure of mineral oil, which is less dense than water droplets. *See, e.g.*, Ex. 1003, 58, 91, 115 (describing use of water droplets in mineral oil). We are persuaded by Dr. Fair's testimony that mineral oil has a lower density than water. *See, e.g.*, Ex. 1008 ¶ 51 (stating water has a density of 1 g/cm<sup>3</sup> while mineral oil has a lower density of between 0.8 and 0.9 g/ml). Whether Thorsen also discloses use of an oil having the same density as water, does not negate its disclosure of aqueous droplets in mineral oil.

Third, Patent Owner contends that Thorsen does not disclose anything about the dimensions or design of its outlet wells and if Thorsen's outlet well is in the same plane as the microchannel (as opposed to the outlet well that is perpendicular to the microchannel), then droplets will not separate from the surrounding oil. PO Resp. 29–30 (citing Ex. 2017, 69:2–18; Ex. 2016 ¶¶ 125–126). Patent Owner also points to Dr. Fair's testimony that, if an outlet well has the same height as the microchannel, then it would be very difficult to do separation of oil and liquid and droplets. *Id.* (citing Ex. 2017, 69:2–18). We disagree with this argument because we disagree with Patent Owner's contention that Thorsen's outlet well has the same height as the microchannel. Rather, as explained above in Section II.E.1.f, we are persuaded by Petitioner's argument and evidence that Thorsen discloses an outlet well that is perpendicular to the microchannel and has a volume sufficient to allow separation of droplets. Patent Owner's argument is also refuted by the evidence about how Thorsen's outlet wells are made. Patent Owner agrees that the outlet wells are made by punching holes in the microchip at the ends of the channels. PO Resp. 2. We are persuaded by Petitioner's argument, supported by the persuasive testimony of Dr. Fair, that Thorsen's fabrication teachings confirm that the outlet wells have a greater height than the microchannel due to punching through the entire PDMS layer. Pet. Reply 14, 22 (citing Ex. 1003, 98–102); Ex. 1074 ¶¶ 34–37.

Therefore, Petitioner persuasively shows that Thorsen discloses separating the plurality of droplets (aqueous droplets) from the immiscible fluid (mineral oil) in the separation chamber (outlet wells) based on the different densities of the droplets and the immiscible fluid. \_

For the reasons stated above, Petitioner persuasively shows that Thorsen discloses separating the droplets from the immiscible fluid based on density in both Thorsen's incubation chamber and outlet wells as required by claim element 1.7.

*h) Conclusion*

As described above, Petitioner has sufficiently shown that Thorsen discloses the subject matter recited in the preamble and every limitation of claim 1 and therefore has shown by a preponderance of the evidence that claim 1 is unpatentable under 35 U.S.C. § 102.

*2. Claim 2*

Claim 2, which depends on claim 1, further requires "collecting the separated droplets." Ex. 1001, 88:23–24.

Petitioner asserts that Thorsen discloses the limitations of claim 2 because Thorsen discloses microfluidic systems, including Thorsen's incubation chamber system of Chapter 3, that include "outlet wells for collecting droplets." Pet. 57–58 (citing Pet. 46–47, 52–53; Ex. 1026, 23); *see also* Pet. 46–47 (stating that Thorsen discloses that the red/green droplets described in Chapter 3 collect in outlet wells (citing Ex. 1003, 91–92, 95–97, Figs. 4.1, 4.2)); *see also* Pet. 52–53 (stating that Thorsen discloses collecting thousands of droplets in each well (citing Ex. 1003, 91–92, 95–97, Figs. 4.1, 4.2)); *see also* Pet. 47 ("Thorsen also discloses that the droplets will collect in the well (citing Ex. 1003, 95–97, Figs. 4.1, 4.2)).

We agree with Petitioner's contention that Thorsen discloses collecting the droplets in its outlet wells. Indeed, Thorsen expressly refers to its outlet wells as "*collection wells*" and states that "thousands" of droplets *collect* in each of them. Ex. 1003, 110–111 (emphases added); Pet. Reply 19 (citing Ex. 1003, 110–111).

Patent Owner contends that Thorsen does not teach the subject matter of claim 2 because Thorsen does not “disclose collection of droplets *from*” the outlet wells. PO Resp. 37; *see also id.* at 35–38 (asserting, *inter alia*, Petitioner has not provided sufficient evidence that micropipettes would be used to collect droplets at Thorsen’s outlet wells). We disagree with Patent Owner’s argument because Petitioner has sufficiently shown that Thorsen discloses collecting droplets *in* the outlet wells, which is sufficient to satisfy the subject matter recited in claim 2.

We determine that the “collecting” droplets step as recited in claim 2 encompasses “collecting” droplets in a well and does not require removal of the droplets from the well. Our determination is supported by the Specification of ’722 patent, which describes collecting droplets *in* wells or reservoirs prior to removal. For example, the ’722 patent states that a “*well or reservoir*” can be used “for *collecting and containing droplets* detected to have a specific predetermined characteristic in the detection module.” Ex. 1001, 44:58–61 (emphasis added); *see also id.* at 44:46–49 (stating a “well or reservoir” may be used “to allow collection or disposal (collection module or waste module, respectively) of the molecules, cells, small molecules or particles.” The ’722 patent further states that the “sorted cells, particles or molecules can be collected from the outlet channels *in collection modules* . . . and used as needed. *Id.* at 42:56–59 (emphasis added).

That “collecting” and “removing” can be performed in two separate steps is also supported by the ’722 patent’s disclosure that the “collected cells, particles or molecules can be removed from the device or reintroduced to the device for additional coalescence, analysis and sorting.” *Id.* at 42:59–61.

Patent Owner also contends Petitioner’s arguments concerning the collection of droplets at outlet wells are undermined by Dr. Fair’s testimony that he had not considered what happens at the outlet wells. PO Resp. 36 (quoting Ex. 2017, 80:19–81:22). This argument is not persuasive because the cited portion of Dr. Fair’s testimony is directed to his opinion as to whether Thorsen’s “incubation chamber” constitutes a “separation chamber” under Petitioner’s construction of that term and satisfies the limitations recited in claim elements 1.6 and 1.7 and is not directed to the limitations recited in claim 2. *See* Ex. 2017, 80:19–81:22.

Neither party addresses whether “collecting the separated droplets,” as recited in claim 2, requires collecting only separated droplets without collecting immiscible fluid. We determine that claim 2 is not so restricted, and it encompasses collecting separated droplets together with immiscible fluid. Although the ’722 Patent discloses configurations in which “substantially only droplets” exit the separation chamber, we do not read this limitation from the Specification into the claim. Ex. 1001, code (57), 3:46–48, 4:56–59, 21:59–63, 55:48–52, 53:33–34, 53:41–44. Furthermore, the Specification teaches that droplets “will exit the chamber . . . into the outlet . . . leaving a large part of the oil behind,” which indicates that a small part of the oil (immiscible fluid) will exit the chamber with the droplets. *Id.* at 54:50–53.

As such, Petitioner has sufficiently shown that Thorsen discloses the subject matter recited in claim 2 and has shown by a preponderance of the evidence that claim 2 is unpatentable under 35 U.S.C. § 102 over Thorsen.

### 3. *Claim 3*

Claim 3, which depends on claim 1, further recites “wherein the separated droplets are collected in a vessel.” Ex. 1001, 88:25–26. Petitioner

contends Thorsen anticipates claim 3 because “Thorsen discloses microfluidic systems that include outlet wells for collecting droplets as described for limitations [1.4]–[1.6].” Pet. 57–58 (citing Ex. 1026, 23); *see also* Pet. 47 (stating Thorsen discloses that “the droplets will collect in the well” and citing, *inter alia*, Ex. 1003 91–92, 95–97).

Patent Owner opposes. PO Resp. 38–39 (asserting claim 3 is patentable for the same reasons as claim 1 and because “neither Thorsen Chapters 3 nor 4 discloses collection of separated droplets in a ‘vessel’”).

We are persuaded by Petitioner’s argument, supported by Dr. Fair’s testimony, that Thorsen discloses the subject matter of claim 3 by disclosing that sorted droplets are collected in an outlet well. Pet. 57–58; *see also* Ex. 1008 ¶ 103 (stating Thorsen discloses generating droplets that are then carried downstream through (optionally) an incubation chamber before “collecting in an outlet well”). Patent Owner does not assert that an outlet well is not a vessel. *See* PO Resp. 38–39. Although the ’722 patent does not define a “vessel,” the ’722 patent does state that vessels are used for collecting droplets. *See, e.g.*, Ex. 1001, 54:66–67 (stating the opening of a nozzle “may lead to a vessel or container for collecting droplets”); *see also id.* at 4:23–22 (identifying a “vessel for the collection of portioned portions”). We agree with Petitioner that Thorsen’s outlet wells are used to collect droplets.

Accordingly, Petitioner has persuasively shown that Thorsen discloses the subject matter recited in claim 3 and therefore has shown by a preponderance of the evidence that Thorsen anticipates claim 3.

#### 4. *Claims 10 and 11*

Claim 10, which depends on claim 1, recites “where in the sample comprises a biological material.” Claim 11, which depends on claim 10,

recites “wherein the biological material is selected from the group consisting of a tissue, cell, particle, protein, antibody, amino acid, nucleotide, small molecule, and pharmaceutical.”

Petitioner asserts that Thorsen discloses the subject matter of claims 10 and 11 by “specifically listing small molecules, proteins, DNA, and single cells” as samples and also by disclosing a chemical screening assay in which the sample is an *E. coli* cell. Pet. 64–65 (citing Ex. 1003, 10, 20–21, 114–120, Fig. 4.4)).

Other than the arguments discussed above as to whether Thorsen discloses a “sample,” Patent Owner does not present any additional arguments directed to claims 10 or 11. *See generally* PO Resp. 39.

For the same reasons discussed above in Section II.E.1.b, we are persuaded by Petitioner’s argument that Thorsen discloses the subject matter recited in claims 10 and 11. For example, we agree with Petitioner’s argument that Thorsen discloses using enzymes, proteins, DNA, and single cells (Ex. 1003, 10, 20–21) as samples and additionally discloses use of *E. coli* cells as a sample, and therefore discloses using biological material as a sample as recited in claim 10 and using a cell as a sample as recited in claim 11.

As such, Petitioner has shown by a preponderance of the evidence that claims 10 and 11 are unpatentable under 35 U.S.C. § 102 over Thorsen.

#### 5. *Independent Claim 14*

The foregoing analysis for claim 1 applies equally to claim 14. As discussed above, claim 14 differs from claim 1 only by reciting “reducing sample loss” instead of “reducing contamination” in the preamble and by omitting a recitation in claim element 1.3.

We agree with Petitioner's undisputed contention that Thorsen discloses the preamble of claim 14 ("method of reducing sample loss associated with sample handling") by stating its microfluidic systems have the ability to "reduce individual assay volumes to picoliters" and to "reduce[] reagent consumption." Pet. 28 (quoting Ex. 1003, 20).

As such, Petitioner has sufficiently shown that Thorsen discloses the subject matter recited in claim 14 and has shown by a preponderance of the evidence that claim 14 is unpatentable under 35 U.S.C. § 102 over Thorsen.

*F. Asserted Obviousness of Claims 1–4, 10, 11, and 14 over Thorsen*

Petitioner contends that claims 1–4, 10, 11, and 14 would have been obvious under 35 U.S.C. § 103(a) over Thorsen. For the reasons stated below, we determine that Petitioner has shown by a preponderance of the evidence that claims 1–4, 10, 11, and 14 would have been obvious over Thorsen.

*1. "Sample"—Claims 1, 10, 11, and 14*

Petitioner asserts that to the extent Thorsen does not expressly teach use of a sample (e.g., a biological material such as molecules, DNA, enzymes or other proteins, or cells) in connection with the incubation chamber of Chapter 3, that such a disclosure would have been obvious to a POSA. Pet. 34–37, 64–65. Patent Owner opposes. PO Resp. 23–25.

As stated above, we agreed with Petitioner that Thorsen discloses using samples, such as molecules, DNA, enzymes or other proteins, and single cells, a sample as required by claims 1, 10, 11, and 14. We also agree with Petitioner that, to the extent any such disclosure is not explicit, that it would have been obvious to a POSA that other samples, such as molecules, DNA, enzymes or other proteins, and single cells, could be used in the incubation chamber system disclosed in Chapter 3. Pet. 36–37 (citing

Ex. 1003, 20, 21, 52, 54, 111, 112, 114, 147). Thorsen expressly states its disclosed systems allow “thousands of single cells or small molecules such as DNA or proteins [to] be individually compartmentalized and examined.”

Ex. 1003, 21.

Therefore, we find Thorsen teaches or suggests a “sample” as recited in claims 1, 10, 11, and 14.

2. *Claim 2*

Petitioner argues that claim 2 would have been obvious over Thorsen as Thorsen discloses the additional limitations recited in the dependent claim. Pet. 60.

We agree with Petitioner. Claim 2 depends from claim 1. As noted above in Section E.2, Thorsen discloses all of the limitations recited in claim 2. As noted above in Section F.1, Petitioner has sufficiently shown that claim 1 would have been obvious over Thorsen. Therefore, we determine that Petitioner establishes by a preponderance of the evidence that claim 1 would have been obvious over Thorsen, and that Thorsen discloses all of the limitations recited in claim 2, we also determine that claim 2 would have been obvious over Thorsen.

3. *Claims 3 and 4*

Claim 3, which depends on claim 1, further recites “wherein the separated droplets are collected in a vessel.” Ex. 1001, 88:25–26. Claim 4 depends on claim 3 and further requires that the “vessel is a PCR tube or a test tube.” *Id.* at 88:27–28.

Petitioner argues that claim 3, as well as claim 4, would have been obvious over Thorsen because it would have been obvious to use a micropipette to transfer the droplets collected in Thorsen’s output wells into a vessel, such as a PCR tube, a test tube, or another container, for further use

or processing. Pet. 58 (citing Ex. 1008 ¶¶ 104, 166–169); *see also* Pet. 53 (also asserting the collection of the droplets by pipette out of Thorsen’s outlet wells would have been obvious to a POSA in view of Thorsen). Petitioner contends, with supporting testimony by Dr. Fair, that a POSA “would know that the purpose of screening is often to collect the positive results for further use (e.g., by collecting the positive droplets from the outlet well by micropipette and transferring them to a sample test tube for subsequent use”). Pet. 21–22; Ex. 1008 ¶ 85.

Patent Owner argues that there is no evidence that a micropipette would be used with Thorsen’s outlet well and that a POSA would not have known to use a micropipette with Thorsen’s outlet well because Thorsen’s outlet well is not wide enough to insert a micropipette. *See, e.g.*, PO Resp. 47; *see also id.* at 35 (citing Ex. 2016 ¶ 135). In particular, Patent Owner contends Dr. Fair testifies that the smallest micropipette is 1 mm (1000 µm), which is much larger than the dimensions of the wells described in Thorsen. PO Resp. 37–38 (citing Ex. 2017, 159:13–16), 46 (stating there is no evidence Thorsen is enabled to allow collection of droplets using a pipette).

Petitioner responds that, to the extent Thorsen does not expressly disclose an outlet well large enough to accommodate a micropipette, it would have been well within the knowledge and skill of a POSA to produce an outlet well that would accommodate a micropipette tip, such as by using a commercially available 2 mm or 4 mm cork borer, or Thorsen’s disclosed ~5 mm punch. Pet. Reply 20–21 (citing Ex. 2016 ¶¶ 30–31; Ex. 1003, 44; Ex. 1006 ¶ 196 (identifying 2mm diameter wells); Ex. 1076, 2, 4–5 (identifying 4mm reservoir holes); *see also* Ex. 2016 ¶ 68 (stating that Exhibit 2033 describes techniques “common at the time” to “punch a hole through the PDMS at the end of channels”).

We agree with Petitioner that it would have been obvious to a POSA to transfer the droplets collected in Thorsen's outlet wells and move them into a vessel such as a PCR tube or test tube using a micropipette. *See, e.g.*, Pet. 55–61; Ex. 1008 ¶¶ 85, 106, 159–162. Petitioner provides persuasive argument and evidence, supported by the persuasive testimony of Dr. Fair that, after sorting droplets in a chemical screening reaction, a POSA would have collected the sorted droplets for further use or additional processing. Pet. 58 (citing Ex. 1008 ¶¶ 104, 166–169).

We are also persuaded by Petitioner's argument that Thorsen discloses that his fluorescence-based droplet sorter was only 98–99% accurate on a first pass, and that this disclosure provides additional motivation to a POSA to collect Thorsen's sorted droplets by micropipette for another round of additional sorting or other processing. Pet. 58–59 (citing Ex. 1003, 109–111; Ex. 1009 ¶¶ 104, 166–169). We are persuaded by Dr. Fair's testimony that a POSA would collect the sorted droplets, either for another round of additional sorting to improve accuracy, or for other processing. Ex. 1008 ¶ 162.

Patent Owner does not direct us to persuasive evidence rebutting Dr. Fair's testimony that using a pipette to remove droplets from an open well, such as Thorsen's open wells, would have been routine and well-known to a person of ordinary skill in the art. Ex. 1008 ¶¶ 106, 148–149, 161, 162. Although Patent Owner directs us to paragraphs 140 and 141 of Dr. Anna's testimony (PO Resp. 37–38 (citing Ex. 2016 ¶¶ 140, 141)), neither paragraph (nor the related paragraph 142) refutes Dr. Fair's testimony regarding what was known in the art about the use of micropipettes to collect droplets from the open wells of a microfluidic device.

To the extent Thorsen does not expressly disclose an outlet well large enough to accommodate a micropipette tip<sup>9</sup>, we agree with Petitioner that it would have been obvious to a POSA to modify the outlet well of Thorsen to provide an outlet well large enough to accommodate a micropipette tip in order to allow the collection of droplets that contain the desired (screened for) product for further use. Pet. Reply 21 (citing Pet. 21–22, 56, 58–59, 68–69; Ex. 1008 ¶¶ 85, 106, 162). We are persuaded by Petitioner’s argument that Thorsen discloses sorting (physically separating) droplets and that it would have been obvious to use a micropipette to collect and transfer the sorted droplets, as a “standard industry way” of moving solutions containing multiple droplets from wells. Pet. 21–22, 56, 58–59, 68–69; Fair, ¶¶ 85, 106, 162; Pet. Reply 20–22; *id.* at 20 n.5 (citing Ex. 2017, 42:21–43:4, 140:21–142:2).

With respect to claim 4, Petitioner has sufficiently shown that a PCR tube is a well-known vessel for collecting small volumes of liquid and that it would have been obvious to a POSA to move the collected droplets to a PCR tube as a standard vessels for collecting liquids. Pet. 59–60 (citing Ex. 1066, 6–7; Ex. 1008 ¶¶ 104, 166–169). Therefore, we determine

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<sup>9</sup> Thorsen does not expressly disclose the width of its outlet wells. Petitioner and Patent Owner dispute whether Thorsen’s disclosure of the methods used to fabricate its outlet wells provides a disclosure of outlet wells having a sufficient size to accommodate a micropipette tip. Pet. Reply 19–21; PO Sur-reply 9–13. We need not reach a conclusion as to whether Thorsen’s fabrication methods discloses whether Thorsen’s outlet wells are sufficiently large to accommodate a pipette because, as discussed above, we agree with Petitioner that it would have been obvious for a POSA to create an outlet well large enough to accommodate a micropipette in order to collect the droplets for further use and processing.

Thorsen teaches or suggests collecting droplets in a vessel, such as PCR tubes, as required by claims 3 and 4.

4. *Secondary Considerations*

Patent Owner contends that secondary considerations, including long-felt need, commercial success, praise, and acquiescence and licensing weigh in favor of a finding of nonobviousness of the '722 Patent claims. PO. Resp. 49–56.

a) *Presumption of Nexus*

Patent Owner asserts that its “ddPCR™ platform . . . practices the '722 patent.” PO Resp. 49. As support for this assertion, Patent Owner relies on a statement that “[t]he Bio-Rad Digital PCR Systems and/or their use is covered by claims of U.S. patents,” including the '722 Patent and eight other patents. *Id.* at 49–50 (citing Ex. 2018 (Patent Owner’s standard terms and conditions of sale)). Patent Owner also asserts that “[t]he novel features of the '722 patent are repeatedly referenced in Patent Owner’s instruction manuals and are critical to the products’ workflows.” *Id.* at 50 (citing Exs. 2010, 2011). Patent Owner directs us to portions of these manuals that instruct users how to transfer droplets out of the separation chamber of a cartridge. *Id.* (citing Ex. 2010, 18; Ex. 2011, 18). Based on these assertions, Patent Owner contends that “the secondary considerations . . . related to Patent Owner’s products have a direct nexus to the claims of the '722 Patent.” *Id.*

“In order to accord substantial weight to secondary considerations in an obviousness analysis, the evidence of secondary considerations must have a nexus to the claims, i.e., there must be a legally and factually sufficient connection between the evidence and the patented invention.” *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019) (internal quotes

omitted); *see also Lectrosonics, Inc. v. Zaxcom, Inc.*, Case IPR2018-01129, Paper 33 at 32 (PTAB Jan. 24, 2020) (precedential) (“For objective indicia of nonobviousness to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention.”). There is a rebuttable presumption of nexus “when the patentee shows that the asserted objective evidence is tied to a specific product and that product ‘embodies the claimed features, and is coextensive with them.’” *Fox Factory*, 944 F.3d at 1373 (citations omitted); *Lectrosonics*, Paper 33 at 32.

Patent Owner does not present an analysis demonstrating that its products are coextensive (or nearly coextensive) with the challenged claims of the ’722 Patent. At best, Patent Owner directs us to instructions for transferring droplets from outlet wells to a PCR plate. PO Resp. 50 (citing Ex. 2010, 18; Ex. 2011, 18). Even if these instructions were sufficient to establish that Patent Owner’s products have a “separation chamber,” there are numerous other claim limitations that are not addressed by Patent Owner’s evidence of nexus. Although Patent Owner relies on its standard terms and conditions listing the ’722 Patent among eight other patents (PO Resp. 49–50 (citing Ex. 2018)), a simple patent listing is not enough to show coextensiveness or nexus.

Accordingly, Patent Owner has not shown that its products are entitled to a presumption of nexus.

*b) Patent Owner’s Acquisition of ’722 Patent*

Patent Owner asserts that Patent Owner acquired RainDance and all of its intellectual property in January 2017, including the ’722 patent, “demonstrating the value that has been placed on the protected features of the ’722 patent.” PO Resp. 49 (citing Ex. 2014 (press report titled, “Bio-Rad

to Acquire RainDance Technologies”)). Patent Owner does not present arguments or evidence as to the value that was ascribed to the ’722 Patent or the technology covered by the challenged claims in the context of Patent Owner’s acquisition of RainDance. Accordingly, we are not persuaded that Patent Owner has shown a nexus for this asserted secondary considerations evidence.

*c) Long-Felt Need*

Patent Owner asserts that “RainDance’s patented droplet system, which included features embodied in the ’722 patent, fundamentally enhances the way researchers and scientists study cell-based and cell-free biomarkers in cancer, infectious disease, and inherited disorders.” PO Resp. 50 (citing Ex. 2016 ¶ 181).

According to Patent Owner, its “ddPCR™ platform was heralded as a breakthrough that greatly advanced the capabilities of PCR” and was “rapidly adopted in the industry and led to an explosion of research.” PO Resp. 51–520 (citing Exs. 2001–2004). Based on this evidence, Patent Owner contends that “[t]he inventions of the ’722 patent fulfilled a long-term need for a means of isolating sample from the surrounding environment for further analysis using microfluidic droplets by means of the claimed separation chamber.” *Id.* at 52–53 (citing Ex. 2016 ¶ 185).

“A finding that a presumption of nexus is inappropriate does not end the inquiry into secondary considerations.” *Fox Factory*, 944 F.3d at 1375; *Lectrosonics*, Paper 33 at 33. “To the contrary, the patent owner is still afforded an opportunity to prove nexus by showing that the evidence of secondary considerations is the ‘direct result of the unique characteristics of the claimed invention.’” *Fox Factory*, 944 F.3d at 1373–74 (quoting *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996)); *Lectrosonics*, Paper 33 at 33.

Patentee must show a “nexus to the merits of the claimed invention,” meaning “some aspect of the claim not already in the prior art.”

*Lectrosonics*, Paper 33 at 33 (quoting *In re Kao*, 639 F.3d 1057, 1068–69 (Fed. Cir. 2011)).

We determine that Patent Owner has not demonstrated a nexus between the evidence relied upon to show long-felt need and the merits of the claimed invention. Patent Owner asserts that the evidence touts its ddPCR™ platform as “an easy-to-use alternative to the existing technology” that enabled researchers to publish numerous studies and “to detect rare targets with a level of precision that was just not possible with previous technologies.” PO Resp. 51–52 (citing Exs. 2001–2004). Patent Owner makes no attempt to show a nexus between the technology discussed in Exhibits 2001 to 2004 and the features recited in the challenged claims of the ’722 Patent.

*d) Commercial Success*

Patent Owner contends that its products that embody the ’722 Patent have been a commercial success, with the inventions disclosed in the ’722 Patent contributing to this success and representing “a significant improvement on the prior art that greatly advanced the capability of PCR and NGS [Next Generation Sequencing].” PO Resp. 53 (citing Exs. 2005–2009; Ex. 2016 ¶ 186).

Patent Owner also contends that Petitioner’s “products embodying the invention have been a commercial success.” PO Resp. 54 (citing and quoting Ex. 2012 (discussing number of instruments sold in total and to “top research institutions” and “global pharmaceutical companies” and associated revenue increases as of December 31, 2018 and June 30, 2019)).

For the reasons discussed above, Patent Owner has not shown that its products are entitled to a presumption of nexus. Nor has Patent Owner shown a nexus between the merits of the claimed invention and the evidence relied upon to show commercial success of its products or Petitioner's products. Although Patent Owner relies on Exhibits 2005 to 2009 and 2012, it does not show a nexus between this evidence and the unique features of the challenged claims.

*e) Praise by Others*

Patent Owner asserts that its ddPCR™ products have received “repeated accolades for their contributions to the field” and that its “ddSEQ™ system has also received wide acclaim.” PO Resp. 54–56 (citing Exs. 2005–2009). According to Patent Owner, “prior to its acquisition by Patent Owner, Raindance received praise from the industry for its own systems that incorporated the patented features of the ‘722 patent.” *Id.* at 55 (citing Ex. 2016 ¶ 192. Petitioner asserts that both Patent Owner's and Petitioner's products “have received praise because of their turn-key, easy-to-use workflows.” *Id.* at 56 (citing Ex. 2013).

For the reasons discussed above, Patent Owner has not shown that its products are entitled to a presumption of nexus. Nor has Patent Owner shown a nexus between the merits of the claimed invention and the evidence relied upon to show industry praise of Patent Owner's products, RainDance's products, or Petitioner's products. Although Patent Owner relies on Exhibits 2005–2009, and 2013, it does not show a nexus between this evidence and the unique features of the challenged claims. Furthermore, although Patent Owner discusses advantages of the patented inventions (PO Resp. 56), Patent Owner does not show that these advantages are the reasons Patent Owner's and Petitioner's products have received praise. Nor does

Patent Owner show that the evidence of industry praise or other asserted secondary considerations is tied to the novel features of the claimed invention or the claimed combination as a whole. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1331 (Fed. Cir. 2016); *Lectrosonics*, Paper 33 at 33.

### 5. Conclusion

As discussed above, we find that Thorsen discloses, teaches, or suggests the subject matter recited in claims 1–4 and 10–11. We have considered all of Patent Owner’s evidence of nonobviousness and find it unpersuasive. Accordingly, we balance Petitioner’s strong evidence of obviousness against Patent Owner’s alleged objective evidence of nonobviousness, we determine that a preponderance of the evidence supports Petitioner’s position that claims 1–4 and 10–11 are unpatentable under 35 U.S.C. § 103 over Thorsen.

#### *G. Asserted Obviousness of claims 1–7 and 10–17 over Thorsen and Ismagilov 119 or over Thorsen, Ismagilov 119, and Ismagilov 091*

Petitioner contends claims 1–7 and 10–17 would have been obvious over the combined teachings of (1) Thorsen 092 and Ismagilov 119 alone, which incorporates Ismagilov 091 by reference, or over the combined teachings of (2) Thorsen, Ismagilov 119 and Ismagilov 091. Pet. 2, 22–27, 37–41, 48–50, 54–55, 57.

For the reasons stated below, we determine that Petitioner has shown by a preponderance of the evidence that claims 5–7 and 12–13 would have been obvious over the combined teachings of Thorsen either in combination with Ismagilov 119 alone or with Ismagilov 119 and Ismagilov 091, but Petitioner has not shown by a preponderance of the evidence that claims 15–17 would have been obvious over the asserted art; we do not reach Petitioner’s contentions regarding claims 1–4, 10–11, and 14.

1. *Claims 1–4, 10–11, 14*

Having already determined that Petitioner establishes by a preponderance of the evidence that claims 1–4, 10, 11, and 14 are unpatentable, we do not address Petitioner’s additional grounds challenging these claims over the combined teachings of Thorsen, Ismagilov 119 or over Thorsen, Ismaagilov 119, and Ismagilov 091. *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”); *Boston Sci. Scimed, Inc. v. Cook Grp. Inc.*, 809 F. App’x 984, 990 (Fed. Cir. 2020) (nonprecedential) (“We agree that the Board need not address [alternative grounds] that are not necessary to the resolution of the proceeding.”).

2. *Claims 5–7*

Claim 5 depends from claim 3 and further requires “after the partitioning step, further comprising introducing one or more reagents to the droplets.” Ex. 1001, 88:29–31. Claim 6 depends from claim 5 and requires that the “one or more reagents are amplification reagents.” *Id.* at 88:32–33. Claim 7 depends from claim 6 and requires that the “amplification reagents are for a polymerase chain reaction.” *Id.* at 88:34–35.

Petitioner contends that claims 5–7 would have been obvious over Thorsen in combination with either Ismagilov 119 alone (which incorporates Ismagilov 091 by reference) or in combination with Ismagilov 119 and Ismagilov 091. Pet. 62–64 (citing Ex. 1004, 18:16–19, 27:53–58, 45:57–46:5, 47:22–34, 47:10–11; Ex. 1005 ¶¶ 21, 52, 54, 57, 119, 130; Ex. 1008 ¶¶ 175–178; Ex. 1017, 1317–1318).

Petitioner admits Thorsen does not disclose introducing a reagent to the droplet after the partitioning step but contends claim 5 would have been obvious over Thorsen in view of Ismagilov 091 and Ismagilov 119

(collectively “Ismagilov”), which each teach introducing a reagent to the droplet after the partitioning by disclosing merging droplets as a way to add reagents to droplets. Pet. 62–63 (citing Ex. 1004, 18:16–19, 27:53–58; Ex. 1005 ¶¶ 21, 54, 57, Ex. 1008 ¶ 175). Petitioner contends a POSA would have been motivated to combine Ismagilov’s teachings about creating merged droplets to add reagents with Thorsen’s system as an alternative way to add reagents to droplets rather than using Thorsen’s reagent (substrate) inlet channel in order to reduce cross contamination. Pet. 62; Ex. 1005 ¶ 21 (disclosing a “schematic illustration of a possible geometry for merging a plug . . . with a stream . . . to create[] a merged plug . . . without cross-contamination”). Petitioner further contends that Thorsen discloses using microfluidic devices for polymerase chain reaction applications and thus discloses the subject matter recited in claims 6 and 7. Pet. 63 (citing Ex. 1003, 52, 130); *see also* Pet. 63–64 (stating that the amplification reagents used in polymerase chain reactions were well-known since the 1980s). Petitioner further asserts that Ismagilov 091 also discloses the subject matter recited in claims 6 and 7 as it identifies polymerase chain reactions as an “autocatalytic reaction” and states that its devices and methods may be applied to autocatalytic reactions. Pet. 64 (citing Ex. 1004, 45:57–46:5, 47:10–11, 47:22–34).

Patent Owner does not dispute Petitioner’s contentions for claims 5–7. We are persuaded by Petitioner’s undisputed contentions as described above. We thus agree with Petitioner’s contentions that the combination of Thorsen and either Ismagilov 119 alone or in combination with Ismagilov 119 and Ismagilov 091 discloses the subject matter recited in claims 5–7 and that Petitioner has provided sufficient reasoning to combine the teachings to arrive at the claimed subject matter.

3. *Claims 12 and 13*

Claim 12 depends from claim 11 and requires that “the biological material further comprises one or more labels.” Claim 13 depends from claim 12, and further requires that “the one or more labels are DNA tags, dyes, quantum dot, or combination thereof.” Claim 1, from which claims 12 and 13 ultimately depend, require providing “an aqueous fluid comprising a sample through a sample inlet.” Ex. 1001, 88:4–5.

Petitioner contends Thorsen in combination with Ismagilov 091 renders obvious claims 12 and 13. Pet. 65–67 (citing Ex. 1003, 114–120, Figs. 4.4, 4.5). Petitioner further contends that Thorsen discloses use of *E. coli*, a biological material, that has been modified to express pNB esterase, which will convert a reagent into a detectable fluorescein product, a glowing fluorescent dye. Pet. 65–66 (citing Ex. 1003, 116–117). Petitioner further contends that *E. coli* cells that express the enzyme comprise a label that comprises a dye, namely the detectable fluorescein product that labels the droplets containing an *E. coli* cell expressing the enzyme with a glowing green dye. Pet. 66 (citing Ex. 1003, 116–120, Figs. 4.4, 4.5).

Petitioner admits that the experiment disclosed in Thorsen involving providing the modified *E. coli cells* expressing an enzyme through one sample inlet and the fluorescent label substrate through a second inlet, but contends that it would have been obvious to provide an *E. coli* cell comprising a fluorescent dye label through a single inlet in view of the combined teachings of Thorsen and the Ismagilov references. Pet. 67. Petitioner points to Thorsen’s discussion of the “crosstalk” problems that may arise from use of two separate inlets and to Ismagilov’s teaching of using cells that already contain an optically detectable label protein (i.e., a dye). *Id.* (citing Ex. 1003, 114–115, 121–123, Figs. 4.1, 4.7; Ex. 1004,

31:35–40, 34:54–32:2; Ex. 1008 ¶¶ 181–185). Petitioner contends that a POSA would have been motivated to use a cell containing a label as a single sample rather than using two separate inlets in order to minimize cross talk. *Id.* (citing Ex. 1004, 31:35–40, 34:54–32:2; Ex. 1008 ¶¶ 181–185).

Other than asserting the cited art does not render obvious the base claims from which claims 12 and 13 depend, Patent Owner does not dispute Petitioner’s contentions regarding claims 12 and 13. *See generally* PO Resp.

We are persuaded by Petitioner’s contentions as described above and find that Petitioner has sufficiently shown that Thorsen in combination with either Ismagilov 119 alone or in combination with Ismagilov 119 and Ismagilov 091 discloses the limitations of claims 12 and 13 and has provided sufficient reason to combine the teachings of the references to arrive at the claimed subject matter.

#### 4. *Claims 15, 16, and 17*

Claim 15 depends from claim 14 and recites “after the separation step, further comprising placing the droplets onto a second continuous phase carrier fluid.” Ex. 1001, 89:4–6. Claim 16 depends from claim 15 and recites: “wherein the second continuous phase carrier fluid comprises a destabilizing surfactant.” *Id.* at 89:7–8. Claim 17 depends from claim 15 and recites: “after the placing step, further comprising destabilizing the droplets.” *Id.* at 89:9–10.

Petitioner contends that claims 15, 16, and 17 would have been obvious over Thorsen in combination with the Ismagilov references. Pet. 68–69 (citing Ex. 1001, 48:18–27; Ex. 1004, 1:24–28, 3:36–41, 37:23–45, 50:51–52, 61:19–20, 64:65:15; Ex. 1005 ¶ 117; Ex. 1008 ¶¶ 54–56, 104, 186–189).

Petitioner contends that a POSA would have known that, after running the chemical screening assays disclosed in Thorsen, that it would have been necessary to break the emulsion to collect the contents of the droplets for further use. Pet. 68. Petitioner contends that to break an emulsion, it was well-known that chemical surfactants could be used and numerous surfactants to “favor droplet coalescence” (merge droplets and break the emulsion) were known decades before the 722 Patent. Pet. 69 (citing Ex. 1059). Petitioner contends that the Ismagilov references disclose using fluorosurfactants (Pet. 69 (citing Ex. 1004, 37:23–45), including the use of perfluorooctanol (e.g., 1H,1H,2H,2H-perfluoro-1-octanol) for use in merging (coalescing) droplets, which Petitioner contends is the same destabilizing surfactant preferred in the ’722 patent (Pet. 69 (citing Ex. 1004, 61:19–20, 64:8–65:115; Ex. 1001, 48:18–27)). Petitioner thus contends that it would have been “obvious to add perfluorooctanol to stable droplets in a tube as a biocompatible destabilizing surfactant to destabilize and recover droplet contents.” Pet. 69.

Other than the arguments addressed above, Patent Owner does not present any arguments directed to the patentability of claims 15–17. *See generally* PO Resp. Nonetheless, it remains Petitioner’s burden to demonstrate unpatentability. *See Dynamic Drinkware, LLC v. National Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015).

We find that Petitioner’s contentions for claims 15–17 are not sufficiently supported. As noted above, Petitioner cites the ’722 Patent’s disclosure of perfluorooctanol as a de-stabilizing surfactant contained in a second continuous phase carrier fluid (Ex. 1001, 48:18–27), contends that Ismagilov 091 discloses the same surfactant “for use in merging (coalescing)

droplets,” and concludes that it would have been obvious to add the perfluorooctanol to destabilize and recover droplet contents. Pet. 69.

We disagree with Petitioner’s contention. Ismagilov 091 teaches perfluorooctanol as a surfactant to *stabilize* droplets in channels, not to destabilize or merge droplets. *See* Ex. 1004, 21:7–35. More specifically, Ismagilov 091 teaches that “the plugs remain stable and do not leave behind any residue as they are transported through the channels” when “the surface tension at a plug fluid/channel wall interface . . . is set higher than the surface tension at a plug fluid/carrier-fluid interface . . . with a surfactant such as 10% 1H,1H,2H,2H-perfluorooctanol.” *Id.* at 21:11–22. Petitioner does not direct us to any teaching or suggestion in Ismagilov 091 that a surfactant, such as perfluorooctanol, is used as a destabilizing surfactant.

Moreover, even if destabilizing surfactants were known in the art, Petitioner does not direct us to evidence sufficient to establish that it would have been obvious to place the droplets onto a second continuous phase carrier fluid comprising a destabilizing surfactant to destabilize the droplets, as recited in claims 15–17. Dr. Fair’s testimony (Ex. 1008 ¶¶ 54–56, 186–189) is essentially the same as the Petition (Pet. 68–69) and suffers from the same deficiencies.

Therefore, we find Petitioner has not shown by a preponderance of the evidence that claims 15–17 would have been obvious over the combined teachings of Thorsen and the Ismagilov references.

## 5. Conclusion

As discussed above, we find that the combination of Thorsen and Ismagilov 119 either alone or in combination with Ismagilov 091 teaches the subject matter of claims 5–7, 12, and 13. We have considered all of Patent Owner’s evidence of nonobviousness and find it unpersuasive. Accordingly,

we balance Petitioner's strong evidence of obviousness against Patent Owner's alleged objective evidence of nonobviousness, we determine that a preponderance of the evidence supports Petitioner's position that claims 5–7, 12, and 13 are unpatentable under 35 U.S.C. § 103 over Thorsen and Ismagilov 119 either alone or in combination with Ismagilov 091.

We also find, for the reasons stated above, that Petitioner has not shown by a preponderance of the evidence that claims 15–17 would have been obvious over the combined teachings of Thorsen and Ismagilov 119 either alone or in combination with Ismagilov 091.

We do not reach Petitioner's grounds that claims 1–4, 10, 11, and 14 would have been obvious over Thorsen and Ismagilov 119 either alone or in combination with Ismagilov 091.

### III. CONCLUSION<sup>10</sup>

For the foregoing reasons, we determine that Petitioner has shown by a preponderance of the evidence that claims 1–7 and 10–14 are unpatentable but has not shown by a preponderance of the evidence that claims 15–17 are unpatentable.

### IV. ORDER

In consideration of the foregoing, it is hereby:

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<sup>10</sup> 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).

ORDERED that claims 15–17 of U.S. Patent No. 9,896,722 B2 have not been shown to be unpatentable;

ORDERED that claims 1–7 and 10–14 of U.S. Patent No. 9,896,722 B2 have been shown to be unpatentable; and

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

In summary:

| <b>Claims</b>          | <b>35<br/>U.S.C.<br/>§</b> | <b>Reference(s)/Basis</b>                                 | <b>Claims<br/>Shown<br/>Unpatentable</b> | <b>Claims<br/>Not shown<br/>Unpatentable</b> |
|------------------------|----------------------------|-----------------------------------------------------------|------------------------------------------|----------------------------------------------|
| 1–3, 10,<br>11, 14     | 102                        | Thorsen                                                   | 1–2, 10, 11,<br>14                       | 3                                            |
| 1–4, 10,<br>11, 14     | 103                        | Thorsen                                                   | 1–4, 10, 11                              |                                              |
| 1–7, 10–<br>17         | 103                        | Thorsen, Ismagilov<br>119 <sup>11</sup>                   | 5–7, 12, 13                              | 15–17                                        |
| 1–7, 10–<br>17         | 103                        | Thorsen,<br>Ismagilov 119,<br>Ismagilov 091 <sup>12</sup> | 5–7, 12, 13                              | 15–17                                        |
| <b>Overall Outcome</b> |                            |                                                           | 1–7, 10–14                               | 15–17                                        |

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<sup>11</sup> As noted above, we do not reach Petitioner’s challenge of claims 1–4, 10, 11 and 14 as unpatentable over the combined teachings of Thorsen and Ismagilov 119.

<sup>12</sup> As noted above, we do not reach Petitioner’s challenge of claims 1–4, 10, 11 and 14 as unpatentable over Thorsen, Ismagilov 119, and Ismagilov 091.

IPR2020-00089  
Patent 9,896,722 B2

FOR PETITIONER:

Samantha Jameson  
Gina Cremona  
Matthew D. Powers  
Azra Hadzimehmedovic  
Robert L. Gerrity  
TENSEGRITY LAW GROUP LLP  
samantha.jameson@tensegritylawgroup.com  
gina.cremona@tensegritylawgroup.com  
matthew.powers@tensegritylawgroup.com  
azra@tensegritylawgroup.com  
robert.gerrity@tensegritylawgroup.com

FOR PATENT OWNER:

David Bilsker  
Kevin Johnson  
Anne Toker  
QUINN EMANUEL URQUHART & SULLIVAN LLP  
davidbilsker@quinnemanuel.com  
kevinjohnson@quinnemanuel.com  
annetoker@quinnemanuel.com