UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

10X GENOMICS, INC.
Petitioner

v.

BIO-RAD LABORATORIES, INC.
Patent Owner

Case No. IPR2020-00086
U.S. Patent No. 9,562,837

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

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I. INTRODUCTION

The Board found the Challenged Claims likely unpatentable on four grounds. Paper 8 ("ID"), 33-43; IPR2020-00087, Paper 9, 31-48, 55. Rather than rebut the merits of these findings, Patent Owner ("PO") focuses on strawman arguments—such as mischaracterizing the Petition as requiring that "**all** open structures" disclose the Challenged Claims. Paper 26 ("POR"), 2, 18-25. The right question is whether Ismagilov's collection well teachings (and the other Grounds) disclose the disputed "separation chamber"-related limitations under PO's claim constructions. They do. Based on PO's application and constructions of the claims, and in some cases PO's own arguments, no distinction (relevant to the claims) exists between the collection wells accused of infringement and the collection wells disclosed by Ismagilov and Quake.

II. PATENT OWNER'S CLAIM CONSTRUCTIONS CONFIRM GROUNDS 1-5B INVALIDATE THE CHALLENGED CLAIMS

The Board instituted trial relying on claim constructions based on PO's infringement contentions. ID, 9-17. The POR confirms the Petition properly applied PO's understanding of the claims. POR, 18-28; Paper 2 ("Petition"), 17-23.

PO's constructions confirm the Petition shows the Challenged Claims are unpatentable under all grounds applying them (Grounds 1-2, 3b-5b). Ex. 1071 ("Fair2"), ¶¶14-26; Petition, 31-71.

For Grounds 3a/3b-5a/5b, Petitioner respectfully submits that the Petition sufficiently explains that Bio-Rad's broader constructions are met by the disclosures meeting 10X's narrower constructions.

A. "separation chamber"

PO's construction (POR, 18) of "separation chamber" is broad enough to include open wells, as the Petition stated, that are sized to accommodate multiple droplets and an immiscible fluid in separated form as in Ismagilov. Petition, 35-47; Section III.A. (below). The size and separation aspects of Bio-Rad's current construction were also addressed in the Petition in limitations [1.6] and [1.7].

PO's expert confirmed that substantially enclosed spaces (which meet 10X's construction) such as the density sorters in Grounds 3b/4b/5b meet PO's claim construction if sized to accommodate multiple droplets and an immiscible fluid in separated form, again as described also in limitations [1.6]-[1.7]. Ex. 1075, 145:2-146:1, 148:18-149:16; Petition, 56-67.

B. "droplet receiving outlet"

PO's construction (POR, 22) of "droplet receiving outlet" is broad enough to include the open-top of an outlet well, as the Petition stated, as in Ismagilov's collection well where droplets will float to the top of the denser fluorinated oil and collect (and where collection can also be performed by micropipette). Petition, 35-47; Section III.A. PO's expert confirmed PO's construction places no restriction on

"how much droplet and how much other material" is received at the "droplet receiving outlet." Ex. 1075, 156:4-14, 153:16-160:8.

PO's expert confirmed an outlet that receives substantially only droplets (which meets 10X's construction) such as in the density sorter in Grounds 3b/4b/5b meets PO's claim construction because it is a portion where droplets are collected. Ex. 1075, 152:1-153:15; Petition, 58-64.

C. "coupled"

PO's construction of "coupled" in Claims 7-9 as "operably linked" (POR, 26) is broad enough to include any operable linkage, including techniques well-known to a POSA and rendered obvious by Ismagilov, e.g., using a micropipette to move droplets from the collection well to another vessel (as the construction in the Petition stated) such as a sample tube. Petition, 1-2, 35-36, 47-48; Sections III.A., IV.

PO's expert confirmed PO's construction of "coupled" includes objects that are fastened or joined together so long as the objects "still operate in the manner intended, which is essentially what I mean by operably linked." Ex. 1075, 161:25-162:6, 160:21-161:24. The disclosures relied upon in the Petition for coupling, including for Grounds 3b/4b/5b, are all able to operate in the manner intended, as described in the Petition. Petition, 35-36, 47-48, 58-59, 68-70.

III. ISMAGILOV DISCLOSES THE LIMITATIONS DISPUTED BY BIO-RAD AND ANTICIPATES CLAIMS 1-2, 4, 10-13, AND 19-20.

The Board found a reasonable likelihood that Claim 1 is anticipated by Ismagilov and Ismagilov discloses the dependent claims. ID, 33-36. PO disputes only limitations of Claim 1, arguing incorrectly that Ismagilov does not disclose limitations [1.3], [1.4], and [1.6]/[1.7]. POR 28-44. All other POR sections regarding Ground 1 point back to these arguments, tacitly admitting that all claims challenged under Ground 1 rise or fall with the disclosure of these limitations of Claim 1. *Id*. Neither PO's new claim constructions nor the arguments in the POR (largely repeated from the POPR) change the Board's findings at Institution.

A. [1.3] "at least one downstream separation chamber comprising a droplet receiving inlet and at least one droplet receiving outlet."

1. Ismagilov discloses this limitation.

PO's claim constructions confirm that the open-topped collection well disclosed by Ismagilov (which is directly analogous to the open-topped collection well PO accuses of infringement) discloses limitation [1.3] under PO's construction/application.

A POSA reading Ismagilov's teachings of a collection well/reservoir at the outlet would understand Ismagilov expressly discloses a "chamber sized to accommodate multiple droplets and an immiscible fluid in separated form" including a "portion … where droplets are collected" as PO applies those constructions. Ismagilov discloses that its outlet "collects" plugs/droplets (plural) "surrounded by"

immiscible fluid, is in fluid communication with a "well or reservoir" (words connoting vertical, bucket-shaped storage areas), that plugs/droplets are moved to the appropriate outlet, and that "collection" at the outlet "can also be done using micropipettes." Petition, 35-37, 40-41, 44-45; Ismagilov, 9:5-7, 9:39-44, 14:36-40, 17:18-30; Ex. 1008 ("Fair"), ¶¶129-134, 160-161, 167, 170. Before reaching the micropipette disclosure PO disputes, PO has no explanation for why these teachings alone fail to disclose limitation [1.3] under PO's constructions.

These disclosures all describe characteristics of the same outlet and collection well/reservoir in Ismagilov's system. This is not, as PO asserts (POR, 30, 38), a case like *Net MoneyIN* where a reference disclosed "two separate protocols" for processing Internet transactions, neither of which had all of the claimed elements. 545 F.3d 1359, 1371. Instead, these are complimentary and reinforcing disclosures that a POSA would read together. All these disclosures come from Ismagilov's "Detailed Description According to the Invention" in subsections introducing terms (Ismagilov, 7:23-11:18), describing "Channels and Devices" (Ismagilov, 14:20-15:67), and detailing the "Fabrication of Channels, Substrates, and Devices" (Ismagilov 16:1-17:30). Moreover, even if the "outlet port" disclosures of a "well" and the "outlet" disclosures with micropipettes were read as separate embodiments

(which they should not be), each discloses a separation chamber for the reasons noted above.[1]

PO's arguments (POR, 29-33) that these collection well/reservoir teachings apply only to Ismagilov's "inlets" is directly contradicted by the text. Ismagilov, 14:37-40 ("Each of the outlet and inlet ports may also communicate with a well or reservoir"), 17:18-30 (discussing "outlet").

PO's assertion (without citation) that there is "no disclosure in Ismagilov that teaches any chamber with the dimensions and configuration claimed" (POR, 34-38) is similarly contrary to Ismagilov's text and contradicted by PO's own constructions which do not require specific dimensions/configurations beyond sufficient size to hold droplets and immiscible fluid and "a portion" "where droplets are collected."

2. Ismagilov's disclosure of collection by micropipette further confirms disclosure of limitation [1.3] and limitations [1.4], [1.6]/[1.7].

Ismagilov's disclosure that "collection" of plugs/droplets "can also be done using micropipettes" further discloses that the collection well/reservoir in communication with the outlet must have a volume and depth sufficient to allow

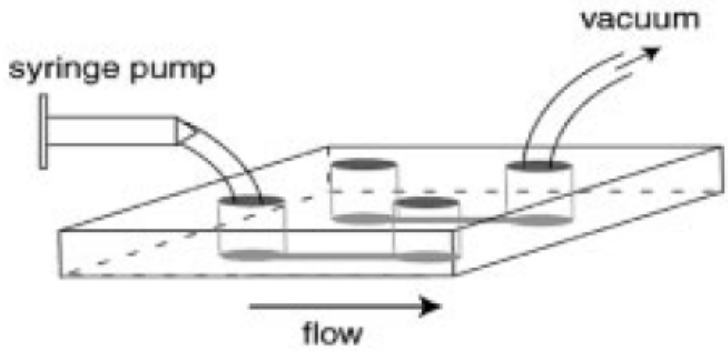
[1] Bio-Rad has no alternative reading of Ismagilov, and Bio-Rad's expert testified regarding Ismagilov 17:18-30 "I can't interpret what Ismagilov means, I can say what he says…" Ex. 1075, 30:5-34:11.

collection by micropipette—namely a volume greater than 0.1 microliters and a vertical depth extending upright to (and out of the plane of) the microchannel.[2] Petition 40-41, Fair, ¶161; *see also* Petition, 35-37, 44-45; Fair ¶¶129-134, 160-161, 167, 170. Indeed, a POSA would understand Ismagilov's use of the words "well or reservoir" in communication with an outlet from which droplets can be collected by micropipette to disclose the well-known collection well structure: "an open-topped, bucket-like structure from which the accumulated droplets could be extracted, e.g., by using a micropipette." Fair, ¶161.

PO and its expert admit the use and formation of such upright bucket-shaped collection well structures at microchannel outlets was well-known, including forming these structures using a cork borer as disclosed by Ismagilov. *See* Ex. 2016

[2] PO argues incorrectly that Dr. Fair has no basis for these opinions because at deposition Dr. Fair could not recall personally using a pipette to remove a ***single*** droplet from a chip. POR, 33-34. This "gotcha" question does not negate Dr. Fair's expertise with the use, operation, and requirements of micropipettes. Fair, ¶¶130-131, 160-161, 170, 186. Dr. Fair testified he was familiar with the standard industry practice of moving solutions containing multiple droplets from wells using a micropipette, and that he has and uses micropipettes in his lab. Ex. 2017, 42:21-43:4, 140:21-142:2.

("Anna"), ¶35 (citing Ismagilov 16:35-36). Dr. Anna confirmed that she interpreted the below figure in Ex. 2033 that she relied on as showing channels as gray lines and four holes, and also that "a cork borer could make holes like that." Ex. 1075, 114:23-115:6; *Id.*, 68 (citing Ex. 2033 as showing it was "common at the time" to "punch a hole through the PDMS at the ends of the channels" to "create inlets and outlets"); POR, 9, 16-17 (same); Ex. 1075, 112:18-115:3;



Ex. 2033, Fig. 1A, 2 ("holes are drilled into the PDMS using a cork borer to produce inlets and outlets."). This confirms, rather than refutes, that Ismagilov discloses wells.

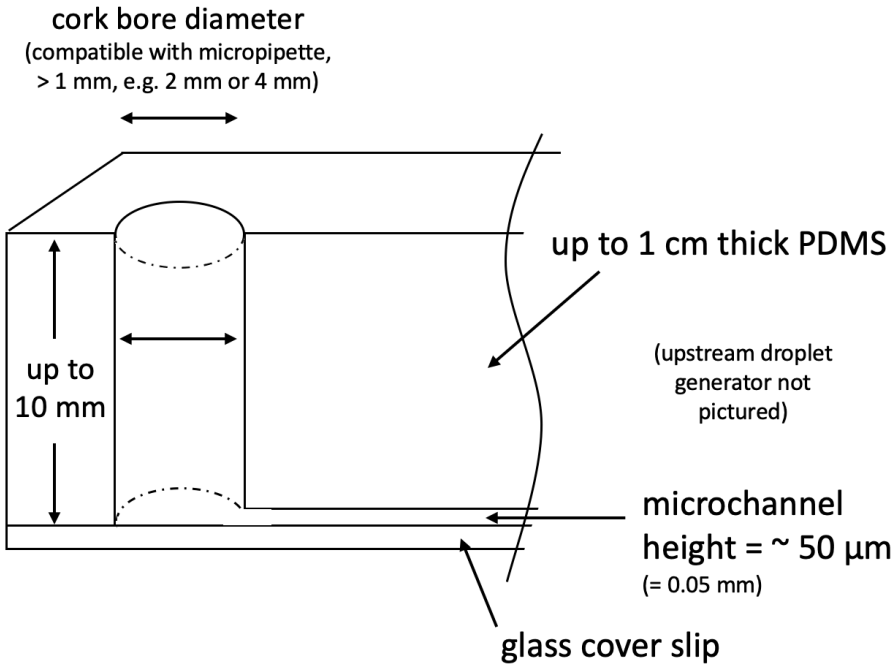
PO argues incorrectly (without citation or support) that collection well structures cut using a cork borer would be no larger than 1 mm in diameter and incompatible with micropipettes, which the experts agree have tips of 1 mm in diameter. POR, 37; Anna, ¶¶131-132; Ex. 2017, 159:13-16. First, PO's argument confirms, rather than refutes, that Ismagilov discloses a separation chamber. An open cork borer hole as PO describes, such as that shown by the front right hole in the above figure, of even 1 mm is sufficient to disclose a "separation chamber" that is

upright, out of the plane of the microchannel, with a larger cross-section than the microchannel (which Ismagilov describes as having a diameter on the order of 28-60 micrometers, Section III.B.), and with a volume sufficient to hold a plurality of droplets under PO's construction/application.

Second, because Ismagilov discloses that collection can be done using micropipettes, PO has the burden of overcoming the presumption that Ismagilov's disclosure is enabling. *See In re Antor Media Corp.*, 689 F.3d 1282, 1289 (Fed. Cir. 2012). PO's expert's conclusory, *ipse dixit* testimony is insufficient to meet that burden and is contradicted by evidence from the time. 37 CFR § 42.65(a). PO's expert admitted she does not know and did not investigate what size cork borers were available. Ex. 1075, 84:24-85:6, 85:25-86:5. Contrary to PO's unsupported assertion, Quake (a reference predating Ismagilov) confirms that POSAs were using cork borers to make collection wells of at least 2 mm in diameter. Ex. 1006 ("Quake"), ¶¶196 ("the wells are 2 mm in diameter"), 216 (confirming holes were cut using "cork borers"); Fair2, ¶¶27-33. A 2005 paper including the same two authors of Ex. 2033 relied on by PO confirms POSAs were also using commercially available cork borers of 4 mm in diameter to create reservoir holes in PDMS. Ex. 1076, 2, 4-5; Fair2, ¶31. Indeed, cork borers are (and were prior to the 837 patent) readily available in sizes ranging from 2 mm in diameter up to 50 mm. Fair2, ¶32 (discussing Exs. 1077, 1078, 1079).

Ismagilov provides additional details for forming the microfluidic substrate chips, further confirming the shape, size, and orientation of the collection well/reservoir. Petition, 31-32, 40-41; Fair, ¶¶120-123, 160. The microchannels are formed on the bottom of a PDMS layer by molding: uncured PDMS is poured onto a silicon wafer with the negative image of the channels inside a Petri dish. Ismagilov, 16:23-32. The thickness of the PDMS is up to "about 1 cm," similar to the depth of a Petri dish. Ismagilov, 16:42-47; Fair2, ¶¶36-37 (discussing Exs. 1080, 1081). After the PDMS is cured, holes such as the collection well/reservoir can then be cut vertically through the PDMS down to the microchannels at the bottom of the PDMS layer using "a tool such as a cork borer." Ismagilov 16:35-36. The PDMS layer is then placed (channels side down) onto a glass microscope slide cover slip or other flat surface which forms the floor of the channels and the collection well. Ismagilov 16:38-41; Petition, 31-32, 40-41; Fair, ¶¶120-123, 160. Ismagilov thus discloses a collection well/reservoir cut through an up to 1 cm/10 mm thick layer of PDMS using a cork borer with a diameter sufficient to allow collection by micropipette (i.e., > 1 mm, e.g. 2 mm or 4 mm), producing a structure with a vertical cross section that looks like:

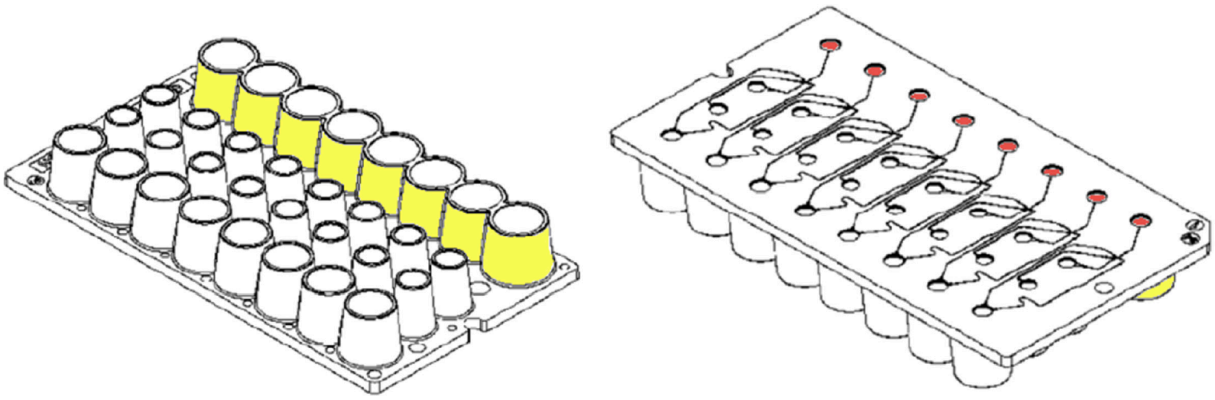
Ismagilov's Collection Well (Illustrative)



Fair2, ¶37 (illustrative image); Fair, ¶¶120-123, 160. This structure would be familiar to a POSA and is what a POSA would understand to be expressly disclosed by Ismagilov's teachings of a collection well/reservoir. *Id*.

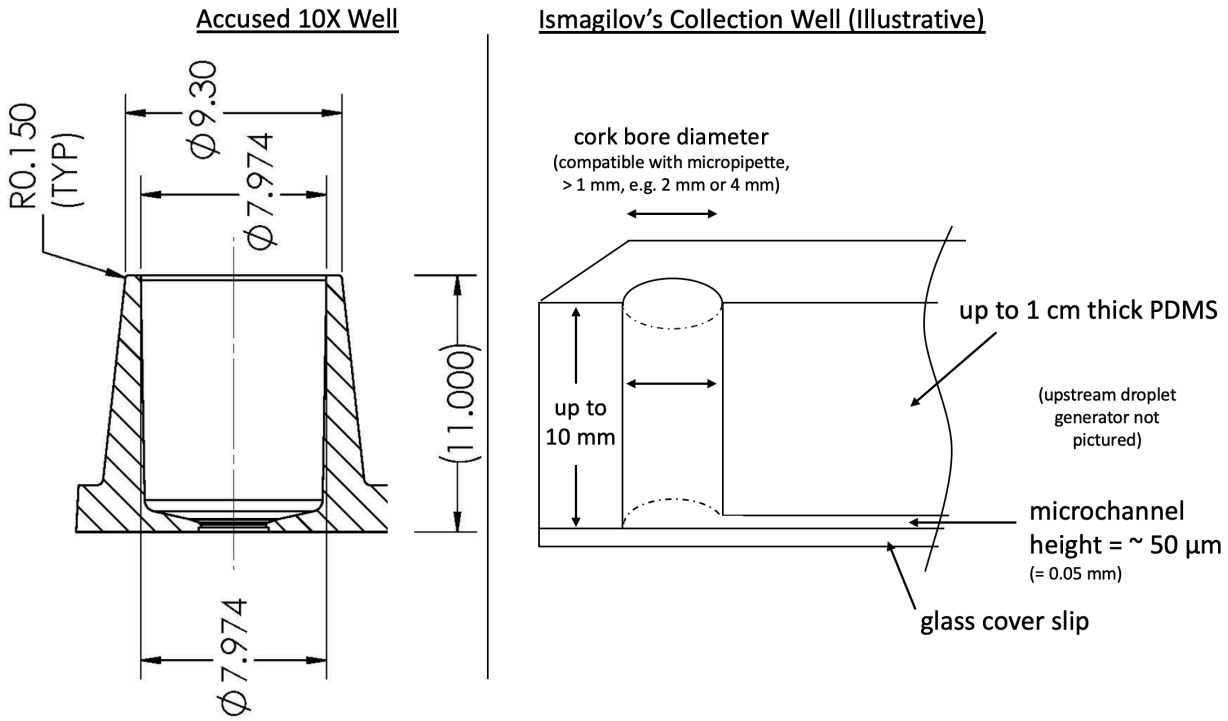
Much of the POR is attorney argument that Ismagilov's collection well is somehow different from the open-topped well in 10X's products that PO accuses of infringing the "separation chamber" and "droplet receiving outlet" limitations. POR, 35-36, 20-21, 24-25. However, PO fails to articulate any limitation of the Challenged Claims or any aspect of PO's claim constructions that, if satisfied by the 10X well accused of infringement, would not be satisfied by Ismagilov's collection well. *Id*. PO's expert repeats the same conclusory arguments from the POR without further

explanation or support. Anna, ¶¶84-87, 101-104, 135-137; 37 CFR § 42.65(a). Although unconnected to the claim limitations, PO appears to argue that Ismagilov discloses only a structure analogous to the holes (annotated red in the POR) at the bottom of the wells in the accused 10X products:



POR, 35-36.

PO's asserted difference is contradicted by Ismagilov's disclosures discussed above and by the cross-section diagrams of the 10X wells relied on in PO's infringement contentions. The cross-sectional view confirms PO is accusing of infringement the same kind of cylindrical bore-hole, bucket-shaped well that Ismagilov discloses with similar dimensions—one with a circumference big enough to accommodate a pipette (7.974 mm) cut through the chip material to a depth of 11.000 mm to connect to the microchannel at the bottom:



Fair2, ¶37; Ex. 1026, 18 (10X's well accused of infringement on left). PO's assertion that Ismagilov discloses only structures analogous to the "red" portions of PO's contention figures is irrelevant under PO's own claim constructions. Ismagilov's collection well is upright, out of the plane of the microchannel, with a larger cross-section than the microchannel, with a volume sufficient to hold a plurality of droplets and immiscible oil, and has a portion where droplets are collected, which is sufficient to disclose the "separation chamber"-related limitations under PO's construction/application. 837 patent, Claim 1; POR, 18-25; Ex. 1026.

PO's argument that Ismagilov does not disclose "separation of droplets from the immiscible fluid . . . and subsequent collection of droplets that is intended to leave behind oil" (POR, 34) is also inaccurate and contrary to PO's application of the claims. Ismagilov discloses collecting droplets "by micropipette"—the same

purported "separation" that PO alleges infringes the claims. Ex. 1026, 11-12, 18-20. Moreover, PO argued against a claim construction requiring "substantially only droplets" be received and specifically disclaimed any arguments that "intent" or actual separation of droplets from oil is required:

> The claims of the '837 Patent are directed to an assembly. **They do not require separation to occur**.

Ex. 1082 (PO's Claim Construction Reply), 34[3]; *see also* POR, 25; MPEP § 2114 ("[A]pparatus claims cover what a device *is*, not what a device *does*."); *Bettcher Indus., Inc. v. Bunzl USA, Inc.*, 661 F.3d 629, 654 (Fed. Cir. 2011); Ex. 1002, 1098-1099.

B. [1.4] "wherein the separation chamber is upright to the microchannel and out of the horizontal plane"

Ismagilov discloses that its collection well/reservoir is upright to the microchannel and out of the horizontal plane. Section III.A.; Petition, 40-41. PO does not dispute that if a POSA reads Ismagilov to disclose vertical collection by micropipette, then this limitation is disclosed. POR 38-41. Instead, PO's two-step argument against this limitation is that a POSA would "just as easily" understand micropipette collection to be performed horizontally (POR, 38-39), and if that is

[3] Emphasis supplied and quotations/citations omitted throughout.

true, the collection well/reservoir could be in the same plane as the microchannel (POR 39-40). Neither step has merit.

PO's assertion that a POSA would "just as easily" understand collection by micropipette to refer to horizontally inserting the micropipette "into the end of the outlet port in the horizontal plane" is contrary to PO's own arguments and contrary to the undisputed evidence of how micropipettes operate. PO and its expert agree that micropipette tips are 1 mm in diameter and could not fit in holes $\leq$ 1 mm. POR, 37; Anna, ¶132. The horizontal microchannels of Ismagilov are repeatedly shown as having a diameter on the order of 28-60 micrometers (~1/20th of 1 mm) or less and a micropipette tip would not fit. *E.g.*, Ismagilov, Figs. 7A-7C, 26A, 27B, 30, 15:24-40, 22:43-44, 41:14-17.[4]

Micropipettes also are not operated horizontally. Neither PO nor its expert contest that Exhibit 1040 accurately describes micropipettes (Fair, ¶130; Petition, 41; Anna, ¶131 (confirming Ex. 1040 includes "an image of a micropipette")), and

[4] Although PO's expert asserts Exhibits 2020-2021 describe pipette tips that "could be placed in much smaller diameter holes" (Anna, ¶134), neither exhibit ever discusses micropipettes. Exs. 2020, 2021; Ex. 2017, 150:25-151:15. The POR also contradicts PO's expert this point. POR, 34 ("a micropipette tip could **not** be placed in much smaller diameter holes … other references … show precisely that.").

it repeatedly states that micropipettes are only to be operated "vertically" or at an angle "< 20° from vertical" and that to "[p]revent liquids from being drawn into the shaft" a user should "[n]ever invert or lay the pipette down if liquid is in the tip." Ex. 1040, 5-7.[5]

The second step of PO's argument—that a well in Ismagilov's system could be in the same plane as the microchannel—also fails. The word "well" connotes an open-topped, vertical, upright structure in microfluidics just as it does in ordinary use, which (as shown above) extends up from the glass coverslip at the bottom of Ismagilov's devices. Fair, ¶¶161, 131; Petition, 36-37. Neither PO nor its expert articulate any other meaning of the word "well." Further, a POSA reading Ismagilov as a whole would also know that the well must extend upright and out of the plane from the microchannel because a well within the same plane as the microchannel (i.e., with the same height) would render Ismagilov's system inoperable. PO agrees that Ismagilov's wells are formed using a cork borer to cut through the entire PDMS layer. Section III.A.2. But cutting an open well with the same height as the

[5] PO also relies on Ismagilov Fig. 22D and its description (without explanation). POR, 39; Anna, ¶141. However, Figure 22D is described as a "schematic diagram" (not a 3D image) and does not depict a collection well or horizontal micropipette collection. Ismagilov 5:25-28.

microchannel would thus mean the microchannel height also extends through the entire PDMS layer, leaving the microchannel open at the top. Fair2, ¶38; Ismagilov, 16:23-41. Ismagilov's "pressure-driven" flows of fluids would result in fluids spilling out the tops of such channels, and thus break the system. *Id*.; *e.g.*, Ismagilov, Title, 2:50-58, 14:19-29; Petition, 37, 43. There must be a layer of PDMS above the microchannel through which the collection well extends.

Dr. Fair's deposition testimony also does not support PO's argument. POR, 39-40. Dr. Fair was questioned about the design of a hypothetical microfluidic chip in the abstract, outside the context of Ismagilov's system and disclosures. Ex. 2017, 67:15-69:18. Tellingly, PO did not ask whether a POSA, reading Ismagilov as a whole, would understand Ismagilov's collection well to be anything other than a vertical structure upright to and out of the plane of the microchannel. *Id*.

C. [1.6]/[1.7] "and wherein the separation chamber has a wider cross-section than the microchannel cross-section to accumulate a plurality of droplets comprising the sample and is of a volume sufficient to separate the plurality of droplets comprising the sample from the immiscible fluid within the separation chamber."

Ismagilov discloses a collection well/reservoir meeting these limitations under PO's construction/application. Section III.A.; Petition, 10-11, 44-46; Fair, ¶¶57, 170, 173-174. PO does not dispute that Ismagilov discloses a collection well with "a wider cross-section than the microchannel cross-section to accumulate a plurality of droplets comprising the sample." POR 41-43. PO does dispute the

"volume sufficient to separate…" aspect of these limitations; however, PO's arguments contradict PO's statements to the District Court, rely on a mischaracterization of Petitioner's arguments, and misapply the law regarding inherency. *Id*.

PO disclaimed any arguments that actual separation of droplets from immiscible fluid is required. Section III.A.2.; Ex. 1082, 12. Under PO's application, Ismagilov need only disclose that the collection well has sufficient volume. Ismagilov expressly and inherently discloses that the collection well has sufficient volume. Section III.A.; Petition, 44-46; Fair, ¶¶170, 173-174. PO does not dispute this. POR 41-43.

If PO is permitted to argue that disclosure of separation is required, Ismagilov discloses that too. Ismagilov discloses that collection of droplets/plugs can "be done using micropipettes"—precisely what PO alleges satisfies this limitation for infringement. Petition, 45-46; Ex. 1026, 12-13, 16-20. Ismagilov also discloses forming water droplets/plugs comprising a sample in fluorinated oil (e.g. perfluorodecaline and perfluorohexane). Petition, 10; Fair, ¶57. PO does not dispute that Ismagilov **expressly** discloses this—no inherency required. POR 41-43.

PO also does not dispute that:

•water's density is 1 g/cm^3;

- perfluorohexane and perfluorodecaline have densities of ~1.7 and ~1.9 g/cm^3;
- densities are constant properties of these chemicals well-known to a POSA; and
- a POSA would know these differences in densities would necessarily mean the less dense water droplets will float to the top of the denser fluorinated oil.

Compare Petition, 10-11 *with* POR 41-43; Fair, ¶57; Ex. 1014, 4-5; *see also* 837 patent, 3:39-58, 4:8-10, 21:45-22:28 (confirming water/aqueous droplets rise in fluorinated oil as natural result of different densities). Ismagilov's teachings of a collection well that collects droplets/plugs and the formation of water plugs/droplets comprising a sample in immiscible fluorinated oil disclose (expressly or inherently) that the collection well "is of a volume sufficient to separate" under PO's application. Petition, 10-11, 44-46; Fair, ¶¶57, 170, 173-174.

PO's counterargument that inherency does not apply because Ismagilov "does not exclude all other oils as carrier fluids" and "the drops will not necessarily separate if the selected oil has substantially the same density as water" (POR, 42-43) misunderstands Petitioner's argument and misapplies the inherency doctrine. Petitioner does not argue the use of fluorinated oil is inherent in Ismagilov—Ismagilov expressly discloses fluorinated oils. The question is whether Ismagilov's

express disclosure of collecting water droplets/plugs in fluorinated oil discloses (at least inherently) a "volume sufficient to separate…" under PO's application. Because density is an inherent, natural property of a substance and separation of less dense water droplets in denser perfluorohexane or perfluorodecaline is the natural result of their different densities, inherency properly applies for both anticipation and obviousness. *Par Pharm., Inc. v. TWi Pharm., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014) (disclosure inherent where "the disclosure is sufficient to show that **the natural result** flowing from the operation as taught would result in the performance of the questioned function…"); *Persion Pharms. LLC v. Alvogen Malta Operations LTD.*, 945 F.3d 1184, 1191 (Fed. Cir. 2019) (prior art "formulation … necessarily exhibited the claimed parameters under these conditions."); *Solenis Techs., LP v. SNF SAS*, 813 Fed. Appx. 565, 571 (Fed. Cir. 2020) (non-precedential) (distinguishing inherency of a material from inherency of a property of disclosed material).

PO's counterargument is also conclusory and unsupported. POR 42-43. Neither PO nor its expert identify even one carrier fluid oil in Ismagilov (let alone a fluorinated oil) that has "substantially the same density as water." *Id*.; Anna, ¶148; *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1330 (Fed. Cir. 2020) (affirming inherency where PO "did not present evidence of even a single sample" that failed to meet the limitation).

IV. GROUND 2 RENDERS OBVIOUS CLAIMS 1-2, 4, 7, 9-13, AND 19-20.

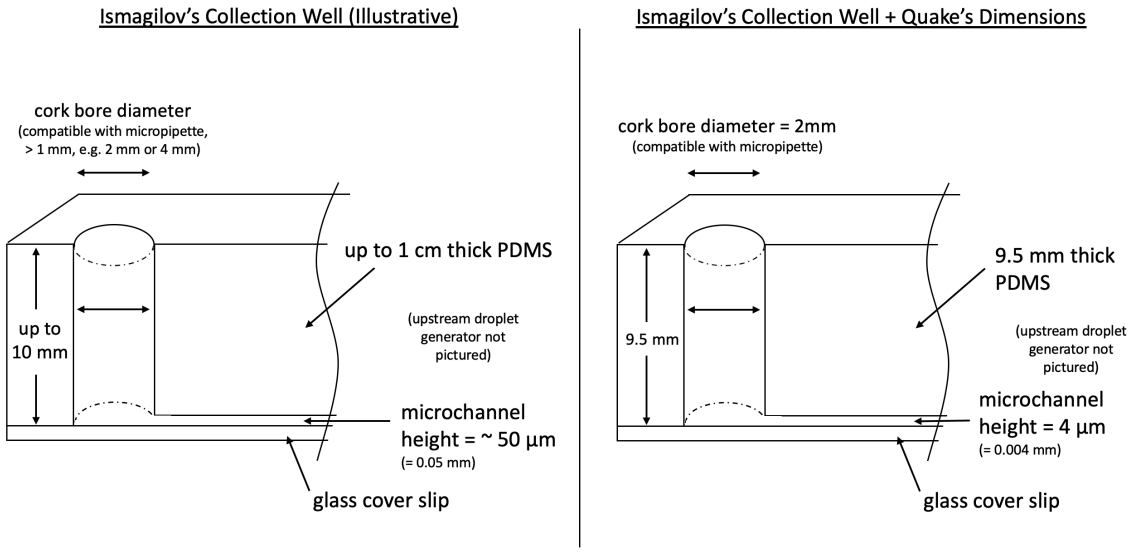
The Board found a reasonable likelihood that Claim 1 is obvious under Ground 2 and Ground 2 discloses the dependent claims. ID, 36-43. PO attempts to rebut this by arguing incorrectly that a POSA would not combine Ismagilov with Quake and that Ground 2 does not render obvious the "separation chamber" limitation of Claim 1 or Claims 7 and 9. POR 45-48, 48-53. All other sections of the POR regarding Ground 2 incorporate these same arguments. *Id*. Neither PO's claim constructions nor the arguments in the POR (largely repeated from the POPR) change the Board's findings at Institution.

The Petition explains "how and why a POSA would have combined" Ismagilov and Quake, and "that Quake provides additional details" of the collection well disclosed by Ismagilov. ID, 40-41; Petition, 11-12, 14-15, 23-28, 38-42, 45-48; Fair, ¶¶59, 104-107, 150-154, [6] 163-165, 172, 176, 186. PO's criticisms of Ismagilov's disclosures—focused largely on purported lack of specific dimensions or pictures of Ismagilov's collection well—are insufficient to overcome the Petition's anticipation showing (Section III.), and in any case are directly addressed by the combination with Quake. Quake teaches a 2 mm diameter well with a volume of at least 30 µl. Quake, ¶¶196, 200; Petition 42; Fair, ¶¶164-165. PO identifies no

[6] Dr. Fair prepared a correction of cross-references. Ex. 1083; Fair2, ¶2.

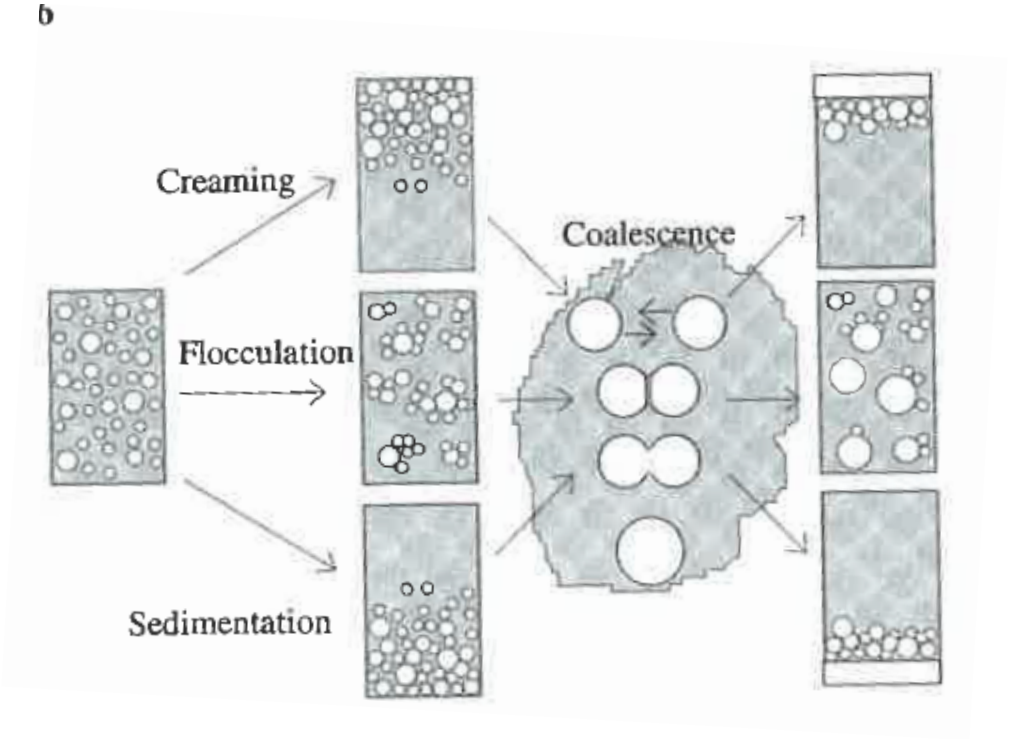
incompatibility in the combination of Ismagilov with Quake. Ismagilov discloses collection by micropipette and formation of collection wells by cork borer (as PO argues). PO does not dispute that Quake's wells are compatible with and obvious to try with the ordinary vertical use of a micropipette, nor does PO dispute that Quake discloses the same fabrication techniques for microfluidic chips as Ismagilov (including the use of cork borers, PDMS molding, and glass cover slips) that lead to a reasonable expectation of success for the combination. Section III.; Ismagilov, 16:1-47; Quake, ¶¶196, 200, 216; Petition, 31-32, 42; Fair, ¶¶6, 122-123, 153-154, 165.

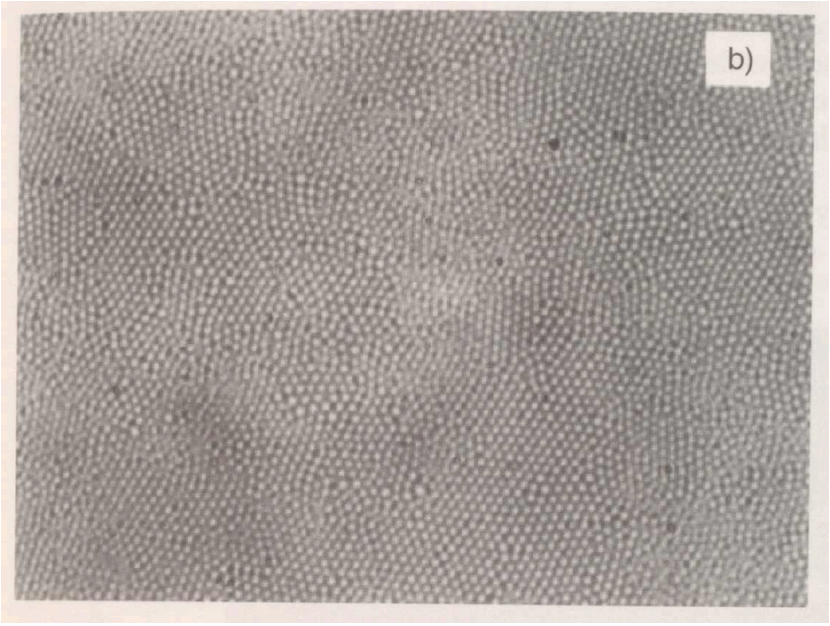
Thus the Petition establishes that, even if Ismagilov's collection well teachings do not expressly or inherently disclose the challenged claims (they do, Section III.), then it would be obvious for a POSA to arrive at the same claimed structure in view of Ismagilov+Quake:



Fair2, ¶¶40-42.

PO also does not dispute Petitioner's showing that (i) the separation of emulsion droplets from a continuous fluid based on their different densities and (ii) the subsequent collection, transfer, and use of the density-separated droplets were already well-known. Petition, 8-10 (citing Exs. 1009, 1012):





The Petition and Dr. Fair confirm that the work of the Quake lab was well-known in the field (which PO does not dispute), motivating a POSA to look to Quake to the extent a POSA needed additional details regarding the collection well disclosures of Ismagilov. Petition, 25-28; Fair, ¶¶104-107, 150-154, 165. PO's assertion (citing *Free-Flow Packaging*) that Petitioner relies merely on similarity of the references for motivation to combine is thus inaccurate. POR, 45-46.

Quake—including the disclosures relied on in the Petition—is also highly analogous art very similar to Ismagilov, further "support[ing] Petitioner's rationale for combining their teachings." ID, 41. Quake is titled "Microfabricated Crossflow Devices and Methods" and disclosed (like Ismagilov) structures of microfluidic devices, including those "designed to compartmentalize small droplets of aqueous solution within microfluidic channels filled with oil." Petition, 14-15, 25-28; Quake, Title, Abstract, ¶¶3-4, 93-95, 195-200, 216. Many of Quakes disclosures are copied into Ismagilov, including using droplets/plugs "as microreactors for chemical reactions..." Petition, 26; Ex. 1065. PO does not dispute this. The disclosure in Ismagilov of wells in microfluidic devices and the well-known, compatible disclosures of those ***well structures*** in Quake is alone sufficient to support the combination of Ismagilov and Quake.

PO nevertheless argues Quake's disclosures of collection wells relate only to a "sorting embodiment" unrelated to Quake's droplet-based systems. POR, 45-47.

Not so. Although Quake's experiments testing the Example 7 device in Figures 6-8—which describe wells in detail—sorted fluorescent beads and cells, Quake discloses that device can be "a component of an integrated microanalytical chip, in sorting cells or biological materials," i.e., as the "T-shape … branch point" of the discrimination region and branch channel. Quake, ¶¶193, 85; Fair2, ¶¶43-45. Quake discloses that the sorting of cells or other particles is an important application of Quake's droplet generation devices and teaches including a "droplet extrusion region" upstream of a "detection region" upstream of a "discrimination region" adapted to direct droplets through the discrimination region and into a branch channel." Quake, *e.g.*, ¶¶12-22, 58-59, 85. Quake similarly discloses that a similar T-shaped branch with wells can be used to sort water-in-oil droplets in Example 8. Quake, ¶¶215-218, 241. These teachings are directly analogous to Ismagilov's collection well disclosures. *E.g.*, Ismagilov, 17:18-30. A POSA in search of details for implementing Ismagilov's collection well would look to the well-known work of Quake including Figures 6-8 and Examples 7-8 containing express teachings of the shape and dimension of "collection wells.". Quake, ¶¶196-197, 200, 213-214, 216, 240-241 (all describing "collection well[s]"); Petition, 25-28, 38-42; Fair, ¶¶104-107, 130-131, 150-154, 163-165.

PO's assertion of "impermissible hindsight" is also incorrect. POR, 47-48. The Petition and Dr. Fair worked forward from the disclosures of Ismagilov,

explained how those disclosures motivate a POSA to seek additional details (if necessary) from other well-known researchers in the field (Quake), and described how the resulting combination renders obvious the challenged claims. Petition, 25-28, 35-42; Fair, *e.g.*, ¶¶6, 60, 104-107, 129-134, 150-154, 160-161, 163-165. Dr. Fair's testimony quoted by PO (taken from more than 7 pages of questioning about issues of sample loss, Ex. 2017, 47:14-54:19) is wholly consistent with this—of course in selecting "appropriate references to cite" Dr. Fair looked at the claim language in addition to what "a person of ordinary skill would have knowledge of" including methods and literature for handling droplets downstream of formation. *Id.*, 52:23-54:8.

Dependent Claims 7 and 9 are also obvious under Ground 2.[7] *See* ID, 36-37. PO is incorrect that the Petition does not identify a "separate vessel." POR, 50-51. Ismagilov discloses the outlet "can be adapted for receiving … a standard 1.5 ml centrifuge tube" and that "[c]ollection can also be done using micropipettes." Ismagilov, 17:27-30; Petition 47-48; Fair, ¶¶183-186, 191-192. Ismagilov's disclosures alone (and as combined with Quake's details regarding the collection

[7] Although there is a typographical error at Petition page 70, the Petition is clear that Claim 9 is also challenged under Ground 2 and PO understood this. Petition, 23-25, 47-48; POR, 45; ID, 36-37.

well) thus renders obvious operably linking the collection well with a sample/centrifuge tube (which is a test tube/vessel) by transferring the droplets from the collection well to the sample/centrifuge tube by micropipette (which PO accuses of infringing). *Id*.; Ex. 1002, 1099-1100.

V. GROUNDS 3A/3B-5A/5B INVALIDATE THE CHALLENGED CLAIMS UNDER EITHER PARTY'S CLAIM CONSTRUCTIONS.

Respectfully, this Board and PO misread Ismagilov 119's disclosure of sorting plugs/droplets "by their density relative to that of the carrier fluid." Ismagilov 119, ¶123 (first and third examples sorting plugs from other plugs "according to their sizes" (plural) and using a magnetic field; second example referring to only a singular "density" of all plugs relative to the carrier fluid); ID, 46-47; POR, 59-60; Petition, 56-71.

However, regardless of how the passage is read, a POSA would recognize the need for a structure that would arrive at the density sorter of Grounds 3a/3b-5a/5b. This is not an application of hindsight—it is a result of a POSA's knowledge that (i) density-based sorting (whether droplets from oil or droplets from other droplets) relies on the vertical force of gravity, (ii) any density-base sorting takes time and space for the droplets to move through the oil, and so multiple droplets would be pooled in the vertical chamber, and (iii) sorting is pointless without collection, and because droplets have a different density than the oil (Ismagilov 119, ¶123), they separate from the oil at the top or bottom of the chamber. Petition, 56-71; Fair, ¶¶102,

108-114, 135-149, 155-159; Fair2, ¶¶46-55 (citing Ex. 1009). If additional structural information is required for either density-based sorting, a POSA would have been motivated to look to Pamula for the structure of a device that operated based on the droplet/oil density difference, and nothing precludes using Pamula's waste and collection wells for droplets. Petition, 29-30, 60-64; Fair, ¶¶113-114, 155-158. Ismagilov 119 (Grounds 3a/3b) and Ismagilov 119+Pamula (Grounds 4a/4b-5a/5b) render the claims obvious that renders the claims obvious under either party's constructions (Sections II.A.-C).

VI. THE ASSERTED SECONDARY CONSIDERATIONS LACK NEXUS

The Board rejected the POPR's secondary considerations assertions for failure to show the required nexus. ID, 41-43. The POR repeats identical assertions without any showing of nexus. *Compare* POPR 27-34, *with* POR, 53-59. PO's expert admitted she was not asked to analyze, did not analyze, and does not know whether the many features of the Bio-Rad and 10X products unrelated to the 837 patent led to their success/praise/meeting any long-felt need, or whether assets unrelated to the 837 patent led to Bio-Rad's acquisition of RainDance. Ex. 1075, 168:7-204:16. No such nexus exists. The ITC determined the success and praise of 10X's products have nexus to 10X's own patents, not the 837 patent. Exs. 1084, 51-57, 74; 1085, 24-25. The ddSEQ product PO asserts practices the 837 patent has been a failure,

further negating any connection between success and the Challenged Claims. Ex. 1086, 29.

VII. CONCLUSION

Claims 1-4, 7-13, and 19-20 are unpatentable as described in the Petition and herein. PO's decision not to allocate words to brief *Arthrex*-related issues waives such arguments. POR, 62.

Dated: November 11, 2020 Respectfully submitted,

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CERTIFICATION OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(c) and (d), the undersigned hereby certifies that the **PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE** complies with the type-volume limitation of 37 C.F.R. § 42.24(c)(1) permitting a reply of up to 5,600 words because, exclusive of the exempted portions, the Reply contains 5,598 words, as identified by Microsoft Word's word-counting feature.

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CERTIFICATION OF SERVICE (37 C.F.R. §§ 42.6(e), 42.105(a))

The undersigned hereby certifies that the foregoing document, including its supporting evidence (Exhibits 1071, 1075-1086), was served in its entirety on November 11, 2020, upon the following parties via Electronic Mail:

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