

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

10X GENOMICS, INC.
Petitioner

v.

BIO-RAD LABORATORIES, INC.
Patent Owner

U.S. Patent No. 9,562,837 to Link
Issue Date: February 7, 2017
Title: Systems For Handling Microfluidic Droplets

Inter Partes Review No. IPR2020-00086

Petition For *Inter Partes* Review of U.S. Patent No. 9,562,837

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<i>MTD Prod. Inc. v. Iancu</i> , 933 F. 3d 1336 (Fed. Cir. 2019)	20

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AIA (Public Law 112-29) § 3(n)(1)	5
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List of Petitioner's Exhibits

Ex./ Doc.	Description
1001	U.S. Patent No. 9,562,837
1002	U.S. Patent No. 9,562,837 Prosecution History
1003	Intentionally Omitted
1004	U.S. Patent No. 7,129,091 ("Ismagilov")
1005	U.S. Patent Publication No. 2006/0094119 ("Ismagilov 119")
1006	U.S. Patent Publication No. 2002/0058332 ("Quake")
1007	U.S. Patent Publication No. 2007/0243634 ("Pamula 634")
1008	Declaration of Richard B. Fair, Ph.D., Attachment A: Curriculum Vitae, Attachment B: Materials Considered List
1009	Excerpts of Encyclopedic Handbook of Emulsion Technology (2001)
1010	European Patent Application No. EP 2 266 684
1011	Mueth, D., et al., "Origin of Stratification in Creaming Emulsions", Physical Review Letter, Volume 77, Number 3, 578-581 (July 15, 1996)
1012	Excerpts of Bibette, et al., Emulsion Science: Basic Principles An Overview (2002)
1013	Sadtler, et al., "Achieving Stable, Reverse Water-in-Fluorocarbon Emulsions", Angew. Chem. Int. Ed. Engl. 1996, 35, No. 17
1014	Dias, et al., "Densities and Vapor Pressures of Highly Fluorinated Compounds", J. Chem. Eng. Data 2005, 50, 1328-1333
1015	Web page titled, "Accoustic Properties for Liquids" available at https://web.archive.org/web/20040305130802/https://www.nde-ed.org/GeneralResources/MaterialProperties/UT/ut_matlprop_liquids.htm
1016	Webpage titled, "Material Safety Data Sheet re: Food Grade Mineral Oil" available at https://web.archive.org/web/20060311055221/http://www.clearco-products.com/pdf/msds/5/msds-f1-1.pdf
1017	Excerpts from Trial Transcripts Vols. I, II, IV, V, Case No. 15-152-RGA (D. Del.)
1018	U.S. Patent Publication No. 2015/0148238 ("Pamula 238")
1019	U.S. Patent Publication No. 2005/0272159 ("Ismagilov 159")

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1020	U.S. Patent No. 7,655,470 ("Ismagilov 470")
1021	U.S. Patent No. 7,294,503 ("Quake 503")
1022	U.S. Provisional Patent Application No. 60/856,440
1023	U.S. Provisional Patent Application No. 60/837,871
1024	U.S. Provisional Patent Application No. 60/874,561
1025	U.S. Provisional Patent Application No. 60/745,058 ("Pamula 058")
1026	Bio-Rad Infringement Contention, Exhibit B (2019-09-18), Case No. 1:18-cv-01679-RGA (D. Del.)
1027	Excerpts from The Compact Oxford English Dictionary, Second Edition (1994)
1028	Excerpts from Merriam-Webster's Collegiate Dictionary, Tenth Edition (1997)
1029	[Public] Order No. 20: Construing Certain Terms of the Asserted Claims of the Patents at Issue (Markman Claim Construction) (4/4/2018), Inv. No. 337-TA-1068
1030	Memorandum Opinion (5/17/17), ECF No. 174, Case No. 1:15-152-RGA (D. Del.)
1031	Johnson, A. et al., "Molecular Biology of the Cell" (2002), available at https://www.ncbi.nlm.nih.gov/books/NBK26837/
1032	Thorsen, T. et al., "Dynamic Pattern Formation in a Vesicle-Generating Microfluidic Device," Physical Review Letters, Volume 86, Number 18, 4163-4166 (April 30, 2001)
1033	Article titled, "Solving the Tyranny of Pipetting", Quake, S., Stanford University, available at https://arxiv.org/pdf/1802.05601.pdf
1034	Anna, S. et al., "Formation of dispersions using 'flow focusing' in microchannels", Applied Physics Letters, Volume 82, Numer 3, 364-366 (January 20, 2003)
1035	Squires, T., et al., "Microfluidics: Fluid physics at the nanoliter scale," Reviews of Modern Physics, Volume 77, 977-1026 (July 2005)
1036	Intentionally Omitted
1037	Intentionally Omitted
1038	Pollack, M., et al., "Electrowetting-based actuation of droplets for integrated microfluidics," Lab Chip, 2, 96–101 (2002)

Ex./ Doc.	Description
1039	Web page titled, "Advanced Liquid Logic", available at https://ece.duke.edu/about/news/entrepreneurs/advanced-liquid-logic
1040	Rainin Classic datasheet, available at https://www.pipettesupplies.com/assets/1/15/Rainin_Classic-User_Manual_2005_(Rainin).pdf
1041	Web page titled, "Resource Materials: Use of Micropipets", available at https://web.archive.org/web/20050507104357/http://abacus.bates.edu/~ganderso/biology/resources/pipet.html
1042	Roach, et al., "Controlling Nonspecific Protein Adsorption in a Plug-Based Microfluidic System by Controlling Interfacial Chemistry Using Fluorous-Phase Surfactants," Anal. Chem. 2005, 77, 785-796 [DTX-0286, Case No. 15-152-RGA (D. Del.)]
1043	Leng, J., et al., "Microfluidic crystallization," Lab on a Chip, 2009, 9, 24–34 [PTX535, Case No. 15-152-RGA (D. Del.)]
1044	Breslauer, D., et al., "Microfluidics-based systems biology," Mol. BioSyst., 2006, 2, 97-112 [PTX536, Case No. 15-152-RGA]
1045	Huebner, A., et al., "Microdroplets: A sea of applications?," Lab Chip, 2008, 8, 1244–1254 [PTX989, Case No. 15-152-RGA (D. Del.)]
1046	Presentation titled, "Sia Rebuttal Slides", Case No. 15-152-RGA (D. Del.)
1047	Pollack, M., et al., "Electrowetting-based actuation of liquid droplets for microfluidic applications," Applied Physics Letters 77, 1725 (2000)
1048	International Publication Number Publication WO 84/02000 (Stewart, et al.)
1049	Web page from Sigma-Aldrich, titled, "Water Molecular Biology Reagent", available at https://www.sigmaaldrich.com/catalog/product/sigma/w4502?lang=en&region=US
1050	Web page from Sigma-Aldrich, titled, "Perfluorodecalin 95%", available at https://www.sigmaaldrich.com/catalog/product/aldrich/p9900?lang=en&region=US&gclid=CjwKCAjwq4fsBRBnEiwANTahcLo57up7qQKT--

Ex./ Doc.	Description
	Y2bDXlx9DNVhXoLPCq_rJjRS5NstHyeBVoiEfO5xoC1XkQAvD_BwE
1051	Web page from Sigma-Aldrich, titled, "Tetradecafluorohexane 99%", available at https://www.sigmaaldrich.com/catalog/product/aldrich/281042?lang=en&region=US
1052	Intentionally Omitted
1053	Intentionally Omitted
1054	Intentionally Omitted
1055	Intentionally Omitted
1056	Intentionally Omitted
1057	Intentionally Omitted
1058	Intentionally Omitted
1059	Intentionally Omitted
1060	U.S. Patent Publication No. 2013/0260447 annotated
1061	U.S. Patent Publication No. 2008/0003142
1062	U.S. Patent No. 7,439,014 ("Pamula 014")
1063	Web page from Sigma-Aldrich, titled, "Mineral oil light", available at https://www.sigmaaldrich.com/catalog/product/sial/330760?lang=en&region=US
1064	Web page from Sigma-Aldrich, titled, "Mineral oil heavy", available at https://www.sigmaaldrich.com/catalog/product/sial/330779?lang=en&region=US
1065	Presentation regarding Quake US2002/0058332 A1 and Ismagilov 60/379,927 Provisional [DDX14, Case No. 15-152-RGA]

I. INTRODUCTION

The microfluidics and fluidic principles the assemblies in U.S. Patent No. 9,562,837 (“the 837 Patent”) (Ex. 1001) claim were well known in the art before the filing of the applications that led to the 837 Patent. The 837 Patent claims cover assemblies that form liquid droplets surrounded by immiscible fluid and then separate the droplets from the immiscible fluid in a chamber. The earliest possible priority date of the 837 Patent (May 2006), is years after patents were filed by the Ismagilov group describing the droplet-formation techniques the 837 Patent claims, and years after the even earlier work of the Quake group showing microfluidic structures for generating and manipulating such droplets.

The principle that droplets float or sink relative to the immiscible fluid in which they form is basic physics: objects float or sink if their density differs from the surrounding fluid. It was nothing new. This was a known property of emulsions years before the earliest priority date of the 837 Patent. The Ismagilov group identified density years earlier as a way to sort droplets, and the Fair group described separating droplets with density before the earliest priority date of the 837 Patent.

The 837 Patent dependent claims also add nothing new. *E.g.*, the dependent claims require attaching a PCR tube or test tube. The Examiner already correctly concluded “it would have been obvious to one having ordinary skill in the art to use a test tube or a PCR tube as a vessel, as the claimed improvement on a device or

apparatus is not more than the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for improvement.” Ex. 1002, 1099-1100. The 837 Patent claims nothing new or non-obvious. Moreover, 10X is aware of no secondary considerations of non-obviousness, let alone any with the required nexus, to rebut 10X’s strong showing on obviousness.

The petitioned prior art was known to the patent applicant. Ex. 1004, Ismagilov Patent No. 7,129,091 B2 (“Ismagilov”); Ex. 1005, Ismagilov Publication No. 2006/0094119 A1 (“Ismagilov 119”); Ex. 1006, Quake Publication No. 2002/0058332 A1 (“Quake”); and Ex. 1007, Pamula Publication No. 2007/0243634 (“Pamula 634”) from the Fair group appear on the face of the patent, but these references were buried amongst nearly 1,700 references and were not discussed.

10X respectfully requests that the Board institute *Inter Partes* Review and cancel claims 1-4, 7-13, and 19-20 (“challenged claims”) of U.S. Patent No. 9,562,837, as unpatentable under 35 U.S.C. §§ 102 and 103.

II. GROUNDS FOR STANDING (37 C.F.R. § 42.104(A)-(B))

10X certifies that the 837 Patent is available for IPR and Petitioner is not barred or estopped from requesting IPR of any claims.

III. PERSON OF ORDINARY SKILL IN THE ART (“POSA”)

A POSA would have (1) 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, (2) a Bachelor of Science in such fields with four years of such experience, or (3) a higher level of education but less relevant practical experience, or more practical experience but less education that would be equivalent to these qualifications before the effective filing date (post-AIA) or before the time of invention (pre-AIA) of the claimed invention. The 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. 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. Before the effective filing date or time of invention, the state of the art included the teachings of the references in this Petition. A POSA would have been aware of other important references on handling microfluidic droplets.

IV. THE 837 PATENT

The 837 Patent was filed April 2, 2013, and has an earliest possible priority date of May 11, 2006. Ex. 1001. It is assigned to Bio-Rad per the Office’s electronic

records. The 837 “generally relates to assemblies for displacing droplets from a vessel that facilitate the collection and transfer of the droplets while minimizing sample loss.” Ex. 1001, abstract. The alleged inventions were known or obvious before the earliest possible priority date of May 11, 2006, or before the December 20, 2006, provisional application. 10X is aware of no evidence of any earlier invention date under pre-AIA §§ 102 and 103 nor evidence that Bio-Rad is entitled to provisional priority dates.

The 837 Patent relates to the field of handling microfluidic droplets, which includes systems and methods for forming and handling droplets, droplet applications, chemistry, components, and reactions in droplets. 837 Patent, title, abstract, 1:42-43 (field: “systems and methods for liquid handling”); 2:35-5:43. Fair, ¶ 62.

During prosecution, the claims were amended multiple times—by the applicant and Examiner—to overcome rejections by adding specificity to the claimed droplet formation module and the separation chamber. Ex. 1002 (837 Patent FH), 1054, 1057, 1110, 1113, 1134, 1137, 1165, 1168, 1184, 1188. Even the added elements were well-known and disclosed in references that were never the basis of a rejection.

V. THE AIA APPLIES

The 837 Patent is a transition application, and is subject to the America Invents Act (“AIA”). The AIA applies to any patent issuing on an application that “contains or contained at any time [] a claim to a claimed invention that has an effective filing date as defined in section 100(i) of title 35, United States Code, that is on or after” March 16, 2013. AIA (Public Law 112-29) § 3(n)(1). The application that led to the 837 Patent, 13/855,318, was filed April 2, 2013, and contained new matter and claims to that new matter with an effective filing date of April 2, 2013. For example, at least Claims 5 and 6 covering particular connections to a slide have an effective filing after March 16, 2013. The 13/855,318 application is similar to Application No. 11/803,104 (“104 Application”), as published on January 3, 2008, but Patent Owner added new matter (¶¶ 3-20), Figs. 38-41, ¶¶ 254-293 (“Methods and assemblies for droplet handling” and “Droplet Displacement and Amplification Reactions”), and other additions (¶¶ 424 “Incorporation by reference” and 425 “Equivalents”). *Compare* Ex. 1060 with Ex. 1061. The only disclosure of the outlets, nozzles, and slides claimed in Claims 5 and 6 is in the added new matter (e.g., ¶¶ 267, 274). Ex. 1060 at 29-30. *See also* Declaration of Dr. Richard B. Fair (Ex. 1008, “Fair”), ¶¶ 66. Thus, the AIA applies.

Nevertheless, if the AIA is found not to apply, the same art invalidates the challenged claims for the same reasons identified below. Fair, ¶ 67. Thus, both pre- and post-AIA §§ 102 and 103 are addressed.

VI. STATE OF THE ART

The art regarding droplet formation and the behavior of emulsions was well-developed before the earliest priority date of the 837 Patent. *See* Ex. 1008, Fair, ¶ 50.

The claimed droplet formation was long known. Ex. 1048. *E.g.*, the 1984 Stewart publication (WO84/02000) disclosed (Figure 1 reproduced below) droplet formation by flowing carrier fluid (1) in a conduit, introducing reactant fluid in a second conduit, and the carrier fluid separating and carrying droplets downstream. Ex. 1048, 4-7; Fair, ¶ 51.

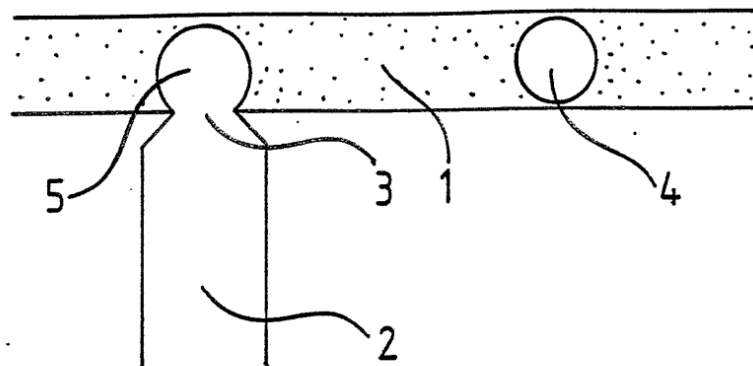


Figure 1.

By 2002, the Quake group had described generating droplets by similar means (Fig. 16A reproduced below). Quake, ¶ 84. The Quake group also disclosed detailed

microfluidic structures—such as wells—that were included in microfluidic systems.

Fair, ¶ 52.

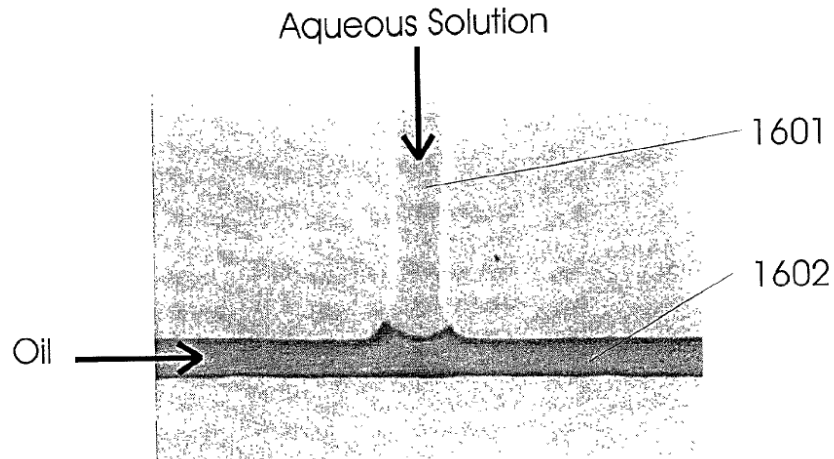


FIG. 16A

By 2003, the Ismagilov group had described droplet generation by similar means. *See*. Fig. 10A, 3A, Ismagilov, 2:50-59, 14:52-61; Fair, ¶ 53.

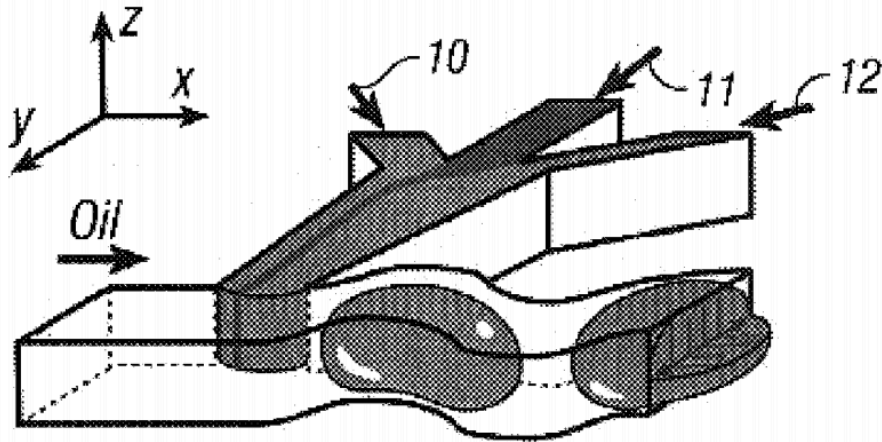


FIG. 10A

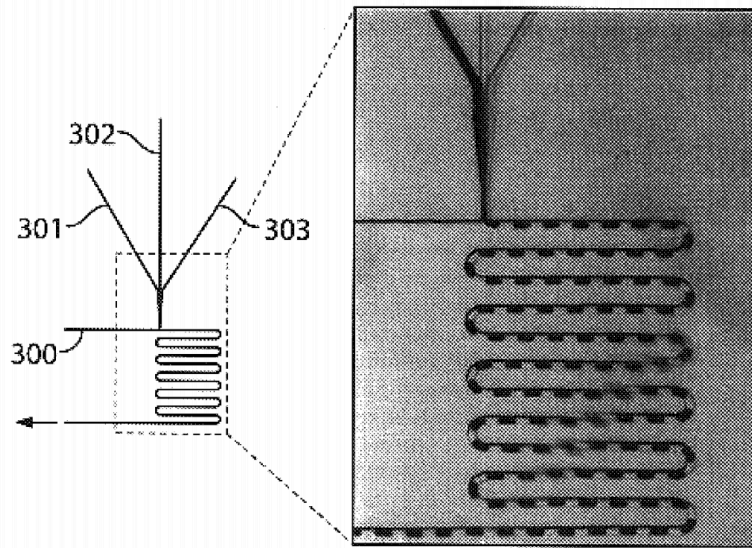
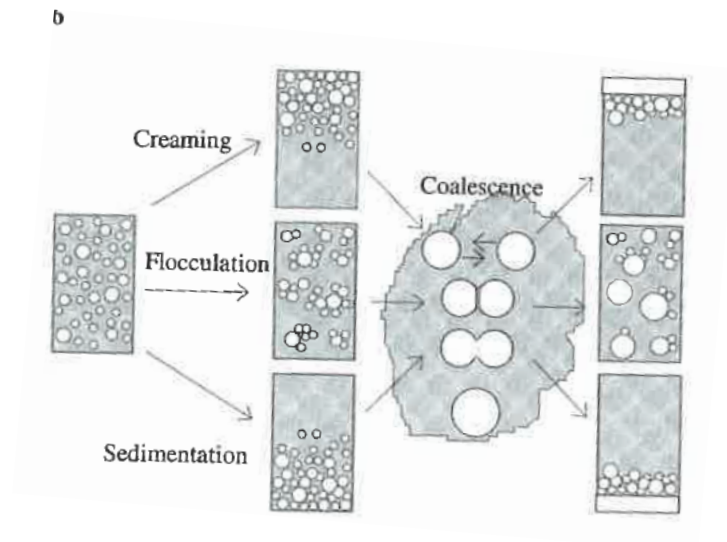


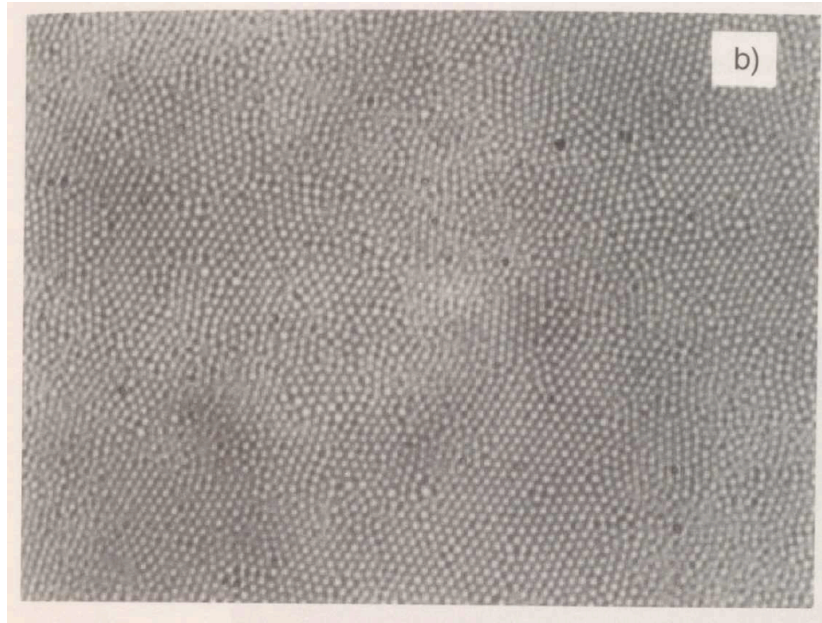
FIG. 3A

The natural property that fluids of different densities—including droplets—float or sink was well-known, as were the features of the containers in which that occurred. An emulsion reference book from 2001 illustrated creaming (floating) and sedimentation (sinking) of droplets, and stated: “[i]f a density difference exists between the dispersed and continuous phases, dispersed droplets experience a vertical force in a gravitational field” and “[t]he rate of creaming of noninteracting particles depends on density differences and the square of the droplet radius.” Ex. 1009, 146, 361, 567, 622. An emulsion placed in a relatively large volume will cream or sediment:



Id., Fig. 36. Other references described that different density droplets and fluids inherently float or sink. Ex. 1010, ¶ 3 (“After emulsification, droplets tend to rise by buoyancy.”); Ex. 1011, 578 (“Stratification has been seen for buoyant particles which cream to the top of their suspension as well as for dense particles which settle to the bottom.”). Fair, ¶¶ 54-55.

Another emulsion reference book from 2002 explained that “depending upon the densities of the solvent and the droplets, sedimentation or creaming occurs.” Ex. 1012 at 47-48. This book recognized the inherent property of density separation as useful: “the creamed droplets can be removed from the initial emulsion and redispersed” in a large vessel in a process for making monodisperse emulsions. Fair, ¶ 57. Ex. 1012 at 48. Figure 3.1(b) illustrates this:



It was well-known to generate droplets using fluids of different densities. Stewart disclosed mineral oils, silicon oils, and fluorinated hydrocarbons as immiscible carrier fluids. Ex. 1048, 6. Quake taught “decane (e.g., tetradecane or hexadecane) or another oil (for example, mineral oil)” as carriers. Quake, ¶ 15. Ismagilov disclosed a preferred embodiment with “an aqueous buffer solution, such as ultrapure water” and other reagents, and “fluorinated oil” as a preferred carrier fluid with many examples including perfluorohexane and perfluorodecaline. Ismagilov, 20:17-22, 20:37-44, 47:22-34; *see also id.*, 4:64-5:3, 19:40-47, 21:16-29, 34:21-26, 56:42-61, 58:52-55, 61:14-21, 71:53-62, 74:6-15. Aqueous (water) solutions and fluorinated oils have different densities. Ex. 1013 at 1977 (“Coalescence of water droplets in a fluorocarbon phase should be favored by the *large difference in densities*”). Water has a density of 1 g/cm³, while

perfluorohexane and perfluorodecaline have densities of around 1.7 and 1.9 g/cm³, respectively. Ex. 1014, 4-5. Given different densities, the less dense water droplets necessarily float in denser oil. By contrast, mineral oil is less dense than water (between 0.8 and 0.9 g/ml), and so aqueous droplets would sink. Ex. 1015-Ex. 1016, Exs. 1063-64, Exs. 1049-51; Fair, ¶¶ 56-57.

Bio-Rad elicited testimony of Dr. Ismagilov to support Bio-Rad's claims in prior litigation asserting Ismagilov (*Bio-Rad Labs. Inc. v. 10X Genomics, Inc.*, Case No. 15-cv-152-RGA in the U.S. District Court for the District of Delaware, ("152 case")), including that the droplets in Ismagilov were stable because of the "OEG-terminated surfactants high values of N": "we're emphasizing that the longer fluorinated tails are preferred in this chemistry, and they would be useful for **creating droplets, biological reactions with high stability** and high performance." Ex. 1017, 222:18-223:9.¹ Bio-Rad's assertion means the emulsions in Ismagilov could stably be pooled and would float.

The art also disclosed microfluidic structures for pooling droplets (after which they would float or sink based on density) and density separation itself. Ismagilov and Quake both disclosed wells or reservoirs. Ismagilov, 9:5-8, 14:36-38; Quake,

¹ Ismagilov includes similar text to that referred to in the question leading to this testimony. *Id.*, 37:23-45; Fig. 24.

¶ 196, Figs. 6, 8. Before the 837 Patent’s earliest possible priority date, the Ismagilov and Fair groups had each disclosed density separation in droplet systems. The Ismagilov group disclosed that “plugs [droplets] can be sorted by their density relative to that of the carrier fluid.” Ismagilov 119, ¶ 123. The Fair group described that droplets can be released and allowed to “*float or sink to the target destination.*” Ex. 1018, U.S. Patent Publication No. 2015/0148238 A1 (“Pamula 238”), ¶ 418; Pamula 634, ¶ 418; Ex. 1025 (Pamula 058) at 8-9; Fair, ¶ 59.

The 837 Patent added nothing new to microfluidic droplet handling. It took known prior art principles and patented them, often years after others disclosed them. The challenged claims of the 837 Patent are invalid. Fair, ¶ 60.

VII. PRIOR ART RELIED UPON IN 10X’S GROUNDS

A. Ex. 1004, U.S. Patent No. 7,129,091 B2 to Ismagilov et al. (“Ismagilov”)

Ismagilov was filed May 9, 2003, published as Publication No. 2005/0272159 on December 8, 2005 (Ex. 1019²), and issued on October 31, 2006. Ismagilov is prior art at least under post-AIA §102(a)(2) and pre-AIA 35 U.S.C. §102(e) because it is a U.S. patent that was effectively filed before the earliest possible effective filing date or alleged invention; under post-AIA §102(a)(1) and pre-AIA §102(a) because

² Citations throughout are to the issued 091 Patent; the published application contains the same substantive disclosures relied on herein.

the application published before the earliest possible effective filing date or alleged invention; and under pre-AIA 35 U.S.C. §102(b) if the 837 Patent claims are not entitled to their earliest priority date, as described in section VII(D) because the application published more than one year before the earliest date of application. Ismagilov was cited, buried, and not discussed during prosecution.

Ismagilov discloses substrates and methods for reactions in droplets (“plugs”) in a flow of carrier fluid in a substrate. Ismagilov, abstract. The plugs in Ismagilov are droplets that are surrounded by immiscible fluid: “aqueous plug-fluid is surrounded by a non-polar or hydrophobic fluid such as an oil.” *Id.*, 9:39-44; *see also id.* 4:64-5:3, 12:9-14, 21:7-35, 49:61-50:1, Fig. 10; Ex. 1017, 222:18-223:9, 261:3-11 (Ismagilov testifying regarding creating stable “droplets”). Ismagilov relates to droplet handling, as described in section V. *Id.*, 2:52-3:48, 37:23-45, 20:17-22, 20:37-44, 45:57-49:4, Fig. 24. Thus, Ismagilov is analogous art in the same field of endeavor as the 837 Patent and is pertinent to the problems of microfluidic droplet handling. Fair, ¶¶ 68-69.

B. Ex. 1005, U.S. Patent App. Pub. No. 2006/0094119 A1 to Ismagilov et al. (“Ismagilov 119”)

Ismagilov 119 was filed March 16, 2005, published on May 4, 2006, and issued on February 2, 2010, as U.S. Patent No. 7,655,470 B2 (Ex. 1020). Ismagilov 119 is prior art at least under post-AIA §102(a)(2) and pre-AIA 35 U.S.C. §102(e) because it is a U.S. patent effectively filed before the earliest possible effective filing

date or alleged invention; and under post-AIA §102(a)(1) and pre-AIA §102(a) because the application published before the earliest possible effective filing date or alleged invention. Ismagilov 119 was cited, buried, and not discussed during prosecution.

Ismagilov 119 discloses “microfluidic technology enabling rapid and economical manipulation of reactions on the femtoliter to microliter scale.” Ismagilov 119, abstract, ¶¶ 3, 7-9, 28. The Ismagilov 119 plugs are droplets: “plugs are kept from coalescing by surfactant assemblies at the interfaces between the reagent solutions and the carrier fluid, and by a layer of the carrier fluid between the two plug fluids.” *Id.*, ¶ 83; ¶ 77. This is confirmed because Ismagilov 119 uses “droplets” and “plugs” interchangeably: “At the junction, aqueous *droplets, or plugs*, form spontaneously.” *Id.*, ¶ 22; *see also* Ex. 1017, 222:18-223:9 and 261:3-11 (Dr. Ismagilov’s testimony in the 152 case). Ismagilov 119 discloses droplet handling, as described in section IV below. *E.g.*, Ismagilov 119, ¶¶ 7-9, 28, 72, 77, 94, 123. In particular, Ismagilov described sorting droplets by density relative to the carrier fluid. Fair, ¶¶ 70-71.

C. Ex. 1006, US Patent App. Pub. No. 2002/0058332 A1 to Quake et al. (“Quake”)

Quake was filed September 14, 2001, published on May 16, 2002, and issued on November 13, 2007 as U.S. Patent No. 7,294,503 B2 (Ex. 1021). Quake is prior art at least under post-AIA §102(a)(2) and pre-AIA 35 U.S.C. §102(e) because it is

a U.S. patent effectively filed before the earliest possible effective filing date or alleged invention; under post-AIA §102(a)(1) and pre-AIA §102(a) because the application published before the earliest possible effective filing date or alleged invention; under pre-AIA 35 U.S.C. §102(b) because the application published more than one year before the earliest date of application for the 837 Patent. Quake was cited, buried, and not discussed during prosecution.

Quake discloses “microfluidic devices and methods,” including particularly devices “designed to compartmentalize small droplets of aqueous solution within microfluidic channels filled with oil.” Quake, ¶¶ 3-4. Quake discloses aqueous droplets “encapsulated or separated from each other by oil.” *Id.*, ¶¶ 100, 93. Quake discloses droplet handling, as described in section IV below. *E.g., Id.*, ¶¶ 95, 195-200. Fair, ¶¶ 72-73.

D. Ex. 1007, U.S. Patent Application Publication No. 2007/0243634 A1 (“Pamula 634”); and Ex. 1018, No. 2015/0148238 A1 (“Pamula 238”) to Pamula et al. (collectively, “Pamula”)

Pamula 634 was filed December 15, 2006, published on October 18, 2007, and issued on October 21, 2008 as U.S. Patent No. 7,439,014 B2 (Ex. 1062). Pamula 634 is prior art at least under post-AIA §102(a)(2) and pre-AIA 35 U.S.C. §102(e) because it is a U.S. patent effectively filed before the effective filing date or alleged invention of the claimed invention. The 837 Patent claims priority to provisional applications as early as May 11, 2006, but the provisional applications through at

least December 12, 2006, do not support the claims of the 837 Patent. Many 837 Provisionals before December 12, 2006, do not relate to droplet separation at all, and others—Application Nos. 60/856,440, 60/837,871, 60/874,561—merely describe creaming without any description of the claimed separation chamber or its connections to other claimed microfluidics. Ex. 1022, 3; Ex. 1023, 2-3; Ex. 1024, 3. Pamula 634 was cited, buried, and not discussed during prosecution. Fair, ¶ 74.

Pamula 238 was filed January 30, 2015, published on May 28, 2015, and claims priority to U.S. Provisional Application No. 60/745,058 (Pamula 058) which was filed April 18, 2006. It is entitled to the priority date of Provisional Application No. 60/745,058 (“Pamula 058”) (Ex. 1025), making it prior art under post-AIA §102(a)(2) and pre-AIA 35 U.S.C. §102(e) because it is a U.S. patent publication effectively filed before the effective filing date or alleged invention. The disclosures on which 10X relies are substantially identical between the publication and provisional. *See* Pamula 238, ¶ 418; Pamula 058 at 8-9. Pamula 238 includes claims supported by that provisional. *See Ex Parte Ihara*, No. 2018-004744, 2019 Pat. App. LEXIS 4133, *4-5 (P.T.A.B. June 10, 2019) (*citing Dynamic Drinkware, LLC v. National Graphics, Inc.*, 800 F.3d 1375 (Fed. Cir. 2015)) (“For a prior art reference under 35 U.S.C. § 102(e) to be entitled to the benefit of the filing date of a provisional application under 35 U.S.C. § 119(e), the provisional application must (1) support the subject matter relied upon to make the rejection in compliance with

35 U.S.C. § 112(a), and (2) support at least one of the claims of the patent in compliance with 35 U.S.C. § 112(a).”). At least Claims 56 and 62 in Pamula 238 are supported by the provisional Pamula 058. Pamula 058 discloses droplet reservoirs, a droplet microactuator with substrates and a filler fluid selected to have a particular density relative to that of the droplet to exploit buoyancy forces, electrodes and transported droplets, an input port, and releasing the droplet to float or sink to the target destination. Ex. 1025 at 1-3, 5, 8-9, 12, Figs. 1, 4-6, Fair, ¶ 75. Pamula 238 was not cited art during prosecution.

Pamula 634 and Pamula 238 (collectively “Pamula”) disclose droplet systems. Pamula 058, 1; Pamula 238, ¶ 3, Pamula 634, ¶ 3. In these systems, the droplets are surrounded by filler fluid. Pamula 058, 3 (“the secondary phase merely serves as a filler fluid separating the droplets from each other” and “evaporation of the droplets can be prevented when the liquid filler completely bathes all surfaces of the droplet”), 8, Fig. 5; Pamula 238, ¶ 21, Pamula 634, ¶ 21. Pamula relates to droplet handling, as described in section IV below. *E.g.*, Pamula 058, 7-11; Pamula 238, ¶¶ 54, 412-13, 427, Pamula 634, ¶¶ 54, 412-13, 427. Fair, ¶ 76.

VIII. CLAIM CONSTRUCTION

Although the parties have not yet exchanged claim constructions in the related district court proceeding, Bio-Rad has served infringement contentions showing Bio-Rad’s expected claim interpretations. *See* Ex. 1026 (Bio-Rad’s infringement

chart regarding certain accused products). Bio-Rad is expected to take the same positions here, and based on these constructions the prior art discloses all limitations of the challenged claims. The infringement contentions are patent owner's statements before a Federal court on the scope of a claim of a patent and may thus be cited here per 35 U.S.C. §301(a)(2) and per §301(d) the Office may consider them to determine proper meaning of patent claims in IPR proceedings under §314. *Donnelly Distribution LLC v. Russo Trading Co., Inc.*, IPR2019-00761, Paper 8, 17-18 (PTAB Sept. 6, 2019).

10X provides its proposed constructions for terms that may be relevant to institution, and addresses 10X's constructions and Bio-Rad's expected interpretations (if known) based on Bio-Rad's infringement contentions. *Gen. Elec. Co. v. Vestas Wind Sys. A/S*, IPR2018-00928, Paper 9 at 12-17 (PTAB Nov. 5, 2018).

Claim Term	10X Construction	Bio-Rad Expected Construction
"droplet receiving outlet" (Claim 1)	<p><u>Subject to 112(f):</u></p> <p>Structure: the outlet structure described at 3:46-58, 53:21-35, or outlet 805 as described at 54:34-46, and Figure 38 and equivalents thereof</p> <p>Function: receiving substantially only droplets when exiting from the chamber</p>	Broad enough to include the opening at the top of an open outlet well (Ex. 1026, 11-12.)

	Alternatively, if not subject to 112(f): “a structure connected to the interior space of the chamber and configured so that substantially only droplets flow into it when exiting the chamber”	
“separation chamber” (Claim 1)	“a space that is substantially enclosed”	Broad enough to encompass an open well. Ex. 1026.
“droplet” (Claim 1)	“an isolated portion of a first fluid that is completely surrounded by a second fluid”	N/A
“sample” (Claim 1)	“a compound, composition, and/or mixture of interest, from any suitable source(s)”	Bio-Rad agreed to this construction in prior litigation.
“coupled” (Claims 7-8)	“fastened or joined”	Broad enough to encompass transporting by pipette between an alleged outlet/chamber and vessel. See Ex. 1026, 21-22.
“polymerase chain reaction” (“PCR”) (Claim 13)	“Method of amplifying a target sequence of nucleic acids that involves repeated cycles of DNA replication, wherein 1) strands of DNA are denatured to form single-strand templates; 2) the templates are treated with oligonucleotide primers and a polymerase enzyme is used to extend the primers to produce	Broad enough to encompass any amplification reaction. See Ex. 1026, 27-29.

	<p>replicated double-stranded DNA; 3) the replicated DNA then serves as a template for additional replication. The target sequence need not be specifically identified as a target in advance of the reaction.”</p>	
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A. “droplet receiving outlet” (Claim 1)

The term “droplet receiving outlet” should be construed as a means-plus-function limitation under 35 U.S.C. § 112(f) as it is not in the specification and has no well-understood meaning in the art. Fair, ¶ 80; *MTD Prod. Inc. v. Iancu*, 933 F.3d 1336, 1343-45 (Fed. Cir. 2019). The term is also described in functional terms, i.e., an outlet for receiving droplets, without any further language in the claim that might inform the structure. *Id.* The specification also consistently describes the chamber outlet in functional terms: “*configured to receive substantially only droplets*” and that “*substantially only droplets to exit the chamber*,” and that droplets “flow into the outlet.” 837 Patent, Abstract, 3:46-58, 53:21-35; *see also id.*, 53:21-41, 54:34-46, 55:41-44. Accordingly, the corresponding structure are the outlets described in these same passages, for example Figure 38 shows outlet (805) through which droplets exit the chamber is connected to the interior of the chamber. *See also* 837 Patent, 54:34-46; Fig. 38; *see also id.*, 3:46-58, 53:21-35. Bio-Rad’s doctrine of equivalents contentions support this construction as well: “[t]he outlet is

configured to allow ***substantially only droplets*** to be removed from the separation chamber” and that the outlet “allow[s] droplets to ***flow out*** of the separation chamber ***through*** an outlet.” Ex. 1026, 12; Fair, ¶¶ 80-85 . If 112(f) does not apply, then for the same reasons the alternative construction applies.

B. “separation chamber” (Claim 1)

The ordinary meaning of “chamber” is “[a]n enclosed space, cavity, etc.” Ex. 1027, 234 (Compact Oxford Dictionary, 1994); Ex. 1028, 190 (Merriam-Webster’s Collegiate Dictionary, 1997) (“a natural or artificial enclosed space or cavity”). A POSA would understand this ordinary meaning applies here. A primary purpose of the invention was to “displace sample droplets from one location to another without the need for operator handling,” which means “the risk of contamination associated with such handling is eliminated.” 837 Patent, 52:33-37; *see also id.*, 2:4-31, 2:35-40, 4:29-47, 4:60-5:3, 5:21-23, 55:2-4, 55:22-26, 55:57-59, 56:12-19, 56:38-50, 57:66-58:4, Figs. 38-39. Open chambers eliminates neither operator handling nor contamination, and one of ordinary skill would not understand the term “separation chamber” to include open containers. While the specification says a chamber can “***include*** any vessel suitable for holding droplets, for example, test tubes, vials, beakers, jars, and PCR tubes,” *Id.*, 53:35-38, they are consistently and exclusively ***enclosed***—not open—when in use with a “seal” to “minimize potential contamination.” *Id.*, 55:55-65, Fig. 39. All descriptions in the specification

of the separation chamber are also consistent with this construction. *Id.*, 2:43-50, 3:37-58, 4:8-20, 53:21-56:59. Fair, ¶¶ 86-90.

C. “droplet” (Claim 1)

10X’s construction is the specification’s definition of “droplet.” 837 Patent, 15:1-3. Fair, ¶ 91.

D. “sample” (Claim 1)

10X’s construction was agreed in a prior litigation between 10X and Bio-Rad that included patents that were also related to droplet generation with priority dates within years of each other. Ex. 1029. The specification references: “*samples can be analyzed*,” “*sample to be analyzed*,” a “*sample under study*,” and a “*fluid of interest (e.g., sample fluid)*.” 837 Patent, 5:21-23, 18:46-48, 35:27-30, 21:52-56. This is consistent with other examples and usages of “sample[s]” in the specification. Fair, ¶¶ 92-94.

E. “coupled” (Claims 7-8)

“To couple” means “[t]o fasten or link together (properly in pairs); to join or connect in any way” Ex. 1027, 350 (Compact Oxford Dictionary, 1994); Ex. 1028, 266 (Merriam-Webster’s Collegiate Dictionary, 1997) (“to fasten together”). Relevant uses of “coupled” in the specification are consistent. 837 Patent, 4:26-31, 37:10-14 (“A preferred detector is an optical detector, such as a microscope, which may be *coupled* with a computer and/or other image processing or enhancement devices”), 55:1-4 (“In certain embodiments, the outlet 805 may be sealably

coupled to the vessel. Sealably *coupling* the outlet 805 to the vessel prevents contamination from outside sources as the droplets are transferred to the vessel.”), 55:11-21, 59:66-60:3. Fair, ¶ 95.

F. “polymerase chain reaction” (“PCR”) (Claim 13)

The court adopted the construction 10X proposes here in the 152 case, which included Ismagilov (a patent in the relevant field and from a similar time to the 837 Patent). Ex. 1030. This is also the ordinary meaning of PCR to a POSA. [Fair]; Ex. 1031, Fig. 8-39. The specification’s descriptions are consistent with this construction and confirm that not all methods of amplification are PCR. 837 Patent, 60:5-11; 69:49-51, 68:38-40, 83:4-17. Fair, ¶¶ 96-99.

IX. IDENTIFICATION OF CHALLENGE (37 C.F.R. § 42.104(b))

Petitioner challenges the validity of claims 1-4, 7-13, and 19-20 of the 837 Patent. Per 37 C.F.R. § 42.6(c), copies of the references accompany the Petition. The Grounds for unpatentability are further supported by the declaration of Dr. Fair, an expert in microfluidic droplet handling, emulsions, droplet reactions, droplet composition and chemistry.

10X challenges Bio-Rad’s claims under two main theories. First, 10X identifies prior art disclosures meeting the broad constructions implied by Bio-Rad’s infringement contentions: specifically, collection wells. Ismagilov discloses a collection well (**Ground 1**) and anticipates. Further, a POSA would have been

motivated to combine Quake for additional information regarding the structure of a well of a microfluidic device (**Ground 2**). Fair, ¶ 101.

Second, under 10X's proposed constructions, Ismagilov 119, which incorporates by reference in its entirety Ismagilov, discloses a density sorter in which droplets are sorted by their density relative to that of the carrier fluid (**Ground 3a**). Further, a POSA would have been motivated combine it with Pamula for additional information regarding that structure (**Grounds 4a and 5a**). The two Pamula references are addressed together because their relevant disclosures are substantively identical but they have different dates as prior art. The same disclosures that meet 10X's constructions also meet Bio-Rad's broader expected constructions (**Grounds 3b, 4b, 5b**). Fair, ¶ 102.

Ground	Basis	Challenged Claims	References	Claim Construction
1	§ 102	1-2, 4, 10-13, 19-20	Ismagilov	Bio-Rad's
2	§ 103	1-2, 4, 7, 9-13, 19-20	Ismagilov and Quake	Bio-Rad's
3a	§ 103	1-4, 7-13, 19-20	Ismagilov 119	10X's
3b	§ 103	1-4, 7-13, 19-20	Ismagilov 119	Bio-Rad's
4a	§ 103	1-4, 7-13, 19-20	Ismagilov 119 and Pamula 634	10X's
4b	§ 103	1-4, 7-13, 19-20	Ismagilov 119 and Pamula 634	Bio-Rad's

5a	§ 103	1-4, 7-13, 19-20	Ismagilov 119 and Pamula 238	10X's
5b	§ 103	1-4, 7-13, 19-20	Ismagilov 119 and Pamula 238	Bio-Rad's

The relevant provisions of §102 for each prior art reference are identified in the preceding section. Post-AIA §103 and pre-AIA §103(a) are the relevant statutes for obviousness.

X. OVERVIEW OF GROUNDS 1-5

A. Ground 1

Ismagilov anticipates claims 1-2, 4, 10-13, and 19-20 of the 837 Patent. As is described further below, Ismagilov's teachings related to a microfluidic device that contains a droplet formation module and an output well disclose all limitations of the identified claims under Bio-Rad's interpretations of the claims. Fair, ¶ 103.

B. Ground 2

Even if Ismagilov did not expressly disclose all the challenged claim limitations, which it does, the challenged claims are obvious in view of Ismagilov in combination with Quake. While Ismagilov disclosed a droplet formation module and wells (a separation chamber under Bio-Rad's interpretations), to the extent a POSA would not have known the structure of such features (which a POSA would), a POSA would also have been motivated to look to art that further describes the structure of wells. Per section VII(C), Quake was such a reference that related to "microfluidic

devices and methods” and included further descriptions of wells or reservoirs. Quake, ¶ 3. Fair, ¶ 104.

A POSA would have been motivated to combine Ismagilov with Quake. Stephen Quake was well-known in microfluidics, and a POSA with Ismagilov would have been motivated to combine with Quake for additional microfluidic structures, including particularly wells or reservoirs. Quake was an early, leading researcher in droplet microfluidics. In 2001, Quake’s group published a Physical Review Letter showing generation of water droplets in a continuous oil phase. Ex. 1032. Quake later wrote that this work “attracted interest in the fluid physics community.” Ex. 1033; e.g., Ex. 1034 (publication citing Quake’s work). Fair, ¶ 105.

The Ismagilov group was well aware of Quake’s work and was specifically aware of Quake as included in the grounds here. Quake was cited prior art considered by the Examiner during prosecution of Ismagilov (and identified on the face of the 091 patent). Indeed, Ismagilov copied portions of Quake. *Compare, e.g.*, Ismagilov, 17:23-30 (manifolds, described below), with Quake, ¶¶ 148; Ex. 1017, 227:17-22, 230:21-231:23, 313:22-315:7 (Dr. Ismagilov’s testimony that Quake’s work was provided to team preparing patent applications, portions of another Quake patent application were copied); Ex. 1065 (exemplary sections Ismagilov copied from Quake); Ex. 1004 [Ismagilov] at pages 1-2 (identifying Quake 332, Thorsen, et al., “Microfluidic Large-Scale Integration”, *Science*, vol. 298, pp. 580-584, 2002,

Thorsen, Todd et al., “Dynamic Pattern Formation in a Vesicle-Generating Microfluidic Device”, *Physical Review Letters*, vol. 86, No. 18, 2001, pp 4163-4166 (Ex. 1032)). Ismagilov testified in the 152 case that he followed Quake’s work, sought Quake’s help specifically on making a microfluidic system, discussed Quake’s work with others, and was “disappointed” and “upset” when Quake was first to publish the physics of droplets. Ex. 1017, 228:16-230:9, 235:10-239:24, 243:12-245:5, 249:14-18. Ismagilov testified that he knew of Dr. Quake’s patent publications and articles shortly after they were published. Ex. 1017, 319:12-17, 321:2-12. Fair, ¶ 106.

Quake wrote an important review of the field in 2005, and work from both Quake and Ismagilov was included, further confirming that Quake was a known leader whose work a POSA would consider. Ex. 1035. Multiple publications that Bio-Rad relied on in a trial supposedly to show praise of Ismagilov’s work also discussed the Quake’s work. Ex. 1017 [152 Tr.] at 1290-1293, 1306-1311; Ex. 1042 [DTX-0286.0001], Ex. 1043 [PTX535-006,007,010], Ex. 1044 [PTX 536-10] (highlights in original), Ex. 1045 [PTX989-004], Ex. 1046 [Sia Rebuttal Demonstrative, slides 4-7] [Sia secondary consideration articles & referenced demonstrative slides]. If a POSA with Ismagilov would want additional information regarding microfluidic structures, the POSA would have looked to the work of a

leader in developing early microfluidic devices: Quake. Fair, ¶ 107. The combination of Ismagilov and Quake is further discussed in Section XI.

C. Ground 3

Ismagilov 119 incorporates Ismagilov in its entirety by reference in the first section under the heading “detailed description of the invention,” and then again in the section “reactions within plugs”: “Plug-based microfluidic manipulation of solutions has been described previously by the present inventors in U.S. Ser. Nos. 10/434,970 [Application for Ismagilov 091] and 10/765,718, incorporated herein in their entirety by reference.” Ismagilov 119, ¶¶ 30, 118 (same). *See Husky Injection Molding Sys. v. Athena Automation Ltd.*, 838 F.3d 1236, 1248-49 (Fed. Cir. 2016); *Harari v. Lee*, 656 F.3d 1331, 1335-36 (Fed. Cir. 2011). U.S. Ser. No. 10/434,970 (“970 Application”) issued as the Ismagilov patent. Ismagilov 119 is therefore a single reference that includes all of its own disclosures as well as all disclosures of Ismagilov based on incorporation by reference. Fair, ¶ 108.

As is described further below, under Grounds 3-5, Ismagilov discloses microfluidic devices that may have a droplet formation modules and detection regions and/or sorting regions. *E.g.*, Ismagilov 7:61-64, 11:23-40, 15:10-15, 15:46-50, 28:7-12, 28:67-29:5, 29:6-8, 31:20-22, 31:22-34:3. The density sorter of Ismagilov 119 would be such a module and was disclosed as part of such a modular

system, or it would have been obvious to include in such a modular system. Fair, ¶ 109.

Ismagilov 119, including Ismagilov, describes components that can work as a single system. The references describe similar and compatible features of the same modular microfluidic system, as the prominent placement of incorporation by reference confirms. Fair, ¶ 110.

Even if Ismagilov 119 and 091 were not a single reference, combining them was obvious. Incorporation by reference, the same group of researchers, and the later reference building on and complementing the other, reflect motivation to combine the references. Fair, ¶ 111.

D. Grounds 4 and 5

The challenged claims are obvious in light of Ismagilov in combination with Pamula. In the event that the Board determines that only one of Pamula 634 or Pamula 238 is prior art, this petition identifies Grounds based on each—Grounds 4a and 4b—based on Ismagilov in view of Pamula 634, and Grounds 5a and 5b based on Ismagilov in view of Pamula 238. The teachings and disclosures of Pamula 634 and Pamula 238 are substantively identical and so these grounds are addressed collectively in Section XII below. Fair, ¶ 112.

A POSA would have been motivated to combine Ismagilov with Pamula. Ismagilov disclosed density sorting. If Bio-Rad argues a POSA would need

additional information regarding density sorting, a POSA would have been motivated to consider art describing density sorting related to droplet handling, such as Pamula as explained in section VII(D). Fair, ¶ 113.

The work arising from the Fair lab (including Pamula 634 and Pamula 238) was well-known in the field particularly for droplet handling techniques, and a POSA with Ismagilov would have been motivated to consider Pamula from the Fair lab for additional information regarding droplet handling methods, including density separation, if required. Fair, ¶ 113. Dr. Fair was an early leading researcher in droplet handling. Dr. Fair's group began publishing on droplets in 2000. Ex. 1038 (2002 publication); Ex. 1047 (2000 publication); Fair, ¶ 114. Work from Dr. Fair and Dr. Pamula's group was also included in the 2005 Quake review, including Ex. 1038, along with the work of Drs. Ismagilov and Quake. Ex. 1035. This confirms that Fair and Pamula's group was a well known source a POSA would consider in the field at the time. Ex. 1035. Dr. Fair and his group were well-known cofounders of Advanced Liquid Logic, another well-known microfluidics company formed in 2004. Ex. 1039. Thus, if a POSA with Ismagilov would want additional information regarding droplet methods, the POSA would have looked to the work of early leaders in the field, the Fair and Pamula group, including the teachings of Pamula 634 and Pamula 238. The combination of Ismagilov and Pamula are discussed Section XII.

XI. GROUNDS 1-2 INVALIDATE THE IDENTIFIED CLAIMS BASED ON THE DISCLOSURE OF WELLS

A. Claim 1

1. [1.0] “An assembly, the assembly comprising:”

To the extent that the preamble is limiting, Ismagilov discloses the preamble, e.g.: “The present invention provides *microfabricated substrates* and methods of conducting reactions within these substrates,” which are or are part of an assembly. Ismagilov, Abstract; *see also id.*, 11:19-23.³ Fair, ¶ 119.

2. [1.1] “a microchannel in a horizontal plane;”

Ismagilov meets this limitation, describing substrates containing microchannels and their formation, which confirms there are microchannels in a horizontal plane.

Per Ismagilov, to form channels, such as PDMS channels, the channels are molded and then 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.” Ismagilov, 16:23-41. Ismagilov discloses using the flat glass as the “floor,” showing

³ Emphasis is added, internal quotation marks are omitted, and internal citations are omitted unless otherwise stated.

that the substrate would be placed with that surface down and the channels run parallel to that surface, i.e. horizontally. Fair, ¶¶ 120-123.

Ismagilov confirms that the “channel[s]” are “microchannels that are of dimensions suitable for use in devices.” Ismagilov, 7:34-52. “Microfluidics,” which “deals with the transport of fluids through networks of channels, typically having micrometer dimensions,” plays a “central role” in Ismagilov. Ismagilov, 1:14-18; Fair, ¶ 124.

3. **[1.2] “at least one droplet formation module comprising a sample inlet, an immiscible fluid inlet, and a junction, wherein the junction is located between the sample inlet and the microchannel and the droplet formation module is configured to produce droplets comprising the sample surrounded by the immiscible fluid; and”**

Ismagilov describes this limitation, first by disclosing droplet formation modules in which there is a sample inlet for droplet fluid, an inlet for immiscible fluids, and a junction:

The different *plug-forming regions* may each be connected to the same or different channels of the substrate. Preferably, *the sample inlet intersects* a first channel such that the pressurized plug fluid is introduced into the first channel at an angle to a *stream of carrier-fluid passing through the first channel*. For example, in preferred embodiments, the sample inlet and first channel intercept at a *T-shaped junction*; i.e., such that the sample inlet is perpendicular (i.e. at an angle of 90°) to the first channel.

Ismagilov, 14:52-61; *see also id.*, 2:50-59, 9:55-61, 14:20-30, 14:36-43, 15:53-60,

50:48-54, 22:5-16. Ismagilov provides multiple examples of samples that are a compound of interest under 10X's construction and are in droplets. *E.g.*, Ismagilov, 46:2-5; 47:41-44 ("Preferably, the systems and methods of the present invention are used in the **visual detection** of a single molecule of **DNA, RNA, or protein** labeled with nanoparticles via an autocatalytic pathway."), 52:60-62, 67:58-61 ("On the left side of the microfluidic network, the approximately 1 μm^3 plugs of the **sample to be analyzed** form at a junction of two channels (shown in green)."). Ismagilov describes a "sample inlet" through which the disclosed samples would be provided. Fair, ¶¶ 125-126.

Second, Ismagilov discloses the droplet formation module configured to produce droplets with sample surrounded by immiscible fluid. Sample inlet fluid is in the droplets surrounded by the carrier fluid, as the foregoing shows and as is further shown by figures 10A and 3A below. *See also*, Figs. 2-10. Ismagilov discloses droplets, typically aqueous, surrounded by immiscible fluid, as described in section VII and shown in the below figures. Ismagilov, 9:39-44 ("[A]queous plug-fluid is **surrounded by** a non-polar or hydrophobic fluid such as an oil."). The droplets (plugs) may be aqueous and contain a sample (e.g., DNA): "Plug-fluids may comprise a solvent and optionally, a reactant. . . . In a preferred embodiment, the solvent may be an **aqueous** buffer solution, such as ultrapure **water** Suitable reactants for use in the invention include synthetic Small molecules, **biological**

molecules (i.e., proteins, **DNA**, RNA, carbohydrates, Sugars, etc.) . . .” Ismagilov, 20:10-23, 21:1-6. Ismagilov confirms that “plugs” “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*.” Ismagilov, 9:20-34; *see also id.*, 2:50-59, 8:41-47, 9:55-61, 9:35-54. Fair, ¶ 127.

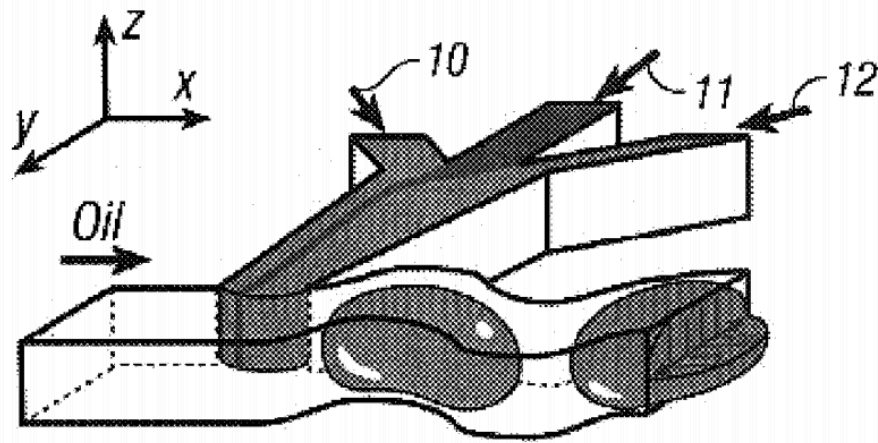


FIG. 10A

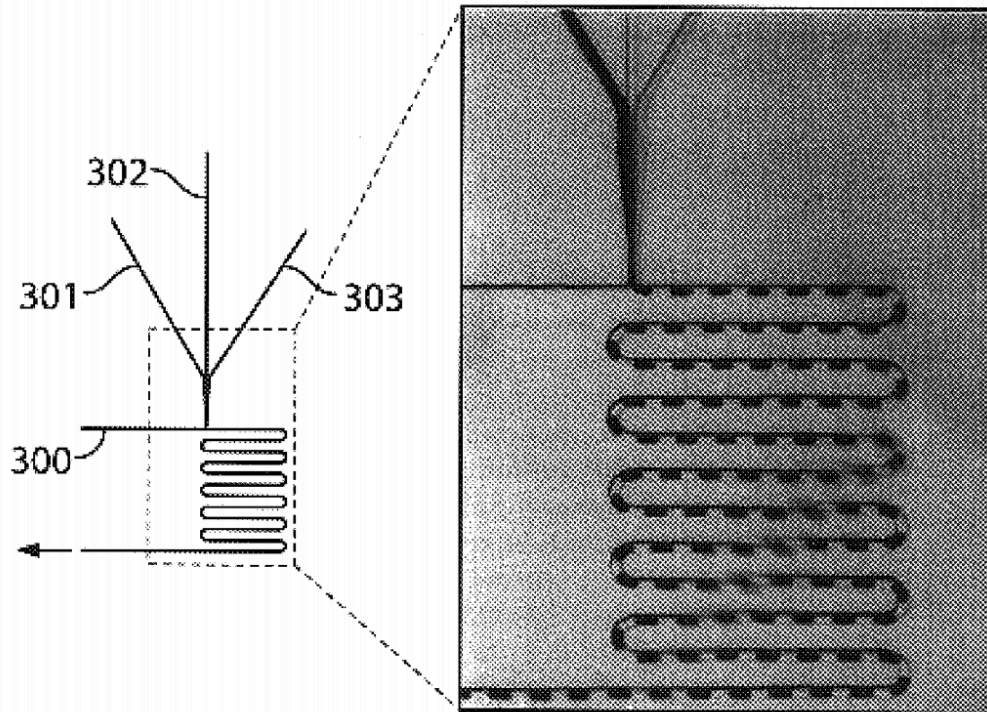


FIG. 3A

Third, these figures show the junction between the sample inlet and the microchannel, and that the microchannel contains droplets downstream of their formation. Fair, ¶ 128.

4. [1.3] “at least one downstream separation chamber comprising a droplet receiving chamber inlet and at least one droplet receiving outlet,”

a. Ground 1

Ismagilov discloses this limitation under Bio-Rad’s interpretations. Bio-Rad interprets separation chamber and droplet receiving outlet as broad enough to encompass an open well and the opening at the top of an open outlet well, which Bio-Rad describes as the location in the well where a pipette is inserted. Ex. 1026,

11. Ismagilov discloses collection wells or reservoirs that are a separation chamber with a droplet receiving outlet under Bio-Rad's interpretations. Ismagilov discloses an "outlet port," "an area of a substrate that *collects* or dispenses . . . plugs" and may "communicate with a *well or reservoir*." Ismagilov, 9:5-8, 14:36-38. Ismagilov describes after a manifold an "outlet" that "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*." Ismagilov, 17:27-30. Collecting fluids by micropipette requires a container with a volume of liquid to pipette and an opening to insert the pipette, *i.e.* a collection well. Fair, ¶¶ 129-132 (citing Ex. 1040, Ex. 1041).

Ismagilov discloses a droplet receiving chamber inlet for these wells or reservoirs (separation chambers): the outlet port "may be in fluid communication with the channels or reservoirs that [it is] connecting." Ismagilov, 14:38-40. The manifold outlet likewise connects to channels and a well. Ismagilov, 17:27-30. Fair, ¶ 133. As described for limitation 1.2, Ismagilov's droplets form in channels, and the fluids from those channels flow through the substrate to the outlet and into the well or reservoir, where the "outlet" of the manifold is the droplet receiving chamber *inlet* for the wells or reservoirs (separation chambers).

Ismagilov also discloses the separation chamber and droplet receiving outlet under Bio-Rad's interpretations by disclosing a well or reservoir with an opening at

the top. A well in the context of an outlet has an opening at the top, and Ismagilov confirms there is an opening in the manifold outlet well by describing the ability to collect the fluids by micropipette. The description of “collect[ing]” with the outlet port further confirms that the collected items would be accessible. Under Bio-Rad’s interpretation, a well with an opening into which a pipette can be inserted meets this limitation. Fair, ¶ 134.

The separation chamber is also downstream of the droplet formation module. Ismagilov discloses microfluidic devices with a pressure-driven flow through the substrate from where the fluids enter (inlet) to where they exit (outlet). Ismagilov, 21:48-54, 14:21-29 (“applying continuous pressure to a fluid within the substrate”). The “inlet port” to “receive[s] plug-fluids,” and an “outlet port” to “collect[s] or dispense[s] the plug-fluids.” Ismagilov, 3:15-20, 8:41-42, 9:5-7. The fluids, including after they form plugs, flow through the substrate from where they enter (inlet) to where they exit (outlet). *See* Ismagilov, 21:48-54; *see also id.*, 14:33-35 (“The substrates of the present invention may comprise an array of connected channels.”). Thus, the plugs formed as described for limitation 1.2 are the same plugs that enter the wells or reservoirs described for limitation 1.3. The plugs enter the separation chamber downstream of their formation, and so the separation chamber is downstream of the droplet formation module.

b. Ground 2

While Ismagilov describes this limitation, Quake also renders this limitation obvious under Bio-Rad's interpretation of the claims. The motivation to combine the wells in Quake with Ismagilov is described in section X(A). Fair, ¶ 150.

Quake describes and shows the wells or reservoirs as large, open structures with inlets from channels, as shown below in Figures 6 and 8.

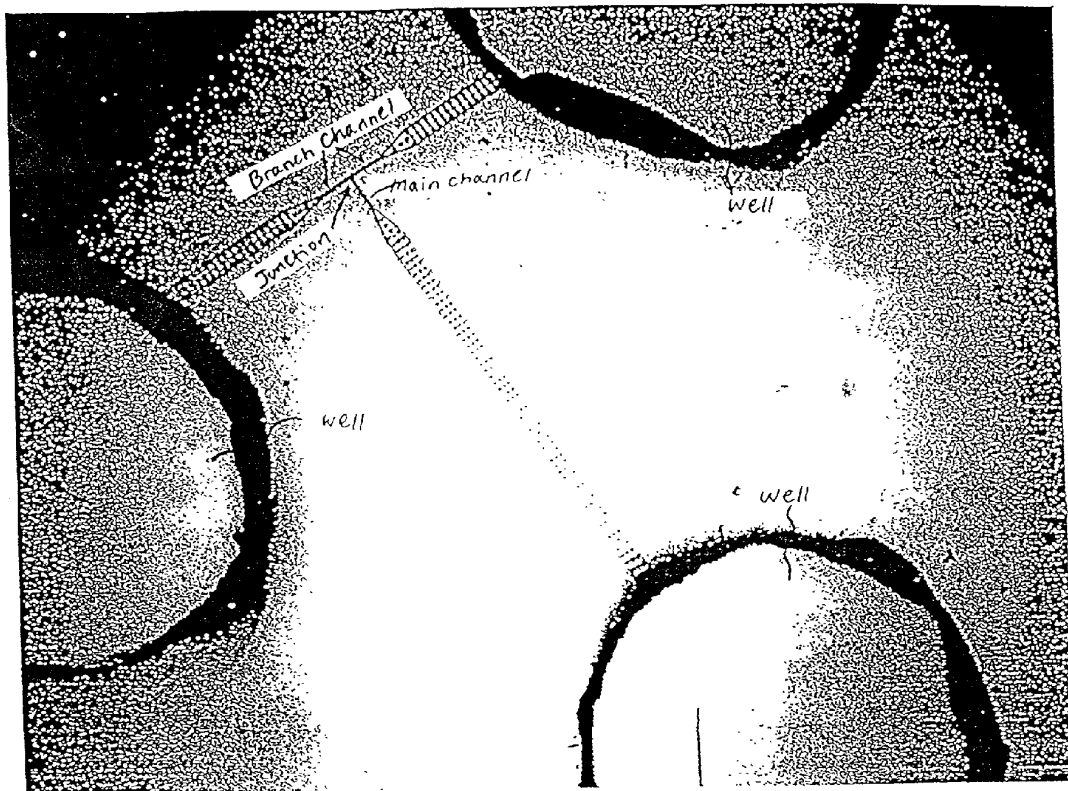


Fig 6

Quake confirms the wells are open, showing electrodes inserted into the open wells in Figure 8 and describing both inserting electrodes and adding fluids into the wells. Quake, ¶¶ 198-200. Fair, ¶¶ 151-152.

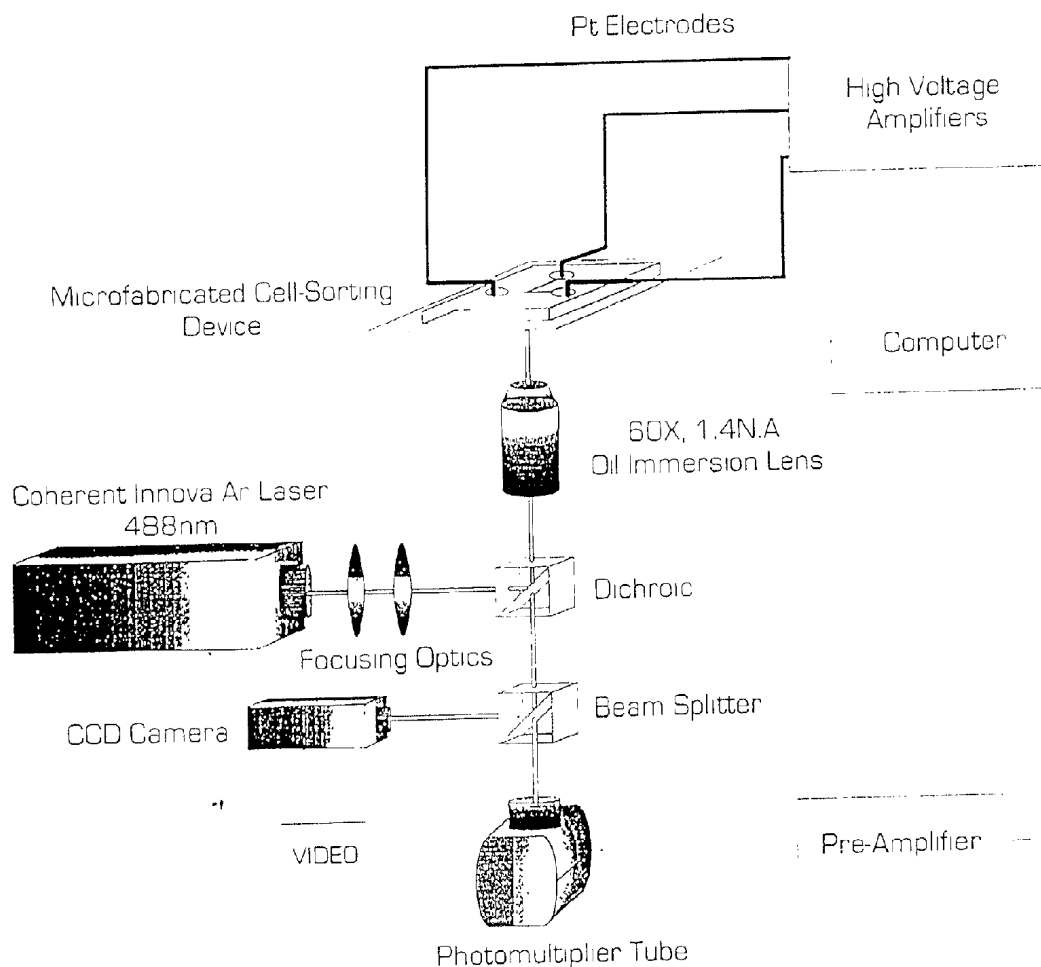


Fig 8

A POSA would know to combine Ismagilov and Quake. The differences between Ismagilov and Quake are minor and relate to additional structural details provided by Quake. A POSA would combine the microfluidic configurations, organizations, uses, substrate compositions, and fluids from Ismagilov—including placement of wells, reservoirs, or chambers—with the structures disclosed for wells

or reservoirs, their inlets and outlets, and channels in Quake. *E.g.*, Ismagilov at 16:2-47. The well or reservoir in the combination would be part of the Ismagilov substrate with the other features described throughout that are disclosed in Ismagilov, with the well of dimensions disclosed in Quake with an inlet like that disclosed by Quake, through which the droplets of Ismagilov in the immiscible fluid of Ismagilov would pass. Based on this combination, a droplet receiving chamber inlet was obvious. The structure of the output well of Ismagilov in the combination would have an opening as in Quake, and just as fluids could be added to the Quake well, so too could they be removed through the opening as described by Ismagilov. There is also a well (separation chamber) and a droplet receiving chamber inlet through which the droplets enter the well, and so the combination renders this limitation obvious. Fair, ¶¶ 153-154.

5. [1.4] “wherein the separation chamber is upright to the microchannel and out of the horizontal plane”

a. Ground 1

Ismagilov discloses this limitation. The outlet wells or reservoirs of Ismagilov are upright. As the preceding section describes, wells or reservoirs in Ismagilov “collect” plugs or permit collection by a micropipette. Ismagilov, 8:41-44, 9:5-8, 14:36-38, 27:53-58, 28:67-29:5. Because Ismagilov describes forming the substrate and closing the channels with a glass coverslip, the well or reservoir would extend

up and out of the plane of the microchannels. *See* Ismagilov, 16:37-41, 30:2-9; Fair, ¶ 160.

The extension of the well or reservoir out of the horizontal plane of the microchannels is confirmed because the volume of an outlet well or reservoir in Ismagilov must permit collecting multiple droplets and must be large enough that the fluid can be collected by micropipette. Ismagilov, 17:27-30. A volume sufficient to collect by micropipette must be greater than 0.1 μ l. Ex. 1040, Ex. 1041, 1. By contrast, examples of droplets in Ismagilov are as small as 16 pL, and so this well or reservoir would collect multiple droplets and extend above the channels, which are shown as not having a cross-section that can accommodate multiple droplets. *E.g.*, Ismagilov, 19:61-66, Figs. 2, 10. In order to be pipetted, the volume to be collected would need to be deep enough for the pipette to extend into it, and so the wells or reservoirs will extend out of the horizontal plane to permit that. Fair, ¶ 161.

b. Ground 2

While Ismagilov describes this limitation, to the extent that Bio-Rad argues otherwise, Ismagilov in combination with Quake renders this limitation obvious. As was shown for limitation 1.3, Quake further confirms that wells or reservoirs would have a significant dimension extending above the plane of the microchannels. The combinations with Quake are those described in detail in limitation 1.3. Fair, ¶ 163.

Quake confirms that wells or reservoirs have a large volume that would extend upright and above the height of the channels. The “wells are 2 mm in diameter” and can hold at least 10 to 30 μ l of fluid. *Id.*, ¶¶ 196, 200. The height of a cylinder with this volume and diameter would be approximately 3.2 to 9.5 mm. By contrast, the channels in Quake have a depth of only 4 μ m. Thus, the well or reservoir in the combination of Quake and Ismagilov extends upward above the plane of the microchannels. Thus, in the combination with Quake the well would extend vertically above the plane of the microchannels. Fair, ¶ 164.

This is also confirmed by the description of the manufacture in Quake. As in Ismagilov, the microfluidic chip is manufactured by molding the channels, incorporating the wells into the chip, and then bonding the chip to a glass coverslip that closes the channels on the bottom. Quake, ¶¶ 196-97, Figs. 6-7. As shown in Figure 8 by the electrodes placed in the open wells, the glass coverslip is placed down with the open wells facing up, which permits imaging on an inverted optical microscope through the glass slide, which would be contacted by the oil immersion lens. Quake, ¶¶ 196-98, Fig. 8. Thus, the well or reservoir in the combination is upright and out of the plane of the microchannels. Fair, ¶ 165.

6. [1.5] “wherein the droplet formation module and the separation chamber are in fluid communication with each other via the microchannel;”

Ismagilov discloses this limitation. As described for limitation 1.3, the droplets are driven by pressure flow, and the plugs move from the inlet to the outlet. Ismagilov 21:48-54, 14:21-35, 3:15-20, To illustrate this movement through the microfluidics, some figures contain an arrow at the end of the portions of the microfluidics shown, indicating that the droplets continue to flow through the microfluidic substrate to downstream features until they arrive at the outlet. Thus, Ismagilov discloses the separation chamber (outlet well) and droplet formation module as being in fluidic communication via the microchannel that extends downstream from the droplet formation module. Fair, ¶¶ 167, 169.

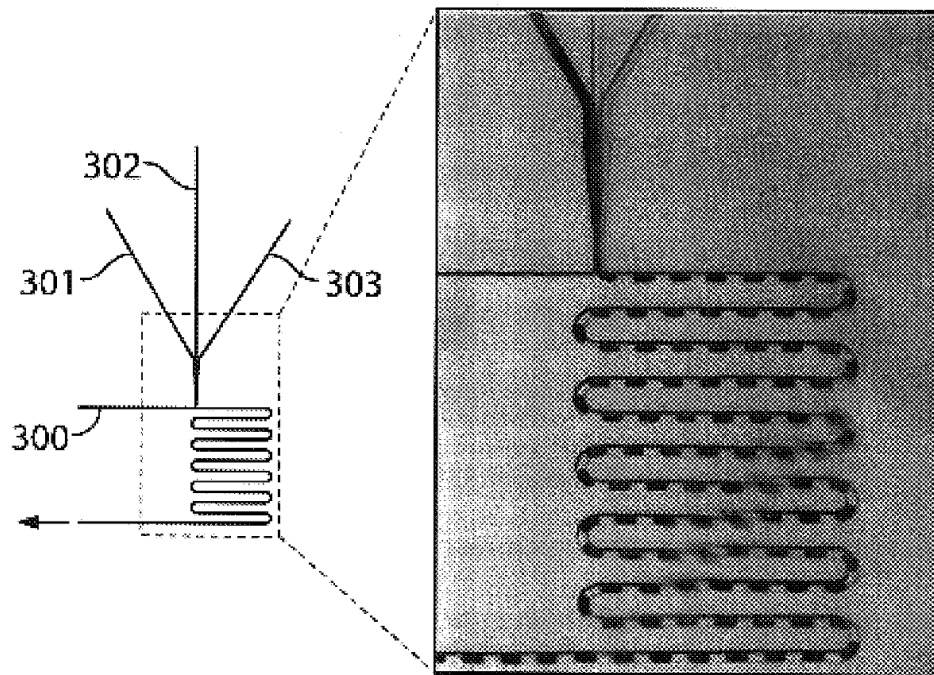


FIG. 3A

7. [1.6] “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”

a. Ground 1

Ismagilov discloses this limitation. As described in limitation 1.3, the wells or reservoirs “collect” plugs. Ismagilov, 8:41-44, 9:5-8, 14:36-38, 17:27-30. Thus, the outlet separation chamber disclosed in Ismagilov accumulates a plurality of droplets that comprise the sample, as described for limitation 1.2. The droplets are not being accumulated single file in structure with the cross-section of a channel, instead they are being pooled. This is confirmed because the collection container permits

removing droplets with a pipette, as described for limitations 1.4-5, confirming that droplets are pooled in a deep and wide vessel. Fair, ¶ 170.

b. Grounds 2

While Ismagilov describes this limitation, to the extent Bio-Rad argues otherwise, Ismagilov in combination with Quake renders this limitation obvious. The combination of the references is described for limitation 1.3. Quake describes the wells used in the combination as being “2 mm in diameter.” *Id.*, ¶ 196. The channels have a depth of only 4 µm and a width of between 3 and 100 µm. *Id.* Thus, the combination of Ismagilov and Quake renders this limitation obvious because the output wells of the combination have a wider cross-section than the channels. The volume of the wells can accumulate a plurality of droplets. Fair, ¶ 172.

8. [1.7] “[the separation chamber] is of a volume sufficient to separate the plurality of droplets comprising the sample from the immiscible fluid within the separation chamber.”

a. Ground 1

This limitation is disclosed by Ismagilov under Bio-Rad’s interpretation. Because a plurality of droplets is collected, as described above, the well or reservoir collects both a plurality of droplets and a volume of immiscible fluid. *E.g.*, Ismagilov, Figs. 2-10. Those droplets have a density different from that of the immiscible fluid, (section VI, above). Under Bio-Rad’s interpretation, an outlet well that collects droplets of different density from the immiscible fluid is a separation chamber of a

volume sufficient to separate the plurality of droplets . . . from the immiscible fluid. Ex. 1026, 12-13, 16-20. Ismagilov also teaches that collection of the droplets from the outlet “can also be done using micropipettes.” Ismagilov, 17:18-30. Fair, ¶ 173.

If Bio-Rad argues this is not explicit, the droplets floating or sinking relative to the oil is at least inherent because it necessarily occurs with liquids of different densities. *See Monsanto Tech. LLC v. E.I. DuPont De Nemours & Co.*, 878 F.3d 1336, 1344 (Fed. Cir. 2018) (inherent anticipation applies if the disclosures “must *necessarily* include the unstated limitation” (emphasis in original)). Ismagilov discloses aqueous droplets in fluorinated oil, and so there is a density difference between those two liquids, meaning they will separate under Bio-Rad’s contentions when the droplets and immiscible fluid are pooled in the outlet well or reservoir. *See* section VI; Fair, ¶ 174.

b. Ground 2

Ismagilov in combination with Quake renders this limitation obvious under Bio-Rad’s interpretation. As described in the preceding section, the output well or reservoir collects a plurality of droplets. Because multiple droplets are collected, the well or reservoir collects both a plurality of droplets and a volume of immiscible fluid, particularly given the large size of the wells specified by Quake. *E.g.*, Ismagilov, Figs. 2-10. Thus, the volume of the well or reservoir will be sufficient to separate droplets under Bio-Rad’s contentions because it is sufficient to accumulate

a plurality of droplets in a volume of immiscible fluid where the droplets have a different density from the immiscible fluid (section VI). Thus, if Bio-Rad argues this is not explicit, a POSA would at least know that the separation will necessarily (and obviously) occur when the droplets are pooled. Fair, ¶ 176.

B. Claim 2: “The assembly of claim 1, wherein an aqueous fluid from the sample inlet is segmented with an immiscible fluid from the immiscible fluid inlet at the junction.”

See claim 1 analysis above. Ismagilov discloses aqueous droplets and segmenting by immiscible fluid at the junction, as explained for limitation 1.2 and VI. Fair, ¶ 178.

C. Claim 4: “The assembly of claim 1, wherein the at least one droplet receiving outlet is located on the upper portion of the separation chamber.”

See claim 1 analysis above. Ismagilov describes the droplet receiving outlet on the upper portion of the separation chamber, as described for Claim 1. Fair, ¶ 182.

D. Claim 7: “The assembly of claim 1, wherein the droplet receiving outlet is coupled to a vessel.” (Ground 2 only)

See claim 1 analysis above. Ismagilov in combination with Quake renders obvious the additional limitation of this dependent claim under Bio-Rad’s construction. Under the interpretation that the well is the separation chamber, as described for limitation 1.3, outlets can have a volume of fluid for collection by micropipette, and they are described as having wells or reservoirs. As is also explained above, to permit the collection of fluids by micropipette, there must be an

opening into which the micropipette can be inserted. It is understood by a POSA or obvious that the droplets collected from a well by pipette would be transferred to another vessel for downstream use, and such vessels were well known. Ismagilov, 17:27-30 (“adapted for receiving . . . standard 1.5 ml *centrifuge tube*.”). The droplets would not be pooled, pipetted, and thrown away. Removing the droplets by pipette and transporting them to another vessel meets Bio-Rad’s interpretation. Fair, ¶ 186.

E. Claim 9: “The assembly of claim 7, wherein the vessel is a PCR tube or a test tube.” (Ground 2 only)

See claim 1 analysis above. Claim 9 is challenged under Ground 2. Ismagilov discloses the additional limitation of this dependent claim Bio-Rad’s interpretation. As discussed for Claim 7, it was obvious to place droplets in a centrifuge tube or PCR tube after the droplets were transferred from the well. By a pipette, including, as the Examiner said, because substituting vessels was obvious. Fair, ¶¶ 191-192.

F. Claim 10: “The assembly of claim 1, wherein the droplet receiving outlet receives substantially one or more droplets.”

See claim 1 analysis above. Ismagilov describes the additional limitation of this dependent claim under Bio-Rad’s interpretation. They all include a droplet receiving outlet, and under the applicable constructions or interpretations, that droplet receiving outlet receives one or more droplets for the same reasons it receives substantially only droplets under Bio-Rad’s interpretation, as described for claim 1. Fair, ¶ 195.

G. Claim 11: “The assembly of claim 1 further comprising a reagent inlet, wherein the reagent inlet is in fluid communication with the junction or the microchannel.”

See claim 1 analysis above. Ismagilov discloses the additional limitation of this dependent claim. Ismagilov also discloses a reagent inlet in fluid communication with the droplet formation module junction or the microchannel.

First, Ismagilov discloses a reagent inlet in communication with the junction. *See* Ismagilov, 10:60-11:7 (describing “reagent”). Figure 4 (below) discloses “*reagents* or solvents comprising the plug-fluids.” Ismagilov, 18:49-58. Thus, one or more of the inlets in communication with the junction at which droplets are formed is a reagent inlet.

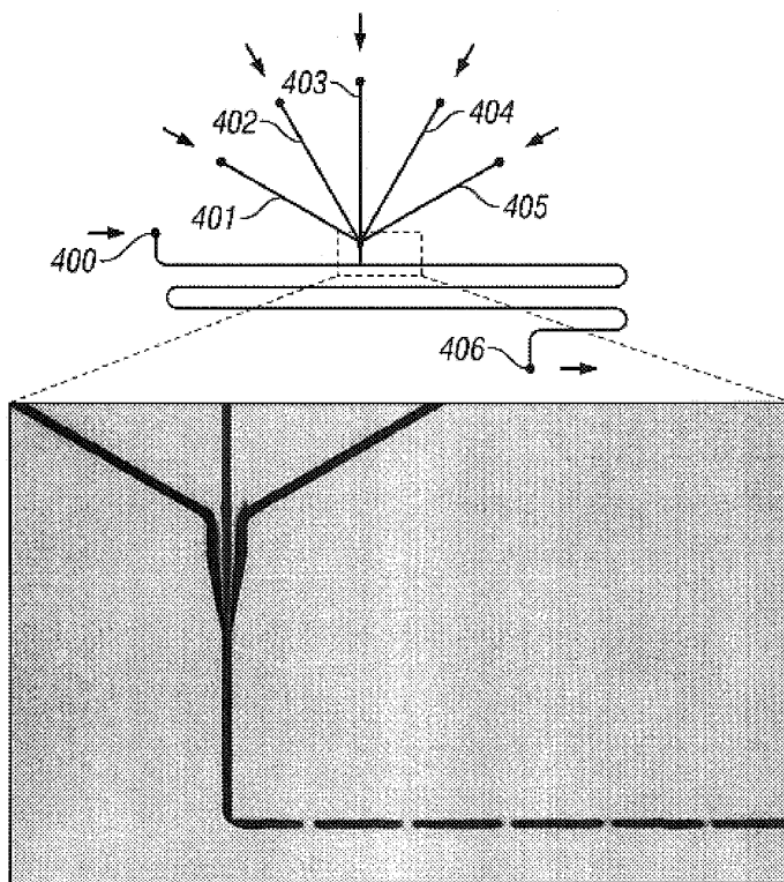


FIG. 4

Ismagilov similarly describes Figure 5 (below) as a microfluidic network “in which several *reagents* can be introduced into the multiple inlets.” Ismagilov, 19:5-18. Fair, ¶¶ 196-199.

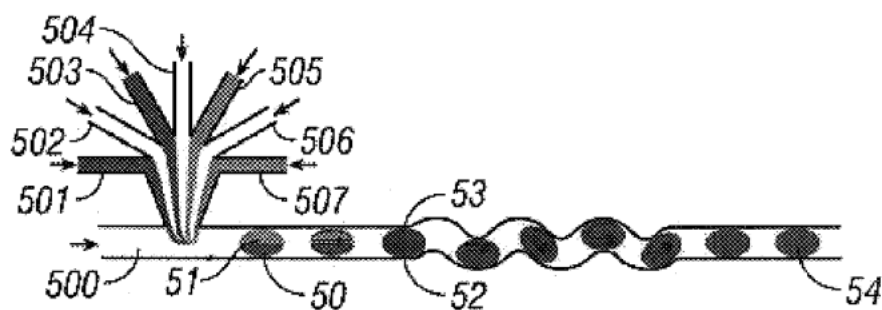


FIG. 5

Second, Ismagilov discloses a reagent inlet in communication with the microchannel. Ismagilov discloses “plugs that form in the plug-forming region” that can “merge with plugs from another channel.” Ismagilov, 18:16-19; *see also id.* 3:14-33, 15:10-23, 27:53-58, 27:37-39, 49:18-19. The droplets that are formed and merge contain reagents that will be introduced into the merged plugs. Ismagilov, 27:53-58, 27:37-39 (“Plugs containing different reagents can be formed by separately introducing different plug-fluids into a channel.”), 49:18-19. Thus, the reagent inlet in fluid communication with the microchannel in which the droplets merge. This is illustrated for autocatalytic reaction mixtures in Figure 37 (reproduced below), in which multiple inlets contain reagents, and are thus reagent inlets. Ismagilov, 6:48-51, 66:32-42. Figure 38 of Ismagilov 091 shows “a schematic diagram that illustrates a method. for a multi-stage chemical amplification which can be used to detect as few as a single molecule.” Ismagilov, 6:52-54. Fair, ¶ 200.

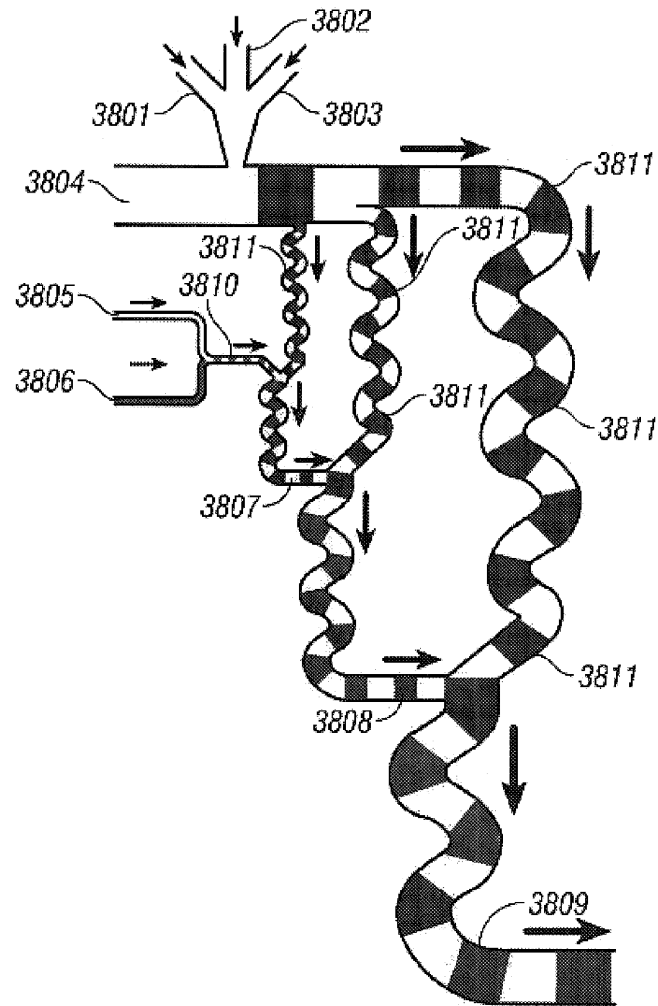


FIG. 38

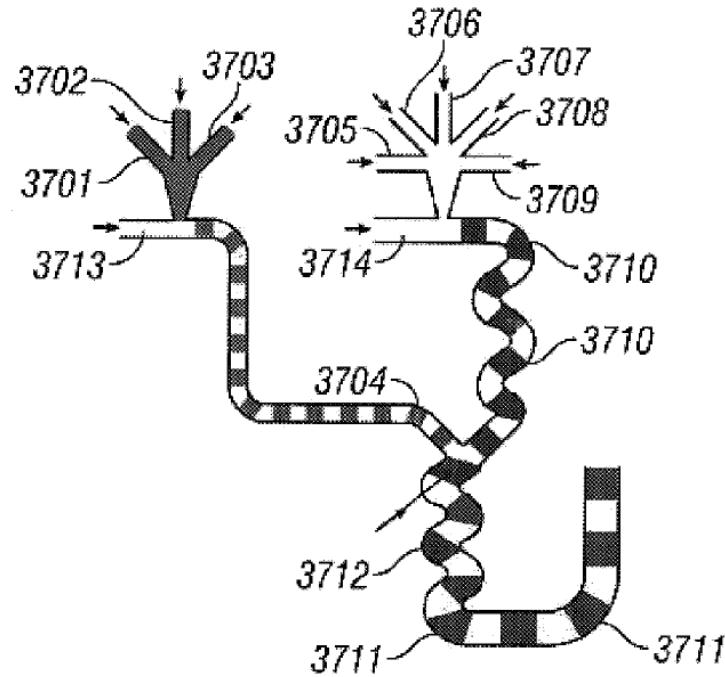


FIG. 37

H. Claim 12: “The assembly of claim 11, wherein the reagent inlet introduces one or more amplification reagents to the junction or the microchannel.”

See claim 11 analysis above. Ismagilov describes the additional limitation of this dependent claim. Ismagilov discloses the use of autocatalytic reactions, and describes “polymerase-chain reaction (PCR)” as such an autocatalytic reaction that “is a *very effective amplification method* that has been widely used in the biological sciences.” Ismagilov, 45:57-46:5; *see also id.*, 47:22-34.

As was described for Claim 11, reagent droplets may be formed and then merged with other droplets in the channel, or reagents may be added at the junction.

Ismagilov teaches that “[t]he devices and methods according to the invention may be applied to other autocatalytic reactions” and the devices in accordance with the alleged invention are “simple in design.” Ismagilov, 47:10-11, 47:59-61. Thus, Ismagilov teaches that amplification reagents, including those for PCR, could be introduced through the reagent inlets identified for the preceding limitation. Fair, ¶¶ 201-203.

I. Claim 13: “The assembly of claim 12, wherein the one or more amplification reagents are for a polymerase chain reaction.”

See claim 12 analysis above. Ismagilov describes the additional limitation of this dependent claim. As described for the preceding limitation, Ismagilov discloses PCR as an autocatalytic reaction, and discloses that autocatalytic reactions could be carried out in the invention. This would involve including the amplification reagents in the disclosed reagent inlets. Thus, for the reasons identified for the preceding limitation, the additional limitation of Claim 13 is described. Fair, ¶¶ 204-205.

J. Claim 19: “The assembly of claim 1, further comprising a sorting module to direct the flow of droplets, wherein the sorting module is located between the droplet formation module and the separation chamber.”

See claim 1 analysis above.

1. Ground 1

Ismagilov discloses the additional limitation of this dependent claim. As described for Claim 1, the separation chamber under Ground 1 is the output well or reservoir. Ismagilov discloses both detectors and sorting droplets. Ismagilov, 15:41-

45, 15:46-52, 21:55-59, 31:54-61, 31:20-33:18. The sorting module is located after the droplet formation module because the sorting module uses droplets formed in the droplet formation module. The sorting module would be located before the outlet in the flow because the outlet is the area where droplets are finally collected. Ismagilov, 9:5-8, 14:36-38; Fair, ¶ 207.

2. Ground 2

Ismagilov in combination with Quake renders this limitation obvious for the same reasons stated in Ground 1. The main structure of the assembly is provided by Ismagilov, and the droplet sorter will be between the droplet formation module where the droplets form and the outlet where the droplets are collected. Fair, ¶ 209.

K. Claim 20: “The assembly of claim 19, wherein the sorting module comprises an apparatus to generate an electric force.”

See claim 19 analysis above.

Ismagilov discloses the additional limitation of this dependent claim. Ismagilov discloses in the section “Splitting and/or Sorting Plugs” that “[a]lternating, nonhomogeneous electric fields in the presence of plugs and/or particles, cause the plugs and/or particles to become electrically polarized and thus to experience dielectrophoretic forces,” and that “dielectric particles will move either toward the regions of high field strength or low field strength.” Ismagilov, 28:35, 29:31-36. Ismagilov also discloses that “electrodes can be fabricated onto a substrate to control the force fields in a micro fabricated device.” Ismagilov, 29:36-39. Thus, Ismagilov

discloses that the sorting module includes an apparatus—electrodes—to generate electrical force, which can move the droplets. Fair, ¶ 211.

XII. GROUNDS 3-5 INVALIDATE THE IDENTIFIED CLAIMS BASED ON THE DISCLOSURE OF DENSITY SORTERS

Discussion below covers **Grounds 3a-5a** under 10X’s claim constructions but all of the evidence discussed in detail below also invalidates **3b**: The evidence above discloses this limitation under Bio-Rad’s broader constructions, which are **Grounds 3b-5b**. 10X’s claim constructions are narrower, and thus the evidence of the more specific disclosures 10X identified equally invalidate under Bio-Rad’s broader views. Fair, ¶¶ 112, 149, 159, 185, 188, 193, 205.

A. Claim 1

1. Limitations [1.0-1.2]

See Grounds 1-2, Limitation 1.0-1.2.

2. [1.3] “at least one downstream separation chamber comprising a droplet receiving chamber inlet and at least one droplet receiving outlet,”

a. Ground 3a

Ismagilov 119 renders this limitation obvious under 10X’s proposed constructions requiring a separation chamber with a space that is substantially enclosed and a droplet receiving outlet that is a structure connected to the interior space of the chamber and configured so that substantially only droplets flow into it

when exiting the chamber, or renders this limitation obvious under 10X's means plus function construction.

Ismagilov 119 discloses that “the plugs can be sorted by their *density* relative to that of the carrier fluid.” Ismagilov 119, ¶ 123. This statement renders this limitation obvious to a POSA. This passage in Ismagilov 119 refers to only two things in the sorting: the droplets that are referred to as having one density, and the carrier fluid that is referred to as having a different relative density. *Id.* This is different from the next example in Ismagilov 119 in which there are two different groups of plugs that are separated from each other based on the differential property of magnetism. *Id.*, ¶ 123 (“Alternately, plugs can also be sorted by applying a magnetic field if one group of the plugs contains magnetic materials such as iron or cobalt nanoparticles or ferrofluid.”). This also contrasts with the preceding example in which the droplets are described as having a range of sizes, and size is used to separate the droplets from each other. *Id.*, ¶ 123 (“For example, the plugs can also be sorted according to their sizes.”). Thus, Ismagilov 119 described sorting to create a fraction of substantially only droplets. Fair, ¶ 135.

Based on the knowledge of one of ordinary skill, a POSA would already be familiar with the features of a system to sort droplets based on density. As described in section VI, droplets either float (cream) or sink (sediment) if they were placed in a large vessel such that the droplets and continuous phase liquid could move freely

past each other if they had different densities. The above quote from Ismagilov 119 described a density difference between the carrier fluid and the droplets. Also, there was a density difference based on the fluids disclosed in Ismagilov, as described in section VI, and a POSA could have observed the droplets floating in the oil. The chamber itself would be a large volume to collect multiple droplets and allow them to move freely through the continuous oil phase to form a fraction enriched for droplets, as was well-known for emulsions. A chamber or reservoir would need to extend vertically to permit the density sorting to occur over the distance parallel with the force of gravity. For the chamber to operate to remove the fraction of floating droplets, an outlet is placed at the top of the chamber to collect the droplets. This would allow the droplet enriched fraction to be collected, which would mean that substantially only droplets would be entering the outlet. There would also be an outlet on the bottom for unwanted fluids (e.g., immiscible fluid) to exit and avoid it overflowing into the outlet for the droplets. Fair, ¶¶ 136-144.

The space of the chamber would be enclosed except for the inlet and outlet to allow the droplets to be extracted (e.g., from the top of the chamber). This is nothing more than combining known elements (e.g., reservoirs or wells, openings in substrates, and outlets) according to known methods to yield the predictable results that Ismagilov 119 itself specifies. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). For example, Ismagilov itself discloses inlet reservoirs or wells in

communication with channels, and connections that are openings or tubes (for introducing fluid under positive pressure) for connections, and an “area” of the substrate for at which reactions can be conducted. Ismagilov, 16:48-50, 27:53-58, 28:67-29:5. Enclosing the chamber would both permit pressure to be maintained in the system to move droplets to the next microfluidic feature and would allow the droplets (which float in Ismagilov) to be collected by rising to the outlet at the top of the chamber. Ismagilov, 21:48-54, 14:21-29; section VI. Fair, ¶ 145.

Moreover, there were only a finite number of places to place an outlet for such a chamber, and there was a design need to remove floating droplets, and so it was obvious to try to place the outlet at the top of the chamber where the droplets will collect. The outcomes (i.e., which fluids will exit the chamber) are predictable, and there is a reasonable expectation of success. *KSR*, 550 U.S. at 421; Ismagilov, 16:54-56, 17:27-30. The placement of the outlet and the use of the large reservoir is also nothing more than a combining of prior art elements according to known methods, again to yield predictable results (density separation). *KSR*, 550 U.S. at 416. Fair, ¶ 146.

This is similarly obvious to try to choose from the finite number of identified options (e.g., the channels, reservoirs, and wells described in Ismagilov), which will provide predictable solutions and a reasonable expectation of success in allowing

the droplets to sort based on their density relative to that of the carrier fluid. *KSR*, 550 U.S. at 421. Fair, ¶ 147.

A substantially enclosed chamber would also be consistent with the system described in Ismagilov 119 which involves a pressure-driven flow through the substrate from where the fluids enter (inlet) to where they exit (outlet), as Ismagilov describes. Ismagilov, 21:48-54, 14:21-29 (“applying continuous pressure to a fluid within the substrate”). A POSA would understand that a structure on the substrate would need to be substantially enclosed, except for the inlets and outlets that connect to other portions of the microfluidic system, because an open chamber would disrupt the pressure driven flow of fluids. Fair, ¶ 148.

In addition to the chamber and outlet, the chamber has an inlet to the chamber to allow the formed droplets to enter, because if there were not such an inlet, there would be no droplets to sort based on density.

b. Grounds 4a-5a

Ismagilov 119 in combination with Pamula renders this limitation obvious under 10X’s proposed constructions. The motivation to combine the chambers in Pamula with Ismagilov is described for limitation 1.3.

Ismagilov 119 discloses that “the plugs can be sorted by their *density* relative to that of the carrier fluid.” Ismagilov 119, ¶ 123. Thus, a POSA would have been motivated to look to art that describes the use of density separation based on the

difference in density between droplets and the immiscible fluid they are in. Pamula is such a reference. As described in section VII(D), Pamula describes handling droplets, and in particular describes sorting droplets based on a difference in density between the droplets and the carrier fluid, including using similar fluids (water and fluorinated oil) to those described in Ismagilov:

The filler fluid may be selected to have a particular density relative to the droplet phase. A difference in density between the two phases can be used to control or exploit buoyancy forces acting upon the droplets. Examples of two-phase systems useful in this aspect of the invention include water/silicone oil, water/flourinert, and water/fluorosilicone oil. When one phase is buoyant, then that effect can be exploited in a ***vertical configuration*** as a means to transport one phase through the other. For example, a waste or collection ***well can exist at the top or bottom of the [droplet microactuator/chip] where droplets are delivered*** to that reservoir by simply ***releasing them at an appropriate point*** and allowing them to ***float or sink to the target destination***.

Pamula 238, ¶ 418; Pamula 634, ¶ 418; Pamula 058 at 8-9. A POSA would have been motivated to look to Pamula. A POSA would have been able to apply Pamula's teachings of a density separation chamber with an outlet (collection well) at the top to Ismagilov's system which itself already included the use of both outlet wells and density-based sorting of droplets from oil. Pamula expressly teaches that channel-based continuous flow elements like Ismagilov's system can be integrated with the Pamula system. Pamula 634, ¶ 385 ("The droplet microactuator may in some cases

be supplemented by continuous flow components and such combination approaches involving discrete droplet operations and continuous flow elements are within the scope of the invention.”); *see also* Pamula 238, ¶ 385; Pamula 058, 2 and 12. Alternatively, both Ismagilov and Pamula constrained the movement of droplets. Ismagilov did so with channels. Pamula discloses microactuators that physically constrained droplets with top and bottom plates, and controlled horizontal movement with electrodes. Pamula 634, ¶¶ 378, 380; *see also* Pamula 238, ¶¶ 378, 380; Pamula 058, 3, 8, 12, Fig. 5. A POSA understood the differences between the combined physical and electrical control of droplets in Pamula and the physical channel-based control in Ismagilov, but also understood the similarities in their function and how teachings related handling microdroplets in one context related to handling microdroplets in the other. They were known and recognized alternatives, and one of ordinary skill knew how to apply the teachings of one to the other. Ex. 1035, 989 (describing 2005 Quake review describing mixing as occurring though “a turning microchannel” citing the work of Ismagilov and “electrowetting” citing the work of Fair; generally describing channel-based and electrowetting approaches). Fair, ¶¶ 155-156.

This was a simple substitution of one known element for another or the application of the known technique in Pamula to the device of Ismagilov 119, which already taught a density sorter and reservoirs. *See KSR*, 550 U.S. at 417-18.

Particularly given the motivation in Ismagilov 119, it would also have been obvious to try what was one of a finite number of identified, predictable solutions (a vertically oriented chamber and outlet to collecting floating droplets) with an expectation of success given the known components and properties of the fluids. *Id.* at 421. This was also a combination of known elements according to known methods of manufacture to yield the predictable result, identified by Ismagilov 119 itself, of separating droplets. *KSR*, 550 U.S. at 416. Fair, ¶ 157.

Thus, a POSA would find it obvious to use a vertically oriented chamber as described in Pamula as a density sorter. As was taught by Pamula, it would have been obvious to either place a collection outlet for droplets at the top or the bottom of the chamber, and would place it at the top for droplets that float. It similarly would have been obvious to place a waste outlet at the opposite end, as taught by Pamula. Such a waste outlet would permit undesired fluids to exit, further confirming that the droplet receiving outlet would receive substantially only the sorted droplets because the excess immiscible fluid would leave through the waste outlet. Pamula further confirmed that substantially only droplets would be exiting through the droplet receiving outlet by stating that the “*droplets* are delivered” to the collection reservoir. This chamber would be enclosed to direct the fluids into the collection or waste containers at the top and bottom of the chamber. Fair, ¶ 158.

The chamber of the combination would also have an inlet to receive droplets, as described in Pamula, attached to the channels of the Ismagilov 119 system in which droplets are generated. Fair, ¶ 159.

Thus, the combined system would use the known structures of Ismagilov 119 (such as reservoirs) in the configuration of the system of Pamula to achieve the goal stated by Ismagilov 119 itself. Any modifications to the disclosures of Ismagilov 119 are minimal and could easily be achieved by a POSA designing a system according to Ismagilov 119.

3. [1.4] “wherein the separation chamber is upright to the microchannel and out of the horizontal plane”

a. Ground 3a

Ismagilov 119 renders this limitation obvious. As discussed for limitation [1.3], there must be a vertical distance through which the droplets can rise or sink. Also, because Ismagilov describes forming the substrate and closing the channels with a glass coverslip, the chamber would be upright and extend out of the plane of the microchannel to accommodate the vertical volume of fluid necessary. *See* Ismagilov, 16:37-41, 30:2-9; Fair, ¶ 162.

b. Grounds 4a-5a

Ismagilov 119 in combination with Pamula renders this limitation obvious. Pamula describes the “vertical configuration” of the structure for density separation. Pamula 238, ¶ 418; Pamula 634, ¶ 418; Pamula 058 at 8-9. Pamula describes that

the waste or collection wells will exist at the top or bottom of the chamber, and that the droplets can be released (in the combination described for limitation 1.3 this would be released from the microchannel in the horizontal plane) “at an appropriate point.” Pamula 238, ¶ 418; Pamula 634, ¶ 418; Pamula 058 at 8-9. One placement of the inlet could be at the bottom of the chamber because, as has been described for the preceding grounds, the channels of the substrates are formed and sealed with, for example, a glass coverslip, and so the inlet could be at the bottom of the chamber, and the droplets could either stay on the bottom or float to the top, and in this case the chamber extends vertically above the plane of the microchannel. Alternatively, the inlet could be in the middle of the chamber, and a portion of the chamber would extend vertically above and below the plane of the microchannel. Thus, the chamber in the combination with Pamula is upright and out of the horizontal plane. Fair, ¶ 166.

4. [1.5] “wherein the droplet formation module and the separation chamber are in fluid communication with each other via the microchannel;”

Ismagilov 119 alone or in combination with Pamula includes structures in which the droplet formation modules described for limitation 1.2 are in communication with separation chamber described in section for limitation 1.3. For Grounds 3-5, the main structure of the assembly is provided by Ismagilov. Ismagilov describes that the fluids flow through the system, and the droplet formation module will be upstream of a module that sorts droplets because otherwise there would be

no droplets to sort. A channel, as shown above in Ismagilov Fig. 3A, provides a fluidic communication for the droplets to pass through to downstream features. Fair, ¶ 168.

5. [1.6] “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”

Ismagilov 119 renders this limitation obvious. As described for limitations 1.3 and 1.4, a POSA would use a chamber for density separation, whether based on Ismagilov 119 alone or with Pamula, that has a large volume to allow the droplets and continuous phase they are in to move past each other, and this accumulates a plurality of droplets that can be removed as a fraction of only droplets, as was well known in the art. Fair, ¶ 171.

6. [1.7] “[the separation chamber] is of a volume sufficient to separate the plurality of droplets comprising the sample from the immiscible fluid within the separation chamber.”

First, Ismagilov 119 alone or with Pamula describes sorting the droplets based on density, and so the volume would be sufficient to allow the droplets to float to the top based on density (see section VI). Because multiple droplets are collected (see limitation 1.6), the chamber under each ground has both a plurality of droplets and a volume of immiscible fluid. *E.g.*, Ismagilov, Figs. 2-10. As described for limitation [1.3], the separation chamber under each ground will also comprise an outlet at the top to receive substantially only droplets as droplets float to the top and

flow into the outlet (thus separating the plurality of droplets from the immiscible fluid). Fair, ¶ 175.

B. Claim 2: “The assembly of claim 1, wherein an aqueous fluid from the sample inlet is segmented with an immiscible fluid from the immiscible fluid inlet at the junction.”

See claim 1 analysis. Ismagilov 119 discloses aqueous droplets and segmenting by immiscible fluid at the junction, as explained for limitation 1.2 and Section VI.

C. Claim 3: “The assembly of claim 1, wherein the at least one droplet receiving outlet is located on the lower portion of the separation chamber.”

See claim 1 analysis. Claim 3 is only challenged under Grounds 3a-5a. Ismagilov 119 in combination with Pamula renders the additional limitation of this dependent claim obvious for the reasons stated for limitation 1.3. Pamula discloses having a collection well at the bottom of the vertical structure, and so it was obvious to place a collection well at the bottom of the chamber in the combination. The chamber in Ismagilov 119 is not limited to sorting only less dense droplets, and so an outlet on the lower portion for more dense droplets, was also obvious. *See* section VI; Fair ¶ 180.

D. Claim 4: “The assembly of claim 1, wherein the at least one droplet receiving outlet is located on the upper portion of the separation chamber.”

See claim 1 analysis above. Ismagilov 119 renders the droplet on the upper portion of the chamber obvious, as described in Claim 1.

E. Claim 7: “The assembly of claim 1, wherein the droplet receiving outlet is coupled to a vessel.”

See claim 1 analysis.

1. Ground 3a

Ismagilov 119 renders obvious the additional limitation of this dependent claim under 10X’s proposed construction. Ismagilov discloses an outlet for a manifold that “can be adapted for receiving, for example, a segment of tubing or a sample tube, such as a standard 1.5 ml centrifuge tube.” Ismagilov, 17:27-30. It was obvious to combine such an outlet that receives a tube with the density sorter. It was well known that creamed emulsions would be collected, as was well-known in the art and described in section VI, such as for early methods of generating monodisperse emulsions. Ismagilov discloses the ways output droplets could be removed from the chip: tubing, sample tube, or micropipette. Ismagilov, 17:27-30. This was a limited set of options, and they were all obvious to try. Thus, it was obvious to join the density sorter to the outlet that receives the centrifuge tube. This was also consistent with the Examiner’s conclusion that “it would have been obvious to one having ordinary skill in the art to use a test tube or a PCR tube as the vessel, as the claimed improvement on a device or apparatus is not more than the ‘simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for improvement.’” Ex. 1002, 1099-1100. Fair, ¶ 184.

2. Grounds 4a-5a

Ismagilov 119 in combination with Pamula renders obvious the additional limitation of this dependent claim under 10X's proposed construction. Pamula specifically describes that the density sorted droplets can be delivered to a collection well. As explained above, the choice of vessel was an obvious and simple substitution well within the grasp of a POSA, and Ismagilov disclosed an outlet that receives a centrifuge tube (Ismagilov, 17:27-30).⁴ Fair, ¶ 187.

F. Claim 8: “The assembly of claim 7, wherein the droplet receiving outlet is sealably coupled to a vessel.”

See claim 7 analysis. Claim 8 is only challenged under Grounds 3-5. Fair, ¶ 189.

Ismagilov 119 discloses the additional limitation of this dependent claim under Bio-Rad's interpretation. As described in the preceding section, the references combined under each ground render obvious a chamber with an outlet “adapted for receiving . . . standard 1.5 ml centrifuge tube.” Ismagilov, 17:27-30. A POSA would understand that an outlet that is “adapted” to receive the centrifuge tube would seal the tube.

⁴ The Examiner also made this conclusion that selecting the vessel was obvious (Ex. 1002, 1099-1100).

G. Claim 9: “The assembly of claim 7, wherein the vessel is a PCR tube or a test tube.”

See claim 7 analysis. Claim 9 is only challenged under Grounds 3-5.

Ismagilov 119 discloses the additional limitation of this dependent claim under 10X’s construction. As described in the preceding two sections, for grounds in which the density sorter is the separation chamber, the references combined under each ground render obvious a chamber with an outlet “adapted for receiving . . . standard 1.5 ml *centrifuge tube*.” Ismagilov, 17:27-30. This discloses the claimed test tube. Fair, ¶¶ 191-192.

H. Claim 10: “The assembly of claim 1, wherein the droplet receiving outlet receives substantially one or more droplets.”

See claim 1 analysis.

Ismagilov 119 describes the additional limitation of this dependent claim. Under 10X’s proposed construction, that droplet receiving outlet receives one or more droplets for the same reasons it receives substantially only droplets under 10X’s construction, as described for claim 1. Fair, ¶ 195.

I. Claim 11-13

See Ground 1, Claims 11-13.

J. Claim 19: “The assembly of claim 1, further comprising a sorting module to direct the flow of droplets, wherein the sorting module is located between the droplet formation module and the separation chamber.”

See claim 1 analysis.

Ismagilov 119 alone or in combination with Pamula renders obvious the additional limitation of this dependent claim. The sorter would be downstream of the droplet generation module. Ismagilov 119 discloses that “[i]f further manipulations are required (further reactions, treatment, merging and/or sorting, for example) the merged plugs could be transported to another holding component or a receiving component.” Ismagilov 119, ¶ 129. Thus, Ismagilov 119 contemplates multiple sorters. There are a limited number of arrangements for multiple sorters, and so it would be obvious to include a different sorter before the density sorter.), Fair, ¶ 208.

K. Claim 20

See Ground 1, Claim 20.

XIII. CONCLUSION

There is at least a reasonable likelihood that claims 1-4, 7-13, and 19-20 are unpatentable. 10X respectfully requests *inter partes* review and a final written decision cancelling all challenged claims.

XIV. MANDATORY NOTICES (37 C.F.R. § 42.8(A)(1))

Real Party-In-Interest (37 C.F.R. § 42.8(b)(1)): 10X Genomics, Inc.

Related Matters (37 C.F.R. § 42.8(b)(2)): **Judicial:** Bio-Rad Laboratories, Inc. v. 10X Genomics, Inc., 1:18-cv-01679-RGA (D. Del. Oct. 25, 2018).

Designation of Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3)):

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Notice of Service Information (§ 42.8(b)(4)): Petitioner identifies the following service information:

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Petitioner consents to electronic service on lead and back-up counsel in this matter at the email address identified immediately above. Electronic service is preferred.

Procedural Statements: This Petition is filed in accordance with 37 C.F.R. § 42.106(a). Concurrently filed are a Power of Attorney and Exhibit List under 37 C.F.R. § 42.10(b) and § 42.63(e), respectively. The required fee is paid through Deposit Acct. No. 603196. The Office is authorized to charge any fee deficiency, or credit any overpayment, to Deposit Acct. No. 603196.

Dated: October 25, 2019

Respectfully submitted,

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CERTIFICATION OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(a) and (d), the undersigned hereby certifies that the **PETITION FOR *INTER PARTES* REVIEW** complies with the type-volume limitation of 37 C.F.R. § 42.24(a)(1)(i) permitting a petition of up to 14,000 words because, exclusive of the exempted portions, the Petition contains 13,986 words, as identified by Microsoft Word's word-counting feature.

Dated: October 25, 2019

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

The undersigned hereby certifies that the above-captioned “Petition for *Inter Partes* Review of U.S. Patent No. 9,562,837 under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123,” including its supporting evidence (Exhibits 1001-1065), was served in its entirety on October 25, 2019, upon the following parties via FedEx:

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Patent owner’s correspondence address of record for U.S. Patent No. 9,562,837

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