

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

DECLARATION OF RICHARD B. FAIR, Ph.D.

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I, Richard B. Fair, hereby declare as follows.

I. OVERVIEW

1. I am over the age of eighteen and otherwise competent to make this declaration. I have been retained as an expert witness on behalf of 10X Genomics, Inc. (“10X Genomics”) for the above-captioned *inter partes* review (“IPR”). I am being compensated for my time in connection with this IPR at my standard legal consulting rate, which is \$600 per hour. I have no personal or financial interest in the outcome of this proceeding.

2. I understand that the petition for inter partes review involves U.S. Patent No. 9,562,837 (“the ’837 patent”), GEN1001, which issued from U.S. Application No. 13/855,318 on February 7, 2017. I further understand that, according to the USPTO records, the ’837 patent is currently assigned to Bio-Rad Laboratories, Inc. (“Patent Owner”).

3. The face page of the ’837 patent cites several related U.S. patent applications, and claims the benefit of U.S. Provisional Application Nos. 60/799,833 and 60/799,834, filed on May 11, 2006. I understand that the ’837 patent is related to those applications. The earliest filing date of any of those listed applications is May 11, 2006, the filing date of the ’833 and ’834 applications. I understand that, based on that date, the earliest possible date to which the ’837 patent may claim

priority is May 11, 2006. I have been asked to provide my analysis of the '837 patent using an earliest filing date of May 11, 2006.

4. In preparing this Declaration, I have reviewed the '837 patent and considered each of the documents cited herein, in light of general knowledge in the art. In formulating my opinions, I have relied upon my experience, education, and knowledge in the relevant art. In formulating my opinions, I have also considered the viewpoint of a person of ordinary skill in the art (*i.e.*, a person of ordinary skill in the field of microfluidic droplet handling) before May 11, 2006.

5. The 837 Patent relates to the field of microfluidic droplet handling. My lectures cover many aspects of liquid flow, including flow-focused droplet flow. I cover details of aqueous droplet generation in an immiscible phase as well as specific applications suitable for high-throughput droplet manipulation, which includes systems and methods for handling droplets, forming droplets, handling droplets downstream of their formation, droplet applications, and droplet chemistry, components, and reactions that occur within them. Ex. 1001, title, abstract, 1:42-43 (field: "systems and methods for liquid handling"); 2:35-5:43.

6. This declaration presents my opinion that claims 1-4, 7-13, and 19-20 of the 837 patent are anticipated by or obvious over the prior art. Specifically, this declaration presents my opinion that Ismagilov 091 anticipates claims 1-2, 4, 10-13, and 19-20 of the 837 patent. This declaration also presents my opinion that claims

1-4, 7-13, and 19-20 of the 837 patent would have been obvious in view of the disclosures of Ismagilov 119 (which incorporates Ismagilov 091) in combination with Quake, Pamula 634, and Pamula 238. And as further discussed in this declaration, before or shortly after the earliest possible priority date of the '837 patent (May 11, 2006), a person of ordinary skill in the art would have had a reason to combine the prior art references to arrive at the claimed system and in so doing, would have had a reasonable expectation of success. This declaration describes how, in reaching my conclusions regarding obviousness, I have considered potential secondary considerations of nonobviousness and concluded that there are none that I am aware of that would support a claim of nonobviousness.

7. The chart below summarizes the grounds of unpatentability presented in this declaration.

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

II. BACKGROUND AND QUALIFICATIONS

8. My qualifications and credentials are fully set forth in my *curriculum vitae*, attached as Ex. 1007. I am an electrical engineer and a Professor of Electrical and Computer Engineering at Duke University. I currently hold an endowed chair position at Duke University (the Lord-Chandran Professor of Engineering).

9. I received a Bachelor of Science degree in Electrical Engineering in 1964 from Duke University. In 1966, I received a Master of Science degree in Electrical Engineering from Penn State University. In 1969, I received a Ph.D. in Electrical Engineering from Duke University.

10. In 1981, I became Professor of Electrical Engineering at Duke University, and I also served in a joint role as Vice President of the Microelectronics Center of North Carolina ("MCNC") in Research Triangle Park, North Carolina, where I led the Center for Microelectronic Systems from 1981-1994. In 1994, I returned to Duke University full-time to start a research program in BioMEMS (Biological microelectromechanical systems).

11. Since 1996 my work has focused on microfluidics technology driven by biomedical applications. One of the applications we studied was DNA sequencing, which had just been demonstrated on a microchip by the Davies group at UC Berkeley in 1995. There were many issues that needed to be solved in performing DNA sequencing on a microchip, so we were funded in 1998 by DARPA to design and evaluate architecture and technology for a reconfigurable microliquid handling system aimed at more general biomedical applications. Our emphasis was on developing lab-on-a-chip technology, and we applied this capability to the areas of enzymatic reactions in assays, genomics, the expansion of proteomics into high throughput microarray platforms, blood chemistries and diagnostics, and chemical sensing.

12. In 1999 we successfully demonstrated that we could actuate droplets on hydrophobic, insulating surfaces over an array of electrodes under voltage control. The mechanism for droplet generation and manipulation was known as electrowetting on dielectric. This technique became known as digital microfluidics (so named by one of my graduate students). Droplet microfluidics research grew quickly, and within 2 years 35 labs worldwide were pursuing electrowetting research.

13. In 2000 we were able to perform the polymerase chain reaction (PCR) on DNA in droplets on an electrowetting platform. In addition we demonstrated the printing of DNA microarrays by vertical electrostatic actuation of droplets

containing DNA onto a receiving plate. In 2001 we were funded by Glaxo Smith Kline to perform research on the transport of simple biological fluids for the development of novel microfluidic assays of protein function, such as kinase assays. We also performed research on bio-molecular systems for defining a separation and sensing platform for a variety of bio-molecules that could reversibly address any protein onto micropatterned surface templates by directly modulating the hydrophobic interaction between a patterned surface and the protein. And in 2003 we worked with BioMachines, Inc. to demonstrate that biological samples prepared with standard laboratory protocols using well-plate formats could be rapidly transferred to droplet-based chips for high throughput assaying and bioagent detection via a parallel reformatting platform.

14. Also in 2003 we began working with the Duke Institute for Genome Sciences and Policy in further developing on-chip PCR of DNA. In 2004 we spun off Advanced Liquid Logic, Inc. out of my lab. Together we were funded by the NIH to demonstrate how existing droplet-based microfluidic electrowetting technology could be modified to perform sequencing by synthesis reaction chemistry and to transport the enzymatic by-products to remote detection sites. The specific goal of this work was to demonstrate a single bead-based sequencing-by-synthesis assay on a droplet-based electrowetting chip platform. During this time we successfully demonstrated on-chip pyrosequencing of DNA with reads up to about 125 bases.

15. Since 2006 we have also worked on isolating genomic DNA from human blood droplets and purifying the DNA using on-chip electrowetting techniques. Integration of optical sensors with DNA probes provide a unique final diagnostic, identifying specific species and also genes encoding for resistance to commonly used drugs. When a genomic DNA fragment binds to a functionalized sensor surface, shifts in sensor signals are detected. Hence from a few drops of human blood, after sophisticated sample handling and analysis, a simple optical signal gives final results.

16. I have continued to teach courses on 1) the design and analysis of analog and digital integrated circuits, 2) semiconductor devices, 3) the chemistry and physics of integrated circuit fabrication, and 4) biochip engineering, which is a course I started in 2004 that addresses specific biochip functions and principles that are relevant to the design of lab-on-a-chip devices. My lectures cover many aspects of liquid flow, including flow-focused droplet flow. I cover details of aqueous droplet generation in an immiscible phase as well as specific applications suitable for high-throughput droplet manipulation. In addition, I have an active funded research program at Duke, currently supported by NSF, which involves undergraduate and graduate students.

17. I have published more than 170 papers in refereed and peer-reviewed journals and conference proceedings, written 12 book chapters, edited nine books or

conference proceedings, and given over 130 invited talks. I am a named inventor on 37 granted U.S. patents and numerous pending patents. I am also a Life Fellow of the IEEE (Institute of Electrical and Electronic Engineers), and Fellow of the Electrochemical Society, past Editor-in-Chief of the Proceedings of the IEEE, and I have served as Associate Editor of the IEEE Transactions on Electron Devices. I am a recipient of the IEEE Third Millennium Medal, and I was awarded the Solid State Science and Technology Medal of the Electrochemical Society in April, 2003. Also, I have served numerous times on proposal review panels for NHGRI (National Human Genome Research Institute) of the NIH.

III. LIST OF DOCUMENTS CONSIDERED IN FORMULATING MY OPINIONS

18. In formulating my opinions, I have considered all documents cited in this declaration, including the documents in the chart attached at the end of this declaration as Attachment B. I have also read and considered the Petition that I understand this declaration will accompany. In formulating my opinion, I have further considered U.S. Patent No. 9,562,837, as well as the file history for this patent.

IV. LEGAL PRINCIPLES

19. I am not a lawyer. I have been provided with an understanding of the legal principles that govern claim construction and patent validity. I have conducted

my analysis in conformance with these principles. I set forth those understandings below.

A. Claim Construction

20. I understand that the Patent Trial and Appeal Board applies the standard for claim construction articulated in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005), including construing the claim in accordance with the ordinary and customary meaning of such claim as understood by a person of ordinary skill in the art.

21. I understand that various sources are available that may help show what a claim term should mean. These sources include the text of the claims themselves, the patent's specification, the prosecution history of the patent, and the prior art cited in a patent or in the prosecution history. Together, I understand that these sources are called "intrinsic" evidence. I also understand that other sources for example concerning relevant scientific principles, technical dictionaries, and other information concerning the state of the art is called "extrinsic" evidence. I understand that extrinsic evidence may not be used to contradict the claim language.

22. I understand that claim terms should be given their ordinary meaning unless the patentee has clearly set forth a different meaning in the specification or the prosecution history, *e.g.*, by acting as his or her own lexicographer.

23. Additionally, I understand that the context in which a claim term is used can be highly instructive. Other claims of the patent in question, both asserted and

not asserted, can also be valuable sources as to the meaning of a claim term. Because claim terms are normally used consistently throughout the patent, the usage of a term in one claim can often illuminate the meaning of the same term in other claims. Differences among claims can also be a useful guide in understanding the meaning of particular claim terms.

24. I understand that a person of ordinary skill in the art is deemed to read a claim term not only in the context of the particular claim in which the disputed term appears, but also in the context of the entire patent, including the specification. The specification is the primary basis for construing the claims and is considered the single best guide to the meaning of a disputed term. For this reason, the words of the claim must be interpreted in view of the specification. The interpretation of a term can only be determined and confirmed with a full understanding of what the inventors actually invented and intended to cover within the claim.

25. A claim term should not be interpreted to exclude embodiments disclosed in the specification absent probative evidence on the contrary. I further understand that, in general, the claimed invention is not limited to a preferred embodiment, even if the specification does not describe any other embodiment.

26. In addition to consulting the specification, one should also consider the patent's prosecution history, if it is available. The prosecution history consists of the complete record of the proceedings before the Patent Office and includes cited prior

art. The prosecution history can inform the meaning of the claim language by demonstrating how the inventor understood the invention. I understand that the prior art cited in a patent or the prosecution history of the patent also constitutes intrinsic evidence.

27. I understand that, when a claim limitation recites a generic term and associated functional language, it may invoke means-plus-function treatment under 35 U.S.C. § 112(f) or pre-AIA 35 U.S.C. § 112 paragraph 6. I understand that when a claim limitation uses the term “means” or “step” and functional language, there is a presumption that means-plus-function treatment applies. I also understand that generic “nonce” terms may also be substitutes for “means” or “step” and may thereby still invoke means-plus-function treatment. I understand that the means-plus-function treatment is not appropriate where the terms have been modified by sufficient structure, material, or acts for performing the claimed function.

28. I understand that when claim language invokes means-plus-function treatment, the specification must provide corresponding structure such that one skilled in the art will understand the structure that performs the recited function. I understand that the scope of means-plus-function terms will be construed to cover that corresponding structure and equivalents thereof. As such, I understand that construction of means-plus-function terms requires identification of a function as well as corresponding structure for that function. I also understand that meeting a

means-plus-function limitation requires structure that is the same as or equivalent to the corresponding structure in the patent specification, but that performs the identical function that is recited by the means-plus-function limitation.

B. Prior Art

29. A patent is entitled to the filing date of an earlier application (the “parent” application) if the later patent (the “child” patent) is issued from a divisional application, a continuation, or a continuation-in-part of the parent application if the child patent claims priority to the parent application during prosecution, or if the patent claims priority to a provisional application, and if the corresponding disclosure in the parent or provisional application supports the later claimed subject matter in the child patent.

30. Also, under the America Invents Act (“AIA”), the effective filing date for a claimed invention is the earliest of: (1) the actual filing date of the patent or the application containing the claimed invention; or (2) the filing date of the earliest application for which the patent or application is entitled, as to such invention, to a right of priority for the claimed invention (including domestic and foreign priority claims). 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 on or after March 16, 2013.

1. Incorporation

31. I understand that a prior art document may incorporate subject matter by reference to another document such that the incorporated materials become part of the host document for the purposes of anticipation. To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents.

2. Analogous Art

32. I have been informed that in order for a reference to be proper for use in an obviousness rejection, the reference must be analogous art to the claimed invention. I understand that a reference is analogous art to the claimed invention if: (1) the reference is from the same field of endeavor as the claimed invention (even if it addresses a different problem); or (2) the reference is reasonably pertinent to the problem faced by the inventor (even if it is not in the same field of endeavor as the claimed invention). In order for a reference to be “reasonably pertinent” to the problem, it must logically have commended itself to an inventor’s attention in considering his problem.

C. Anticipation

33. It is my understanding that a reference anticipates a claim if it discloses each and every element recited in the claim, arranged as claimed. Further, it is my understanding that an anticipating reference must set forth the elements in the claim

in a sufficiently detailed manner such that it would enable a person of ordinary skill in the art to make and use the claimed invention without the need for undue experimentation. Those elements can be either explicitly described or inherently described. Inherent elements are those that are not explicitly described, but nonetheless would necessarily be present if the teachings in the reference are followed. The factors that I have considered in determining whether a reference is enabling with regard to a specific claim include: the breadth of the claims; the nature of the invention; the state of the prior art; the level of one of ordinary skill; the level of predictability in the art; the amount of direction provided in the reference; the existence of working examples; and the quantity of experimentation needed to make or use the claimed invention.

1. Pre-AIA § 102(e)

34. I understand that patents with an effective filing date before March 16, 2013 are subject to the version of 35 U.S.C. § 102(e) used prior to the America Invents Act amendments. I further understand that such patents are invalid as anticipated if, more than one year before the patent application was filed, the claimed invention was: (i) patented (foreign or domestic); (ii) described in a printed publication (foreign or domestic); (iii) in public use in the United States; or (iv) on sale in the United States.

35. I understand that in order for a patent to claim priority from the filing date of its provisional application, the specification of the provisional application must contain a written description of the invention and the manner and process of making and using it, in such full, clear, concise, and exact terms to enable an ordinarily skilled artisan to practice the invention claimed in the non-provisional application.

2. AIA § 102(a)(2)

36. I understand that patents with an effective filing date on or after March 16, 2013 are subject to the America Invents Act amendments to 35 U.S.C. § 102(a). I further understand that such patents are invalid as anticipated if prior to the effective filing date of the patent the claimed invention was described in another inventor's U.S. Patent or U.S. published patent application with an earlier effective filing date. I understand effective filing date to mean either: (1) the actual date on which the patent application containing the claimed invention was filed; or (2) the filing date of an earlier patent application upon which patent application containing the claimed invention relies for priority.

3. Inherency

37. I understand that a limitation may be inherently present in a prior art reference even if it is not expressly disclosed. Anticipation by inherent disclosure is appropriate when the reference discloses prior art that must necessarily include the

unstated limitation. Inherency, however, may not be established by probabilities or possibilities. For example, the mere fact that a certain thing *may* result from a given set of circumstances is not sufficient to establish inherency. Moreover, to establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Similar to anticipation, inherency may supply a missing claim limitation in an obviousness analysis, but the limitation at issue *necessarily* must be present, or the natural result of the combination of elements explicitly disclosed by the prior art. Occasional results are not inherent. An argument that a limitation is inherently disclosed in the prior art should be made explicitly to be a proper assertion of inherency.

D. Obviousness

38. I understand that an obviousness analysis involves properly construing a claim and then comparing that claim to the prior art to determine whether the claimed invention would have been obvious to a person of ordinary skill in the art in view of the prior art, and in light of the general knowledge in the art.

39. I also understand that obviousness can be established by combining or modifying the teachings of the prior art to achieve the claimed invention. It is also my understanding that where this is a reason to modify or combine the prior art to achieve the claimed invention, there must also be a reasonable expectation of success

in so doing. I understand that the reason to combine prior art references can come from a variety of sources, not just the prior art itself or the specific problem the patentee was trying to solve. And I understand that the references themselves need not provide a specific hint or suggestion of the alteration needed to arrive at the claimed invention; the analysis may include recourse to logic, judgment, and common sense available to a person of ordinary skill that does not necessarily require explication in any reference.

40. I also understand when a person of ordinary skill in the art would have reached the claimed invention through routine experimentation, the invention may be deemed obvious. I understand that a combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. I also understand that when there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense and therefore is obvious according to patent laws.

41. I understand that when considering the obviousness of an invention, one should also consider whether there are any secondary considerations that support the nonobviousness of the invention. I understand that secondary considerations of

nonobviousness include commercial success, long-felt but unmet need, failure of others, industry praise, and unexpected superior results.

42. I understand that a claim of commercial success can be supported by evidence that a product (1) practices the claims of the patent and (2) has gained substantial market share (*e.g.*, substantially displaced competing products in the market). I also understand that commercial success requires that the success of the claimed product must have resulted from the merits of the claimed invention as opposed to features of the invention that were known in the prior art or other extrinsic factors (*e.g.*, marketing). In other words, I understand that the patent owner must link the commercial success with features of the invention not shown in the prior art.

43. I understand that a showing of a long-felt and unmet need requires three factors. First, the need must have been a persistent one that was recognized by those of ordinary skill in the art. Second, the long-felt need must not have been satisfied by another before the invention. Third, the invention must in fact satisfy the long-felt need.

44. I understand that praise for the invention by peers in the industry may support nonobviousness if it is directed to the claimed features of the invention and not to elements found in the prior art.

45. I understand that “unexpectedly superior results” can be evidence of nonobviousness if the patent owner shows that the results are unexpectedly greater

than those that would have been expected from the closest prior art and that the results have a significant and practical advantage. It is also my understanding that unexpectedly superior results must be commensurate in scope with the claims.

E. § 325(d)

I understand that when determining whether to institute an *inter partes* review, the Board may consider whether the same or substantially the same prior art arguments were previously presented to the Office. I understand that in evaluating whether to exercise its discretion the Board considers the following factors: (1) similarities and material differences between the asserted art and the prior art involved during examination; (2) the cumulative nature of the asserted art and the prior art evaluated during examination; (3) the extent to which the asserted art was evaluated during examination; including whether the prior art was the basis for rejection; (4) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art; (5) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and (6) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

V. PERSON OF ORDINARY SKILL IN THE ART

46. I understand that anticipation and obviousness must be analyzed from the perspective of a hypothetical person having ordinary skill in the art at the time of the effective filing date or date of invention. Ascertaining the level of ordinary skill is necessary to maintain the objectivity in the obviousness inquiry, and therefore the Board must ascertain what would have been obvious to a person of ordinary skill in the art at the time of the effective filing date, and not to the inventor, a judge, a layman, those skilled in remote arts, or to geniuses in the art at hand. Factors that may be considered in determining the level of ordinary skill in the art may include: (A) type of problems encountered in the art; (B) prior art solutions to those problems; (C) rapidity with which innovations are made; (D) sophistication of the technology; and (E) educational level of active workers in the field.

47. In my opinion, a person of ordinary skill in the art in the context of the 837 patent as of the earliest possible priority date 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 person of ordinary skill in the art 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 person of ordinary skill in the art 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 person of ordinary skill in the art would have been aware of other important references on handling microfluidic droplets. I am well qualified to determine the level of ordinary skill in the art. First, I am very familiar with the technology of the 837 Patent as of the May 11, 2006 timeframe. As mentioned above, by 2006, I had extensive experience relating to handling microfluidic droplets.

48. Based on my 50 years of experience, including 23 years of experience in the fields of BioMEMS and lab-on-a-chip technology for biomedical applications, the acceptance of my publications and professional recognition by societies in my field, I believe that I am an expert in the art of biomedical microfluidics and related applications, including handling microfluidic droplets. I was also at least a person of ordinary skill by the earliest possible priority date of the 837 Patent.

VI. STATE OF THE ART

49. By May 11, 2006, the earliest possible filing date of the 837 Patent, the state of the art included the teachings provided by the references discussed in this declaration. Additionally, a person of ordinary skill in the art would have been aware of other important references relating to droplets (including emulsions), and systems and methods for handling them (including both their formation and handling downstream of formation), their applications, and their chemistry, components, and reactions that occur within them.

50. The art regarding droplet formation and the behavior of emulsions was well-developed before the earliest priority date of the 837 Patent.

51. Droplet formation according to the claims of the 837 Patent was long known. Ex. 1048. For example, the 1984 Stewart publication (WO84/02000) described and illustrated (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 the droplets and carrying them downstream. Ex. 1048, 4-7.

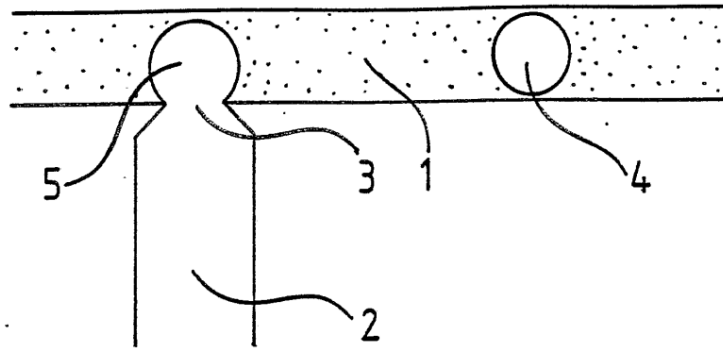


Figure 1.

52. By 2002, the Quake and Thorsen group had also described the generation of droplets by similar means (Fig. 16A reproduced below). Ex. 1006, US Patent App. Pub. No. 2002/0058332 A1 to Stephen Quake and Todd Thorsen (“Quake”), ¶ 84. The Quake group also disclosed details on microfluidic structures—such as wells—that were included in its microfluidic systems.

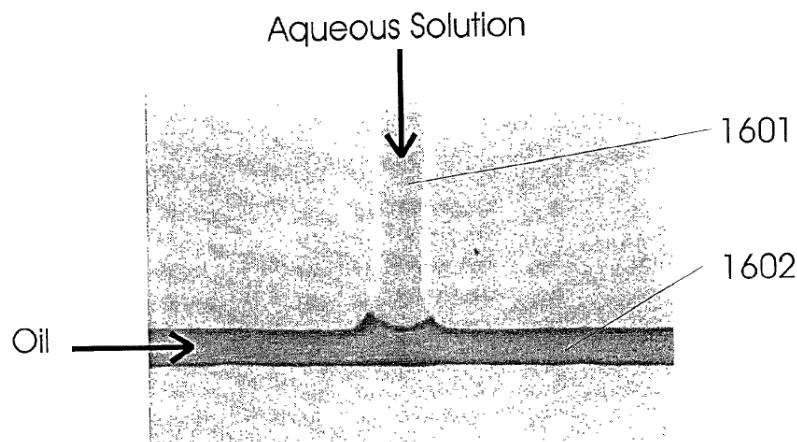


FIG. 16A

53. By 2003, the Ismagilov group had also described droplet generation by similar means. *See* Fig. 10A, 3A, Ex. 1003, 2:50-59, 14:52-61.

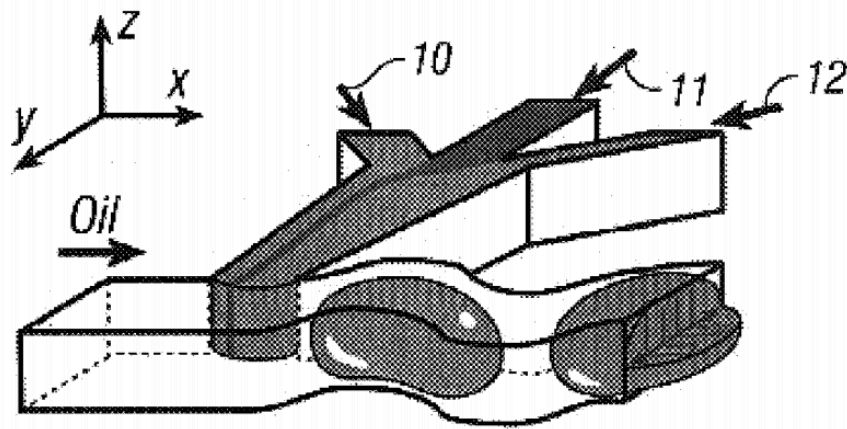


FIG. 10A

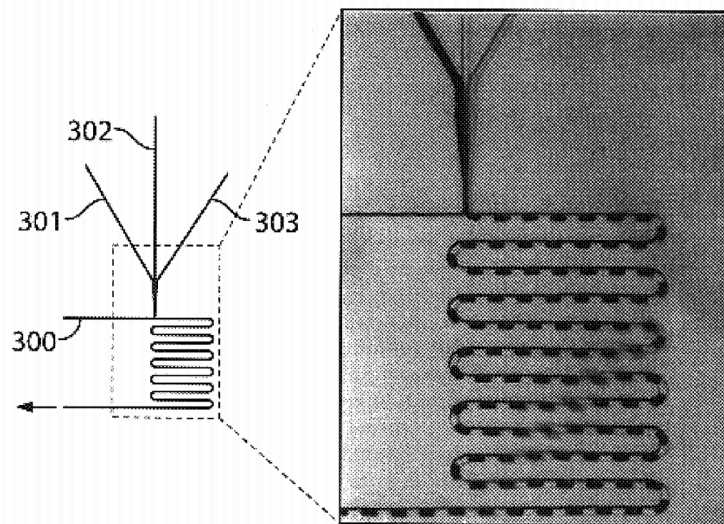
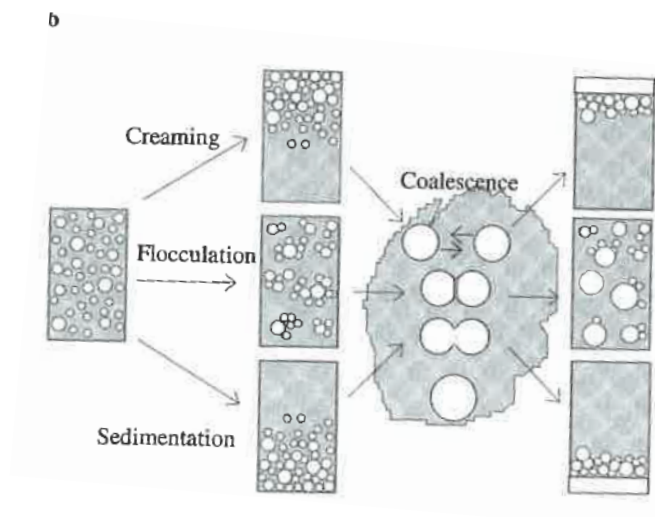


FIG. 3A

54. The natural property that fluids of different densities—including droplets—will separate was also well-known, as were the features of the containers in which that occurred. For example, an emulsion reference book from 2001 illustrated (Figure 36 reproduced below) creaming (floating) and sedimentation

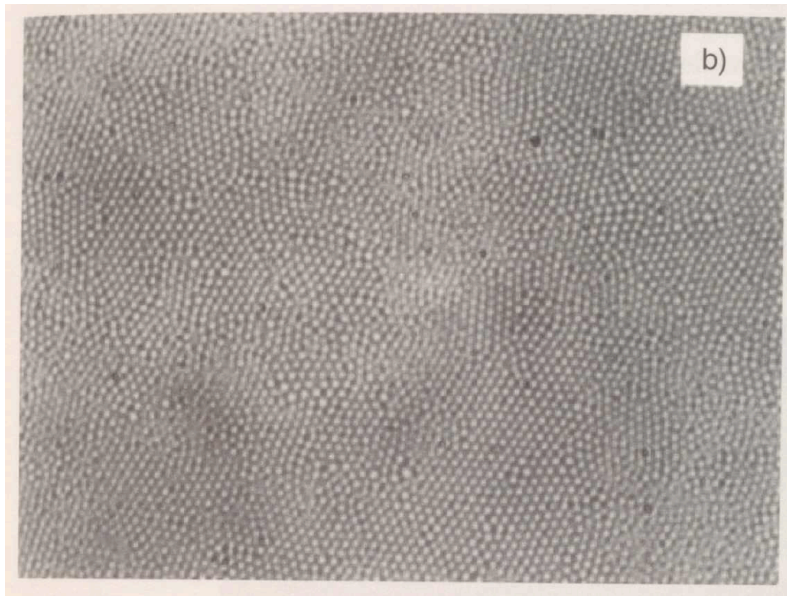
(sinking) of droplets, and describing that “[i]f a density difference exists between the dispersed and continuous phases, dispersed droplets experience a vertical force in a gravitational field” and that “[t]he rate of creaming of noninteracting particles depends on density differences and the square of the droplet radius.” Ex. 1009 at 51, 74, 115, 144. As illustrated, an emulsion placed in a relatively large volume will cream or separate.



55. Other references similarly described that droplets and fluids of different densities have the inherent property of floating or sinking. Ex. 1010, at ¶ 3 (“After emulsification, droplets tend to rise by buoyancy.”); Ex. 1011 at 1 (“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.”).

56. Yet 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 also 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 as part of a process of producing monodisperse emulsions. Ex. 1012, 11. Figure 3.1(b) illustrates this (showing a collection of many monodisperse droplets):



57. It was also well-known to generate droplets using fluids of different densities. For example, Stewart disclosed mineral oils, silicon oils, and fluorinated hydrocarbons as immiscible carrier fluids. Ex. 1048, 6. Quake also taught “decane (e.g., tetradecane or hexadecane) or another oil (for example, mineral oil)” as carriers. Quake, ¶ 15. Ismagilov disclosed a preferred embodiment that uses “an aqueous buffer solution, such as ultrapure water” and other reagents, and a preferred carrier fluid is “fluorinated oil,” for which many examples are provided, including

perfluorohexane and perfluorodecaline. Ex. 1003, 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 2 (“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. These are constant, unchanging properties of these chemicals, and this difference in density means that such fluids would necessarily separate by less dense water droplets floating 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. 1063-64, Ex. 1049-51.

58. I understand that Dr. Ismagilov has testified in a prior litigation for Bio-Rad asserting Ismagilov 091. Dr. Ismagilov testified that the droplets disclosed by Ismagilov 091 were stable because of the surfactant used: “So 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 This statement suggests that emulsions

¹ Similar text to that referred to in the question leading to this testimony appears in Ismagilov 091. *Id.*, 37:23-45; Fig. 24.

disclosed in Ismagilov could stably be pooled and would separate. If there were stable droplets, that means that they will not undergo the numerous process of thermodynamic instability illustrated in the above figure, including coalescence in which multiple droplets merge together. Stable droplets will cream or sediment without, for example, coalescing with other droplets they are close to.

59. The art also disclosed microfluidic structures both for pooling droplets (after which they would separate based on density) and that relate specifically to density separation. For example, Ismagilov and Quake both disclosed wells or reservoirs. Ex. 1003, 9:5-8, 14:36-38; Quake, ¶ 196, Figs. 6, 8. Prior to the earliest priority date of the 837 Patent, both Ismagilov and my own research group had also disclosed the use of density separation in droplet systems. The Ismagilov group described that “the plugs [droplets] can be sorted by their density relative to that of the carrier fluid.” Ex. 1004, ¶ 123. My group similarly described that droplets can be released and allowed to “*float or sink to the target destination.*” Ex. 1018, ¶ 418; Ex. 1007, ¶ 418; Ex. 1025 at 8-9.

60. In my opinion, the 837 Patent added nothing new to the field of microfluidic droplet handling. The principles claimed in the 837 Patent were all previously known, in many cases years after the ideas first arose in the work of others. The challenged claims of the 837 Patent are invalid.

VII. THE 837 PATENT

61. The 837 Patent is titled “Systems for Handling Microfluidic Droplets” and was filed on April 2, 2013. As explained above, the earliest possible priority date is May 11, 2006.

62. The 837 Patent relates to the field of handling microfluidic droplets, which includes systems and methods for handling droplets, forming droplets, handling droplets downstream of their formation, droplet applications, and droplet chemistry, components, and reactions that occur within them. Ex. 1001, title, abstract, 1:42-43 (field: “systems and methods for liquid handling”); 2:35-5:43.

63. **[INTENTIONALLY LEFT BLANK]**

64. The only independent claim of the 837 Patent states:

1. An assembly, the assembly comprising:

a microchannel in a horizontal plane;

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

at least one downstream separation chamber comprising a droplet receiving chamber inlet and at least one droplet receiving outlet, wherein the separation chamber is upright to the microchannel and out of the horizontal plane; wherein the droplet formation module and the separation chamber are in fluid communication with each other via the microchannel; and wherein the separation chamber has a wider cross-section than the microchannel cross-section to accumulate a plurality of droplets comprising the sample and is of a volume sufficient to separate the plurality of droplets comprising the sample from the immiscible fluid within the separation chamber.

Ex. 1001, 88:1-23.

65. During prosecution, the claims were amended multiple times—including both by the applicant and examiner—to overcome rejections by adding additional specificity to the droplet formation module and the separation chamber ultimately claimed. Ex. 1002 (837 Patent FH), 1045, 1057, 1110, 1113, 1134, 1137, 1165, 1168, 1184, 1188. But even the added elements were already well-known in the art and were disclosed in references that were never relied upon in a rejection by the Examiner.

VIII. THE 837 PATENT ISSUED FROM A TRANSITION APPLICATION

66. The application that lead to the 837 Patent was filed on 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 date after March 16, 2013. The text of the application that lead to the 837 Patent is similar to the text of Application No. 11/803,104 (“104 Application”), as published on January 3, 2008, except for the new matter paragraphs 3-20, the addition of figures 38-41, the text in columns 52-61, and other additions. *Compare* Ex. 1060 *with* Ex. 1061. There was no disclosure outside of this new matter (e.g., ¶¶ 267, 274) of the outlets, nozzles, and slides configured as claimed in the claimed apparatus of Claims 5 and 6. Ex. 1060 at 29-30.

67. Nevertheless, to the extent that the AIA is not found to apply, it is my opinion that the same art invalidates the challenged claims based on my understanding of the pre-AIA provisions for the same reasons identified below.

IX. 10X’S GROUNDS RELY SPECIFICALLY ON THE FOLLOWING PRIOR ART REFERENCES

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

68. Ismagilov 091 was filed on May 9, 2003, published as Publication No. 2005/0272159 on December 8, 2005 (Ex. 1019²), and issued on October 31, 2006.

² Citations throughout are to the issued patent, but the published application contains the same substantive disclosures relied on in this Petition.

Accordingly, it is my understanding that Ismagilov 091 is prior art at least under post-AIA §102(a)(2) and pre-AIA 35 U.S.C. §102(e).

69. Ismagilov 091 describes substrates and methods of conducting reactions in droplets (“plugs”) in a flow of a carrier fluid in a substrate. Ex. 1003, abstract. The plugs in Ismagilov 091 are droplets that are surrounded by immiscible fluid: “aqueous plug-fluid is surrounded by a non-polar or hydrophobic fluid such as an oil.” Ex. 1003, 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 and 261:3-11 (Dr. Ismagilov testifying regarding creating stable “droplets”). Ismagilov 091 describes droplet handling, as described in section VI. Ex. 1003, 2:52-3:48, 37:23-45, 20:17-22, 20:37-44, 45:57-49:4, Fig. 24. Thus, in my opinion, the general area of technology of Ismagilov 091 is the same as that of the 837 Patent, which are systems and methods addressing the problems of microfluidic droplet handling.

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

70. Ismagilov 119 was filed on 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). Accordingly, it is my understanding that Ismagilov 119 is prior art at least under post-AIA §102(a)(2) and pre-AIA 35 U.S.C. §102(e).

71. Ismagilov 119 relates to “microfluidic technology enabling rapid and economical manipulation of reactions on the femtoliter to microliter scale.” Ex. 1004,

abstract, ¶¶ 3, 7-9, 28. The plugs in Ismagilov 119 are droplets: “The 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.” Ex. 1004, ¶ 83; *see also id.* at ¶ 77. This is further confirmed because Ismagilov 119 refers to “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 relates to droplet handling, as described in section VI. *E.g.*, Ex. 1004, ¶¶ 7-9, 28, 72, 77, 94, 123. Thus, in my opinion, the general area of technology of Ismagilov 119 is the same as that of the 837 Patent, which are systems and methods addressing the problems of microfluidic droplet handling.

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

72. Quake was filed on 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). Accordingly, it is my understanding that Quake is prior art at least under post-AIA §102(a)(2) and pre-AIA 35 U.S.C. §102(e).

73. Quake relates to “microfluidic devices and methods,” including particularly devices “designed to compartmentalize small droplets of aqueous solution within microfluidic channels filled with oil.” Quake, ¶¶ 3-4. The droplets described in Quake include aqueous droplets that “are encapsulated or separated

from each other by oil.” *Id.*, ¶ 100, ¶ 93. Quake relates to droplet handling, as described in section VI. *E.g.*, *Id.*, ¶¶ 95, 195-200. Thus, in my opinion, the general area of technology of Quake is the same as that of the 837 Patent, which are systems and methods addressing the problems of multi-phase microfluidic droplet handling.

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

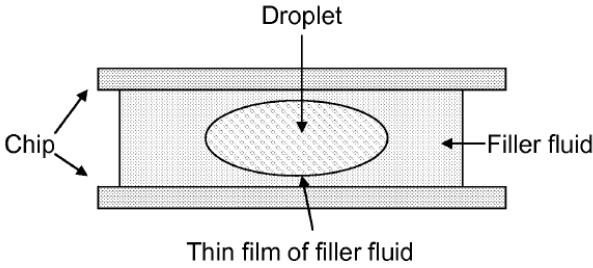
74. Pamula 634 was filed on December 15, 2006, published on October 18, 2007, and issued on October 21, 2008 as U.S. Patent No. 7,439,014 B2 (Ex. 1062). Accordingly, it is my understanding that Pamula 634 is prior art at least under post-AIA §102(a)(2) and pre-AIA 35 U.S.C. §102(e). The 837 Patent claims 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 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 microfluidic elements. Ex. 1022, 3; Ex. 1023, 2-3; Ex. 1024, 3. Pamula 634 was cited during prosecution, but was buried and not relied upon in a rejection by the examiner.

75. Pamula 238 was filed on January 30, 2015, was published on May 28, 2015, and claims priority to U.S. Provisional Application No. 60/745,058 (Pamula

058) which was filed on April 18, 2006. Accordingly, it is my understanding that Pamula 238 is entitled to the priority date of Provisional Application No. 60/745,058 (“Pamula 058”), making it prior art under post-AIA §102(a)(2) and pre-AIA 35 U.S.C. §102(e). My opinion is based on disclosures that are substantially identical between the publication and provisional. *See* Ex. 1018, ¶ 418; Ex. 1025 at 8-9. It is also my understanding that Pamula 238 also contains a claim supported by that provisional application. Claim 62 depends from Claim 56 in Pamula 238 and at least these claims are supported by the provisional Pamula 058. Pamula 058 describes 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. This is illustrated in the below chart.

Claim	Claim Limitation in Pamula 238 (Ex. 1018)	Disclosure of U.S. Provisional Application No. 60/745,058 (Ex. 1025)
56	A method of delivering a droplet to a reservoir, the method comprising:	<p>“The invention relates generally to multi-phase microfluidic systems and specifically to electrowetting-based droplet microfluidic systems.” Ex. 1025 at 1.</p> <p>“In droplet-based microfluidic systems a second fluid phase is required to fill the spaces between the droplets and we refer to this liquid or gas as a filler fluid. The selection of the filler fluid has many important consequences with respect to the dynamics and stability of the droplet phase and plays a very important role in the overall</p>

		<p>performance or capability of the system.” Ex. 1025 at 1.</p> <p>“For example, a waste or collection well can exist at the top or bottom of the 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.” Ex. 1025 at 8-9.</p>
(a)	providing a droplet microactuator, comprising:	<p>“Generally, the ‘droplet’ or ‘primary’ phase refers to the liquid which is either 1) directly microactuated or is 2) the medium in which the chemistry is performed.” Ex. 1025 at 2.</p>
(i)	a first substrate and a second substrate, the second substrate arranged relative to the first substrate and spaced from the surface of the first substrate by a distance sufficient to define a space between the first substrate, wherein the space comprises a filler fluid;	<p>“In droplet-based microfluidic systems a second fluid phase is required to fill the spaces between the droplets and we refer to this liquid or gas as a filler fluid. The selection of the filler fluid has many important consequences with respect to the dynamics and stability of the droplet phase and plays a very important role in the overall performance or capability of the system.” Ex. 1025 at 1.</p> <p>“The ‘filler fluid’ or ‘secondary’ phase is an ambient fluid which bathes the droplets in the system and is generally used to fill the space within the chip which is not occupied by droplets. ‘Droplet’ in this context refers to any liquid body of any size and shape which has at least one free interface.” Ex. 1025 at 2.</p> <p>“‘Chip’ refers generically to any solid structure which contains the droplets to operate as a microfluidic system.” Ex. 1025 at 2.</p> <p>“Surface lubrication. A liquid filler fluid may be advantageous for providing a lubricating layer between the droplet and chip surface. When the filler fluid forms a film between the droplet and</p>

	<p>chip surface this can have the effect of lubricating the droplet by preventing friction-like physical interactions between the droplet and surface.” Ex. 1025 at 5.</p> <p>“Alternatively, the solid-liquid interfacial tension may be selected to control the wetting of the filler fluid on the chip surfaces, for example, to control the formation, thickness or behavior of thin films of the filler fluid between the droplet and chip surfaces or to control the wetting behavior of the fluid when filling or emptying it from the chip.” Ex. 1025 at 8.</p> <p>“The filler fluid may be selected to have a particular density relative to the droplet phase. ... For example, a waste or collection well can exist at the top or bottom of the 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. Density differences can also be used as a means to control or engineer contact between the droplets and chip surfaces. For example, a droplet not normally contacting a top-plate can be released to sink or float to that surface to contact it.” Ex. 1025 at 8-9.</p>  <p>FIGURE 5: Even when the droplet is sandwiched between two chip surfaces, a thin layer or film of filler fluid may exist between the droplet and chip surface (side view). Ex. 1025, Figure 5.</p>
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(ii)	electrodes arranged on one or both of the first substrate and second substrate and configured for manipulating a droplet on a surface thereof;	<p>“The invention relates generally to multi-phase microfluidic systems and specifically to electrowetting-based droplet microfluidic systems.” Ex. 1025 at 1.</p> <p>“Evaporation reduces droplet volume which can interfere with microfluidic operations on the chip - for example a droplet may become too small to be transported to an adjacent electrode in an electrowetting-based system - in other types of systems changes in droplet volumes may likewise alter the fluid dynamics or operability of the system.” Ex. 1025 at 3.</p> <p><i>“Selection based on electrical properties.</i> The filler fluid may be selected to have particular electrical properties. For example, certain applications including electrowetting-on-dielectric favor the use of a filler fluid that is non-conductive (e.g., silicone oil). Or the dielectric permittivity can be selected to control the coupling of electrical energy into the system from external electrodes. In certain applications a non-conductive filler fluid can be employed as an electrical insulator or dielectric in which the droplet floats just above the electrodes without physically contacting them. For example, in an electrowetting system a layer of filler fluid (e.g., silicone oil) between the droplet and electrode can be used to provide electrostatic control of the droplet.” Ex. 1025 at 8.</p> <p>“The thickness of the fluid film if it exists can be influenced by an electrical field applied between the droplet and an electrode located within the chip.” Ex. 1025 at 12.</p>
(iii)	one or more reservoirs at one of the first	“For example, a waste or collection well can exist at the top or bottom of the chip where droplets are delivered to that reservoir by simply

	substrate and second substrate;	releasing them at an appropriate point and allowing them to float or sink to the target destination.” Ex. 1025 at 8-9.
(iv)	one or more input ports disposed in at least one of the first substrate and second substrate; and wherein, the droplet is situated in the space between the first substrate and second substrate;	<p>“The invention also provides means for controlling the introduction or circulation of the filler fluid within the system. In one mode of operation the filler fluid is injected once during the initialization of chip operation. The filler fluid may be provided from an external source using a syringe, dropper, pipettor, capillary, tube or other means. Alternatively, the filler fluid may be provided from a reservoir internal to the chip assembly or cartridge. As an example, the fluid can be contained within a sealed pouch which is punctured or pressed to transfer the liquid into the chip.” Ex. 1025 at 9.</p> <div data-bbox="738 875 1333 1142" data-label="Image"> </div> <p>FIGURE 5: Even when the droplet is sandwiched between two chip surfaces, a thin layer or film of filler fluid may exist between the droplet and chip surface (side view). Ex. 1025, Figure 5.</p>
(b)	transporting the droplet along a path or network of the electrodes; and	<p>“Evaporation reduces droplet volume which can interfere with microfluidic operations on the chip - for example a droplet may become too small to be transported to an adjacent electrode in an electrowetting-based system - in other types of systems changes in droplet volumes may likewise alter the fluid dynamics or operability of the system.” Ex. 1025 at 3.</p> <p><i>“Selection based on electrical properties. The filler fluid may be selected to have particular</i></p>

		<p>electrical properties. For example, certain applications including electrowetting-on-dielectric favor the use of a filler fluid that is non-conductive (e.g., silicone oil). Or the dielectric permittivity can be selected to control the coupling of electrical energy into the system from external electrodes. In certain applications a non-conductive filler fluid can be employed as an electrical insulator or dielectric in which the droplet floats just above the electrodes without physically contacting them. For example, in an electrowetting system a layer of filler fluid (e.g., silicone oil) between the droplet and electrode can be used to provide electrostatic control of the droplet.” Ex. 1025 at 8.</p> <p>“The thickness of the fluid film if it exists can be influenced by an electrical field applied between the droplet and an electrode located within the chip.” Ex. 1025 at 12.</p>
(c)	releasing the droplet at an appropriate point along the path or network of the electrodes and allowing the droplet to float or sink, as applicable, to a target destination.	<p><i>“Selection based on density.</i> 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 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. Density differences can also be used as a means to control or engineer contact between the droplets and chip surfaces. For example, a droplet not</p>

		normally contacting a top-plate can be released to sink or float to that surface to contact it. Density differences and buoyancy effects can also be exploited for sensing applications in which the movement of droplets is detected and related to a change in position, orientation or acceleration.” Ex. 1025 at 8-9.
62	The method of claim 56 wherein the filler fluid is selected to have a particular density relative to the droplet to control or exploit buoyancy forces acting upon the droplet.	“ <i>Selection based on density.</i> 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 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. Density differences can also be used as a means to control or engineer contact between the droplets and chip surfaces. For example, a droplet not normally contacting a top-plate can be released to sink or float to that surface to contact it. Density differences and buoyancy effects can also be exploited for sensing applications in which the movement of droplets is detected and related to a change in position, orientation or acceleration.” Ex. 1025 at 8-9.

76. Pamula 634 and Pamula 238 (collectively “Pamula”) relate to droplet systems. Ex. 1025, 1; Ex. 1018, ¶ 3, Ex. 1007, ¶ 3. In these systems, the droplets are surrounded by filler fluid. Ex. 1025, 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; Ex. 1018, ¶ 21, Ex. 1007, ¶ 21 (“For example, a droplet may be completely surrounded by filler fluid or may be bounded by filler fluid and one or more surfaces of the droplet microactuator.”). Pamula relates to droplet handling, as described in section VI. *E.g.*, Ex. 1025, 7-11; Ex. 1018, ¶¶ 54, 412-13, 427, Ex. 1007, ¶¶ 54, 412-13, 427. Thus, in my opinion, the general area of technology of Pamula is the same as that of the 837 Patent, which are systems and methods addressing the problems of multi-phase microfluidic droplet handling.

X. CLAIM CONSTRUCTION

77. It is my understanding that the claim construction standard includes construing the claim in accordance with the ordinary and customary meaning of such claim as understood by a person of ordinary skill in the art. As explained above, I was at least a person of ordinary skill in the art either before the earliest filing date of the challenged patents.

78. It is my understanding that while the parties have not yet exchanged claim constructions in the related district court proceeding, Bio-Rad has served infringement contentions for the 837 Patent. I have reviewed Bio-Rad’s infringement contentions and its Complaint from the related district court proceeding. Ex. 1026 (Bio-Rad’s infringement chart regarding certain accused products);

Ex. 1052 (Bio-Rad's Complaint). Those infringement contentions show that Bio-Rad interprets the claims expansively for purposes of alleging infringement. The table below summarizes my understanding of Bio-Rad's interpretation of the claims based on its infringement contentions.

79. I address each of 10X's proposed claim constructions below, and the claim constructions are summarized in the following table.

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> <p>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"</p>	Broad enough to include the opening at the top of an open outlet well (Ex. 1026, 11-12.)
"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 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.”	Broad enough to encompass any amplification reaction. See Ex. 1026, 27-29.

A. “droplet receiving outlet” (Claim 1)

80. It is my opinion, that a person of ordinary skill in the art, reading the claims, specification, and file histories, would consider the term “droplet receiving outlet” not to be a term used by persons of skill in the art to designate either a particular structure or a class of structures. While a person of ordinary skill is familiar with numerous outlet structures, a “droplet receiving outlet” does not invoke a class of structures, and is not understood by a person of ordinary skill to refer to a class of structures. The remainder of the claims do not provide a structure for the term “droplet receiving outlet.” Thus, a person of ordinary skill understands “droplet receiving outlet” to be any structure capable of performing the function receiving substantially only droplets when exiting from the separation chamber.

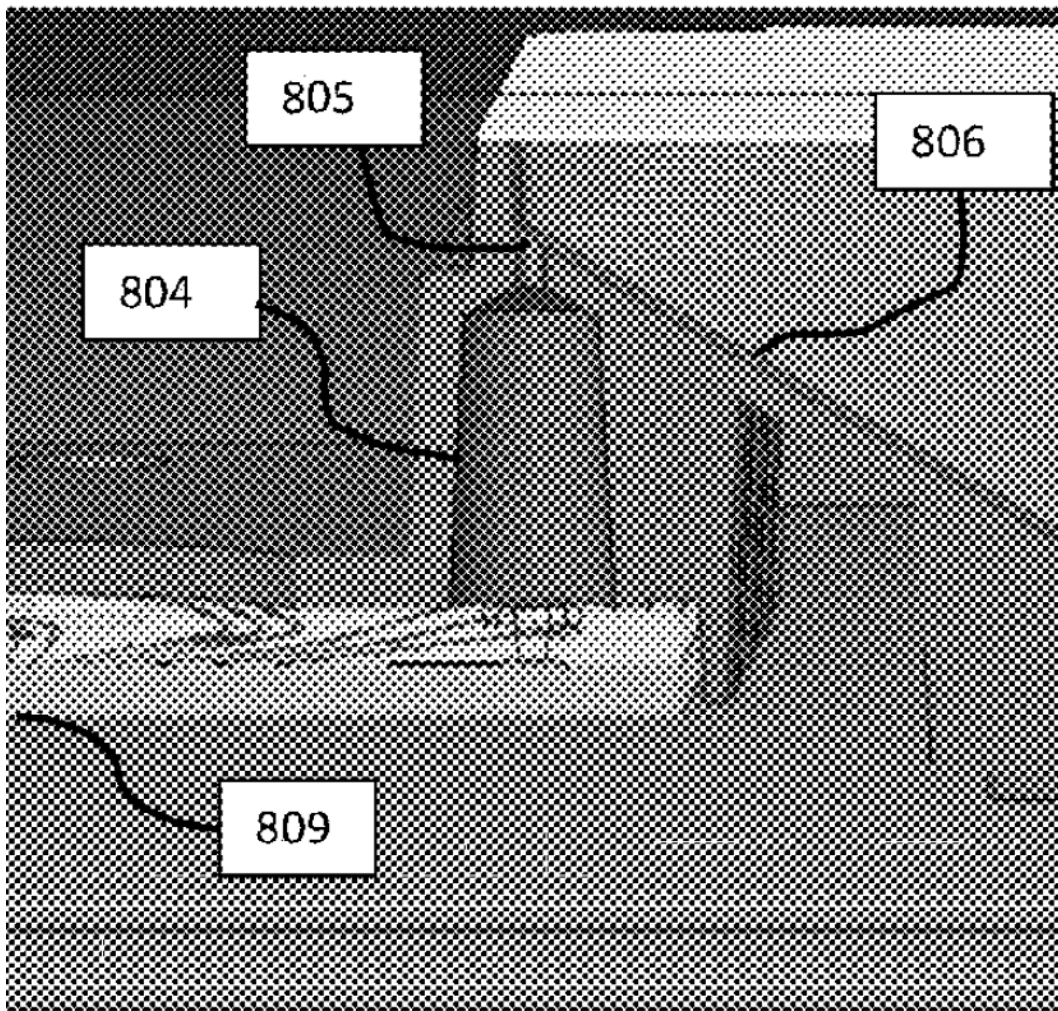
81. The specification consistently describes the chamber outlet in functional terms: “*configured to receive substantially only droplets*” and that “*substantially only droplets to exit the chamber,*” and that droplets “flow into the outlet.” Ex. 1001, Abstract, 3:46-58, 53:21-35; *see also id.*, 53:21-41, 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* Ex. 1001, 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.

82. Alternatively, if “droplet receiving outlet” is found to have a definite structure, it is my opinion that a person of ordinary skill in the art, reading the claims, specification, and file histories would understand that “droplet receiving outlet” in the claims of the 837 Patent should be construed to cover a structure connected to the interior space of the chamber and configured so that substantially only droplets flow into it when exiting the chamber. While the term “droplet receiving outlet” does not appear in the specification, the specification describes the chamber outlet as “*configured to receive substantially only droplets*” and that “*substantially only droplets to exit the chamber,*” and that droplets “flow into the outlet.” Ex. 1001, Abstract, 3:46-58, 53:21-35; *see also id.*, 53:21-41, 54:34-46. The claim limitations themselves further support that the droplet receiving outlet is connected to the interior space of the chamber because it is described as a “separation chamber comprising . . . at least one droplet receiving outlet.”

83. Figure 38 (a portion of which is shown below) shows to a person of ordinary skill that the outlet (805) is the structure connected to the interior space of the chamber (804) through which the droplets exit the chamber. *See also* Ex. 1001, 54:34-35. As the 837 Patent describes: “As shown in FIG. 39, the outlet 805 can be

positioned at an upper portion of the chamber 804 where the rising droplet will ***exit the chamber 804*** into the outlet 805 ***leaving a large part of the oil behind.***” Ex. 1001, 54:41-44. Further confirming that the outlet is a structure, the outlet is connected on one end to the chamber and on the other end is “connected to a slide 806.”



84. Additionally, Bio-Rad’s argument under the doctrine of equivalents further confirms that 10X’s proposed construction is correct. Bio-Rad states that the

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.

85. An opening in a well is not described anywhere in the specification as a droplet receiving outlet, nor would a person of ordinary skill understand it to be.

B. “separation chamber” (Claim 1)

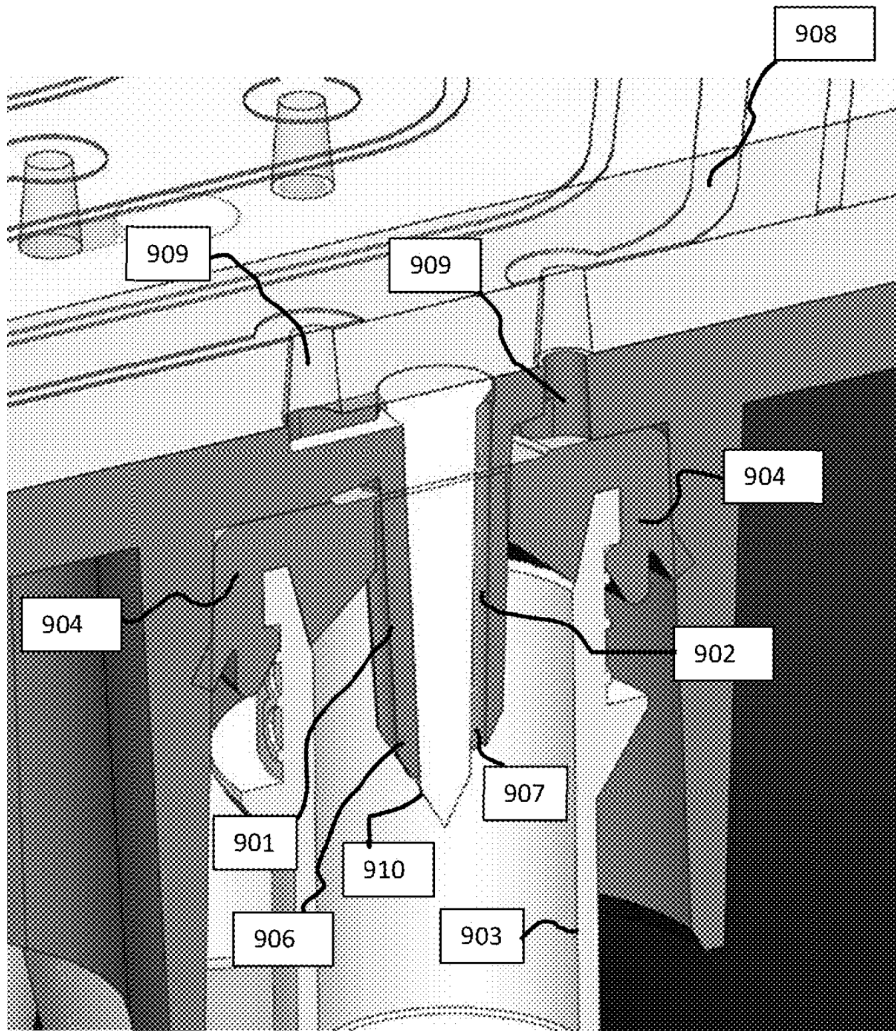
86. It is my opinion, that a person of ordinary skill in the art, reading the claims, specification, and file histories, would understand the term “separation chamber” recited in the 837 Patent claims should be construed to cover a space that is substantially enclosed. A person of ordinary skill in the art would understand that “chamber” has its ordinary meaning here. That meaning is described in dictionaries, and includes “[a]n enclosed space, cavity, etc.” and “a natural or artificial enclosed space or cavity.” Ex. 1027, 234 (Compact Oxford Dictionary, 1994); Ex. 1028, 190 (Merriam-Webster’s Collegiate Dictionary, 1997).

87. A person of ordinary skill would have this understanding after reading the specification. The specification describes that a primary purpose of the invention was to “displace sample droplets from one location to another without the need for operator handling,” which means that “the risk of contamination associated with such handling is eliminated.” Ex. 1001, 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. An open chamber neither eliminates operator handling nor avoids the risk of contamination. An open container requires operator handling and creates a risk for contamination. Thus, one of ordinary skill would not understand the term “separation chamber” to include open containers and thus defeat the primary purpose of the alleged invention.

88. While the specification says that a chamber can “***include*** any vessel suitable for holding droplets, for example, test tubes, vials, beakers, jars, and PCR tubes,” *Id.*, 53:35-38, when it describes droplets as separating in such a container, it shows the container consistently and exclusively as substantially enclosed—not open—when in use with a “seal” to “minimize potential contamination.” *Id.*, 55:55-65, Fig. 39. A portion of Figure 39 is shown below. In this embodiment, there is a vessel 903, but that vessel is shown as having an interior space that is substantially enclosed. One method of enclosure, shown here, is a sealable connection (as opposed, for example, to a vessel that is permanently substantially enclosed as in Figure 38):

89. In addition, the assembly may include. devices configured to sealably connect the vessel 903 to the assembly. The sealable connection and the resultant seal minimize potential contamination as the droplets are displaced from the vessel 903. Any means can be used to sealably connect the vessel. In certain embodiments, the assembly includes a PCR tube cap 904 that lock the vessel 903 into a sealed position.



90. All of the 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.

C. “droplet” (Claim 1)

91. I understand that the 837 Patent defines “droplet” as “[a] ‘droplet,’ as used herein, is an isolated portion of a first fluid that completely surrounded by a second fluid.” Ex. 1001, 15:1-3.

D. “sample” (Claim 1)

92. I understand that 10X’s proposed construction of “sample” was an agreed construction in a prior litigation between 10X and Bio-Rad. Ex. 1029.

93. It is my opinion, that a person of ordinary skill in the art, reading the claims, specification, and file histories, would understand the term “sample” recited in the 837 Patent claims should be construed to cover “a compound, composition, and/or mixture of interest, from any suitable source(s).” Ex. 1029 at 35-36 The specification of the 837 Patent describes a sample as something of interest, or something to be analyzed or studied. The specification describes a “*sample to be analyzed*,” a “*sample under study*,” and a “*fluid of interest (e.g., sample fluid)*.” Ex. 1001, 18:46-48, 21:52-56, 35:27-30. This is consistent with other examples of “samples” or usages of “sample” in the specification. *Id.*, 1:50-55, 2:4-23, 2:35-53, 2:58-3:10, 3:17-31, 4:29-36, 4:40-56, 5:61-67, 6:4-14, 7:49-50, 13:11-15, 13:46-48, 14:47-51, 15:2-4, 16:51-63, 17:5-23, 18:49-66, 19:60-22:34, 24:61-25:3, 26:41-27:4, 27:30-28:8, 28:54-67, 30:28-32, 44:6-17, 44:58-64, 45:34-40, 48:6-15, 52:36-65, 53:56-67, 54:4-38, 56:25-27, 57:52-54, 58:7-10, 58:26-33, 59:43-46, 59:51-54, 60:30-32, 60:40-42, 61:9-12, 66:19-37, 69:12-33, 70:55-67, 71:25-37, 71:60-62, 73:8-26, 74:59-63, 75:37-40, 76:39-77:3, 77:46-50, 78:8-14, 78:43-54, 78:62-66, 79:11-13. For example, the specification states that “The invention provides systems and methods that are designed to minimize sample contact and exposure of the

sample to the surrounding environment, thereby minimizing or eliminating the introduction of contaminants into an amplification reaction.” Ex. 1001, 2:35-43. The “sample” in this case is the substance of interest in the study, while “contamination” is the something not of interest that is introduced into the reaction and that is undesirable. A “sample” is not defined by its location on the microfluidic chip, but by the fact that it is a substance of interest. For example, the 837 Patent describes “A liquid that does not contain *sample molecules, cells or particles* can be introduced into a sample inlet well or channel and directed through the inlet module, e.g., by capillary action, to hydrate and prepare the device for use.” Ex. 1001, 14:43-47. A liquid is not a sample merely because it is placed in the sample inlet. A sample is something more, as described in the specification, which is something of interest or under investigation, such as a molecule or cell.

94. The specification also explains

In particular, the sample concentration should be dilute enough that most of the droplets contain no more than a *single molecule, cell or particle*, with only a small statistical chance that a droplet will contain two or more molecules, cells or particles. This is to ensure that for the large majority of *measurements*, the level of reporter measured in each droplet as it passes through the detection module *corresponds to a single molecule, cell or particle* and not to two or more molecules, cells or particles.

Ex. 1001, 16:46-53. In this example, a person of ordinary skill in the art understands

that the “molecule, cell or particle” is the substance of interest in the investigation because the measurements being performed “correspond[]” to a single molecule, cell, or particle.

E. “coupled” (Claims 7-8)

95. It is my opinion, that a person of ordinary skill in the art, reading the claims, specification, and file histories, would understand the term “coupled” recited in the 837 Patent claims should be construed to cover fastened or joined. A person of ordinary skill in the art would understand that “coupled” has its ordinary meaning here. The ordinary meaning of “to couple” is “[t]o fasten or link together (properly in pairs); to join or connect in any way” or “to fasten together.” Ex. 1027, 350 (Compact Oxford Dictionary, 1994); Ex. 1028, 266 (Merriam-Webster’s Collegiate Dictionary, 1997). A person of ordinary skill would understand that the relevant uses of “coupled” in the specification are consistent with this ordinary meaning. For example, the specification describes “sealably ***coupled***,” which means to a person of ordinary skill there is a particular joining or fastening that results in a seal. Claim 8 is similar in that it narrows claim 7 that says “coupled” to “sealably coupled.” As another example, the specification describes that “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” Ex. 1001, 37:10-14, *see also* 4:26-31. A person of ordinary skill understands that the microscope is joined or fastened

to the computer through a connection. The specification provides no example in which transport would be described as “coupled,” nor would it by a person of ordinary skill. Ex. 1001, 37:10-14, 55:11-21, 59:66-60:3.

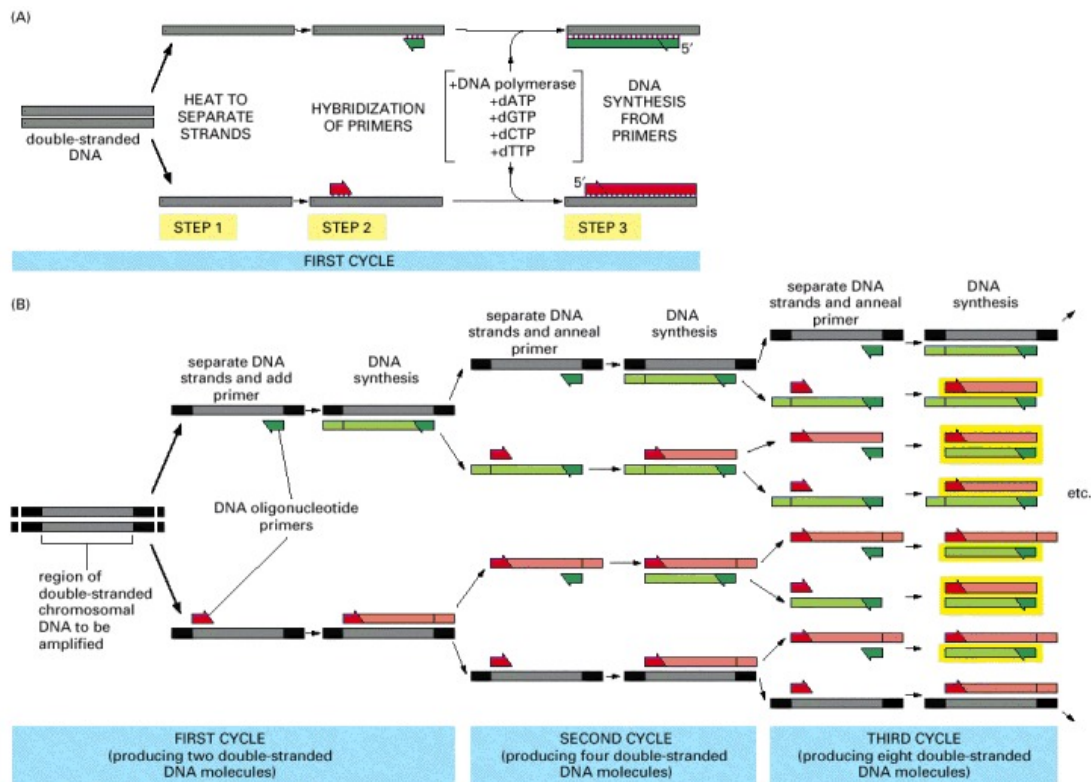
F. “polymerase chain reaction” (“PCR”) (Claim 13)

96. I understand that 10X’s proposed construction of “PCR” was adopted by a court in a prior litigation between 10X and Bio-Rad. Ex. 1030.

97. It is my opinion, that a person of ordinary skill in the art, reading the claims, specification, and file histories, would understand the term “polymerase chain reaction” (“PCR”) recited in the 837 Patent claims should be construed to cover a “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 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.” Ex. 1030, 5.

98. This construction is also the ordinary meaning of PCR to a person of ordinary skill in the art. For example, undergraduate textbooks illustrate this process. The below figure, titled “Amplification of DNA using the PCR technique” shows that the strands of DNA are heated to separate the strands, primers are hybridized, a

DNA polymerase is used to extend the strand from the primer, and then the replicated DNA serves as a template for additional replication. Ex. 1031, Fig. 8-39. It is the last step in which the replicated DNA serves as a template for additional replication that is important to PCR and is the basis for the name “chain reaction.” *Id.* The additional strands that can be used for replication are also what makes the “billionfold” amplification through PCR possible, as the below figure illustrates. If new strands are not used as a template, each cycle would result in only two copies of the sequence. Because new strands are used as templates for PCR, the number of copies of the DNA sequence of interest doubles every reaction cycle.



99. The descriptions of PCR in the specification are consistent with this construction. For example, the 837 Patent specification describes that “[t]he nucleic acid in each of the formed droplets is amplified, e.g., by thermocycling the droplets under temperatures/conditions sufficient to conduct a PCR reaction.” Ex. 1001, 60:5-11. This passage refers to the changes in temperature within a cycle, including particularly a heating and denaturing step, which is included in 10X’s proposed construction. The specification also mentions the PCR primers that are part of the proposed claim construction: “After PCR amplification, the resulting PCR product is in solution along with PCR primers, dNTPs, enzyme, and buffer components.” Ex. 1001, 69:49-51; *see also* 68:38-40. This confirms that a person of ordinary skill would interpret the term “PCR” as in 10X’s proposed construction.

XI. OVERVIEW OF GROUNDS 1-5

Ground	Basis	Challenged Claims	References	Claim Construction
1	§ 102	1-2, 4, 10-13, 19-20	Ismagilov 091	Bio-Rad’s
2	§ 103	1-2, 4, 7, 9-13, 19-20	Ismagilov 091 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

100. I understand that 10X challenges the validity of claims 1-4, 7-13, and 19-20 of the 837 patent.

101. There are two main theories of invalidity. 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 person of ordinary skill in the art would have been motivated to combine Quake for additional information regarding the structure of a well of a microfluidic device (**Ground 2**).

102. Second, under 10X's proposed constructions, Ismagilov 119, which incorporates by reference in its entirety Ismagilov 091, discloses a density sorter in which droplets are sorted by their density relative to that of the carrier fluid (**Ground 3a**). Further, a person of ordinary skill in the art 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 interpretations of the claims (**Grounds 3b, 4b, 5b**).

A. Ground 1

103. It is my opinion that 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.

B. Ground 2

104. 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 person of ordinary skill in the art would not have known the structure of such features (which a person of ordinary skill would), a person of ordinary skill in the art would also have been motivated to look to art that further describes the structure of wells. Quake was such a reference that related to "microfluidic devices and methods" and included further descriptions of wells or reservoirs. Quake, ¶ 3.

105. A person of ordinary skill in the art would have been motivated to combine Ismagilov with Quake. Stephen Quake was well-known in microfluidics,

and a person of ordinary skill in the art 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).

106. I understand that Quake was cited prior art considered by the Examiner during prosecution of Ismagilov 091 (and identified on the face of the 091 patent). Indeed, I have reviewed Quake and Ismagilov 091, and comparisons showing that Ismagilov appeared to copy 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. 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)). I have reviewed Ismagilov's testimony from 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. I have also reviewed Ismagilov testimony that he knew of Dr. Quake's patent publications and articles shortly after they were published. Ex. 1017, 319:12-17, 321:2-12. This further supports that Quake was well-known.

107. 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 person of ordinary skill would consider. Ex. 1035. I have reviewed multiple publications from prior litigation between the parties discussing Ismagilov's work that also discussed Quake 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], Ex. 1045 [PTX989-004], Ex. 1046 [Sia Rebuttal Demonstrative, slides 4-7] [Sia secondary consideration articles & referenced demonstrative slides]. If a person of ordinary skill in the art with Ismagilov would want additional information regarding microfluidic structures, the person of ordinary skill in the art would have looked to the work of a leader in developing early microfluidic devices: Quake.

C. Ground 3

108. I understand 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.” Ex. 1004, ¶¶ 30, 118 (same). I understand that 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.

109. As is described further below, under Grounds 3-5, Ismagilov discloses microfluidic devices with 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.

110. Ismagilov 119, including Ismagilov 091, 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.

111. 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.

D. Grounds 4-5

112. 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.

113. A person of ordinary skill in the art would have been motivated to combine Ismagilov with Pamula. Ismagilov disclosed density sorting. If Bio-Rad argues a person of ordinary skill in the art would need additional information regarding density sorting, a person of ordinary skill in the art would have been motivated to consider art describing density sorting related to droplet handling, such as Pamula.

114. The Pamula references (Pamula 634 and Pamula 238), arose from work in my research group. Our work was well-known in the field particularly for droplet

handling techniques, and a person of ordinary skill in the art with Ismagilov would have been motivated to consider Pamula from my research group for additional information regarding droplet handling methods, including density separation, if required. Our research group was one of the early leaders in the field of droplet handling. Our research group began publishing on droplets in 2000. Ex. 1038 (2002 publication); Ex. 1047 (2000 publication M.G. Pollack, R.B. Fair, and A.D. Shenderov, "Electrowetting-Based Actuation of Liquid Droplets for Microfluidic Applications," *Appl. Phys. Lett.*, 77, 1725 (2000).). Work from me and my research 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 the work from my lab group was a well-known source a person of ordinary skill in the art would consider in the field at the time. Ex. 1035. I and others from my group were also well-known because we founded Advanced Liquid Logic, another well-known microfluidics company formed in 2004. Ex. 1039. Thus, if a person of ordinary skill in the art with Ismagilov would want additional information regarding droplet methods, the person of ordinary skill would have looked to the work of early leaders in the field, which includes my lab group and the teachings of Pamula 634 and Pamula 238.

115.

XII. GROUNDS 1-5 INVALIDATE THE IDENTIFIED CLAIMS

116.

117. As detailed below, Ismagilov 119, Ismagilov 091, Quake, Pamula 634 and Pamula 238 discloses every limitation of claims 1-4, 7-13, and 19-20, and in my opinion, these claims would have been anticipated by Ismagilov 119 or been obvious over the combinations with Ismagilov 119 and Ismagilov 091.

118.

A. Claim 1

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

a. Grounds 1-5

119. Ismagilov 091 or 119 discloses the preamble. For example, the invention in Ismagilov 119 “provides a ***system*** for plug based microfluidic manipulation of small volumes of solutions.” Ex. 1004, ¶ 28. And Ismagilov 091 discloses: “The present invention provides ***microfabricated substrates*** and methods of conducting reactions within these substrates,” which are or are part of an assembly. Ex. 1003, Abstract; *see also id.*, 11:19-23.³ Both of these references are describing modular assemblies.

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

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

a. Grounds 1-5

120. Ismagilov 091 / 119 meets this limitation. Ismagilov 091 / 119 describes substrates containing microchannels and their formation, which confirms there are microchannels in a horizontal plane.

121. Ismagilov 119 discloses that “[c]omponents comprise microchannels that can be formed using methods known in the art,” and those methods include “substrates with etched, or molded, or embossed microchannels, or combinations thereof.” Ismagilov 119, ¶¶ 71-72. A person of ordinary skill in the art would be familiar with such techniques for manufacturing substrates. Ismagilov 091 further describes such methods.

122. Ismagilov 091 describes that to form channels, such as PDMS channels, they are molded by pouring uncured PDMS into molds, and then curing. Ismagilov 091, 16:23-41. Ismagilov 091 teaches that other features of the microfluidics, such as holes, can be cut into the PDMS after curing. *Id.* Generally, the channels are molded as negative indentations into the PDMS. This means that they formed with the side facing the mold open. To close the channels, the PDMS is “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 091, 16:23-41. The same

substance—PDMS—is described in Ismagilov 119, ¶ 22, and so a person of ordinary skill in the art would look to the teachings of both patents in combination.

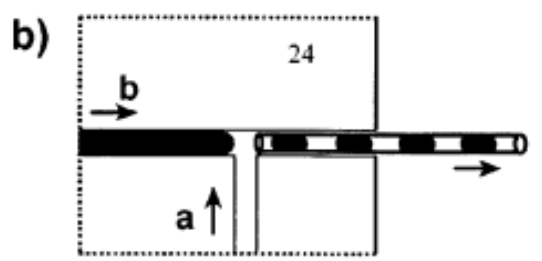
123. Ismagilov 091 describes using the flat glass as the “floor,” which means that the substrate would be placed with that flat glass surface down. The channels are closed by the glass surface, and so they are running parallel to the glass surface. When that surface is placed flat down, such as on a laboratory bench top, meaning that the channels are horizontal (perpendicular to the force of gravity).

124. Ismagilov 091 also confirms that the “channels” are “microchannels that are of dimensions suitable for use in devices.” Ismagilov 091, 7:34-52. Ismagilov 091 / 119 generally, and particularly Ismagilov 091, relates to microfluidics. Ismagilov 091 explains that “[m]icrofluidics deals with the transport of fluids through networks of channels, typically having micrometer dimensions,” and that “[n]onlinearity dynamics, in conjunction with microfluidics, play a central role in the design of the devices and the methods according to the invention. Ismagilov 091, 1:14-18.

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”

a. Grounds 1-5

125. Ismagilov 091 / 119 describes this limitation. Figure 13b (reproduced below) in Ismagilov 119 is described as a “simple T-junction in PDMS” that “can be used . . . *to form plugs*” when “an *aqueous stream can be pumped in through channel a* while the *carrier fluid is pumped through channel b*,” and then “[a]t the junction, aqueous droplets, or plugs, form.” Ismagilov 119, ¶ 22; see also *id.*, ¶ 80, ¶ 84. The figure shows that the immiscible fluid (black) is flowing through channel b, and as the immiscible fluid is flowing, the aqueous fluid (white) is pumped into the channel with the oil flowing through it to form droplets.



126. Ismagilov 091 further supports and expands upon these disclosures. First, Ismagilov 091 discloses 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 091, 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 091 also provides multiple examples of samples included in droplets that are a compound of interest under 10X's proposed construction. *E.g.*, Ismagilov 091, 46:2-5, 52:60-62. For example, Ismagilov 091 states, "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." Ismagilov 091, 47:41-44. The DNA, RNA, or protein being detected is the substance of interest, and thus the sample. Ismagilov 091 teaches that such a sample would be included in the sample inlet. Ismagilov 091 also states that "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 091, 67:58-61. This shows that the sample Ismagilov 091 discloses the same sample that the 837 Patent refers to. Because Ismagilov §091 / 119 describes a “sample inlet,” the samples in the examples could be provided through such an inlet.

127. Second, Ismagilov 091 discloses the droplet formation module configured to produce droplets with sample surrounded by immiscible fluid. The block quotation in the previous paragraph describes the sample inlet fluid as being in the droplets surrounded by the carrier fluid, and this is further shown by the below figures 10A and 3A from Ismagilov 091. *See also*, Figs. 2-10. Ismagilov 091 / 119 discloses droplets, which are typically aqueous droplets surrounded by immiscible fluid, as described in section VI and also shown in the below figures. Ismagilov also describes the droplets, including specifically aqueous droplets as being surrounded by immiscible fluid: “[A]queous plug-fluid is **surrounded by** a non-polar or hydrophobic fluid such as an oil.” Ismagilov 091, 9:39-44; *see also* Ismagilov 119, ¶ 22 (“At the junction, **aqueous droplets**, or plugs, form spontaneously.”). The droplets—including aqueous droplets—are described as containing sample: “[p]lugs can be formed from essentially any fluid such as from one or more **aqueous solutions**, one or more organic solutions, one or more inorganic solutions, or mixtures thereof,” and fluids include “water, stock solutions, buffers, reagents, solvents, salt solutions, polymer solutions, precipitant solutions, metal suspensions,

cell suspensions, or the like.” Ismagilov 119, ¶ 80; *see also id.*, ¶¶ 7-8; Ismagilov 091, 20:10-23, 21:1-6. The sample, aqueous, and plug fluid are all the same fluid (if they are present) in Ismagilov 091. The aqueous fluid forms droplets, and so does the sample fluid, as described above. A person of ordinary skill would also know that work with biological molecules, such as DNA, occurs in water, and so aqueous (water) solutions are favored for at least biological applications. The plug fluids are the fluids in droplets, and so this term includes the previous two categories, and so both water and sample can be included in droplets. Ismagilov 091 also 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 091, 9:20-34; *see also id.*, 2:50-59, 8:41-47, 9:55-61, 9:35-54; Ismagilov 119, ¶¶ 84, 92.

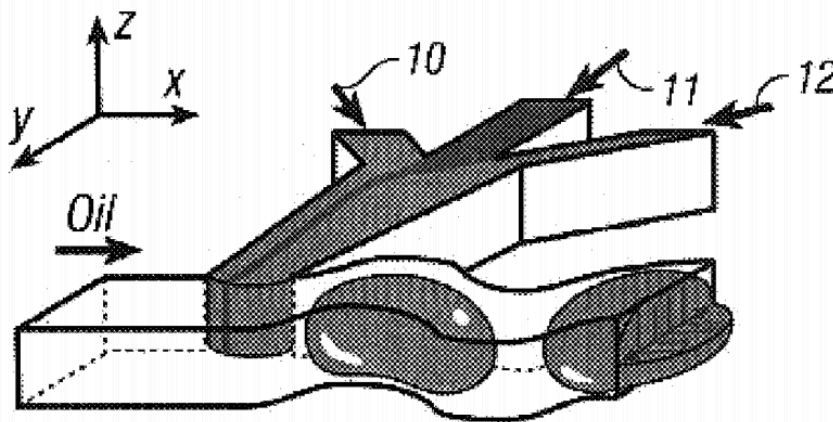


FIG. 10A

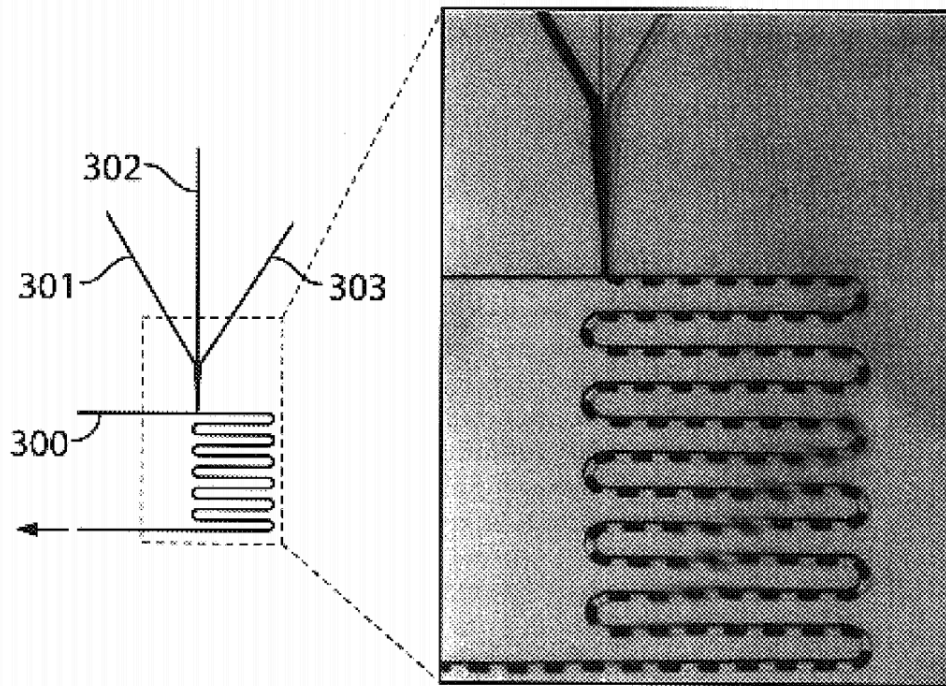


FIG. 3A

128. Third, Ismagilov 091 discloses that the junction is between the sample inlet and the microchannel. This is illustrated by the above figures in which there is a microchannel containing droplets downstream of the droplet formation module.

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

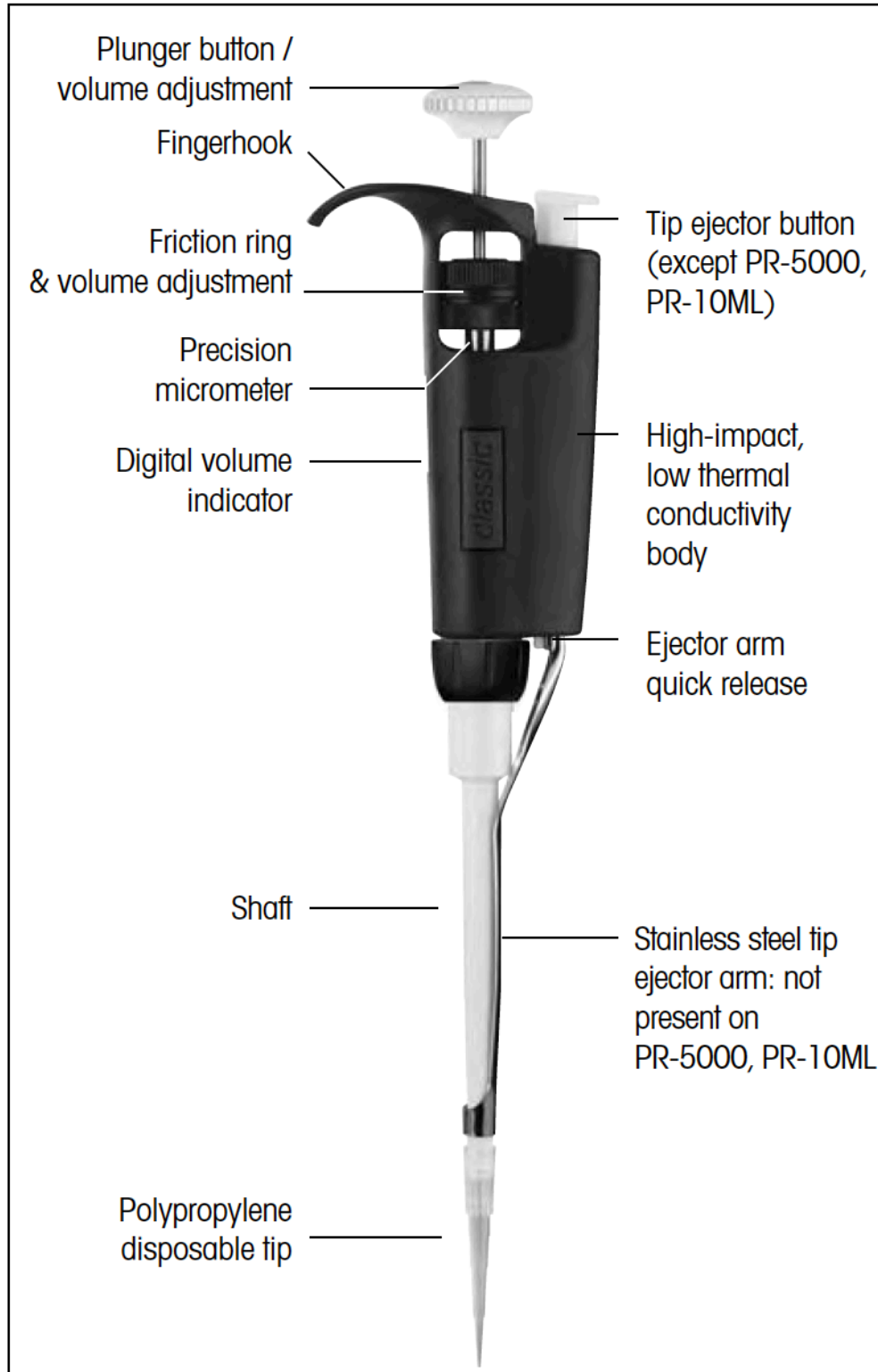
a. Ground 1

129. Ismagilov 091 discloses this limitation under Bio-Rad’s interpretations. Bio-Rad interprets 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. Under Bio-Rad's interpretation, Ismagilov 091 discloses collection wells or reservoirs that are a separation chamber with a droplet receiving outlet. Ismagilov 091 discloses an "outlet port" which is "an area of a substrate that **collects** or dispenses . . . plugs" and may "communicate with a **well or reservoir**." Ismagilov 091, 9:5-8, 14:36-38. Ismagilov similarly describes after a manifold an outlet, and that "outlet can be adapted for receiving, for example, a segment of tubing or a sample tube, such as a standard 1.5 ml centrifuge tube. Collection can also be done **using micropipettes**." Ismagilov 091, 17:27-30.

130. To permit the collection of fluids by micropipette, there must be a container with a volume of liquid that can be pipetted, and an opening into which the micropipette can be inserted, which describes a collection well. A micropipette (or microliter pipette) was a well-known, common piece of handheld laboratory equipment before the earliest possible filing date of the asserted patents. I was personally familiar with micropipettes before the earliest possible filing date of the asserted patents. I have reviewed Ex. 1040 and Ex. 1041. It has a copyright of 2005, and its disclosures described here are consistent with my recollection of micropipettes before the earliest possible filing date of the asserted patents. Figure 1 is reproduced below, and it shows a micropipette. A micropipette is held in the hand, and the thumb is used to depress and release the plunger button to take up fluid (on

release) or dispense fluid (on depression). The fluid is taken up and dispensed through the disposable tip.



131. Thus, for a micropipette to be able to collect liquid, the liquid must first be collected in a container that (1) is of a sufficient volume for the pipette tip to be inserted, (2) has an opening through which the pipette can be inserted, and (3) the liquid is of a sufficient volume that the micropipette can collect it. This describes a collection well.

132. 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.

133. Ismagilov 091 also discloses a droplet receiving chamber inlet for the well or reservoir (separation chamber). Ismagilov 091 discloses that the outlet port

“may be in fluid communication with the channels or reservoirs that [it is] connecting.” Ismagilov 091, 14:38-40. The manifold outlet is similarly described as connecting channels and a well. Ismagilov 091, 17:27-30. As Ismagilov 091 describes, “devices according to the invention may have a plurality of analysis units that can collect the solution from associated branch channels of each unit into a manifold, which *routes the flow of solution to an outlet.*” *Id.*, 17:24-27. Thus, as described for limitation 1.1, the droplets of Ismagilov 091 form in channels, and the fluids from those channels flow through the substrate to the outlet and into the well or reservoir, which makes the “outlet” of Ismagilov the claimed droplet receiving chamber *inlet* for the well or reservoir (separation chamber).

134. Ismagilov 091 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 Ismagilov 091 has an opening at the top. Ismagilov 091 also confirms there is an opening in the manifold outlet well by describing the ability to collect the fluids by micropipette. Ismagilov 091, 17:27-30. The description of collecting droplets itself for the outlet port confirms that there is a way to remove the droplets from the well or reservoir. If the outlet “collects” droplets, they are collected there for some purpose for the user, such as for downstream applications. Thus, a user could access those collected droplets and it was known that can be done through an opening in a well. Because there would be

no purpose in collecting droplets without being able to access them, and there must be an opening or other outlet. Under Bio-Rad's interpretation, Ismagilov's disclosed well or reservoir with an opening into which a pipette can be inserted meets this limitation.

b. Ground 3a

135. **3a:** To the extent Bio-Rad may argue that Ismagilov 119 (together with the incorporated by reference Ismagilov 091) does not anticipate this limitation, then it is my opinion that the combined Ismagilov 119 references still render this limitation obvious to a person of ordinary skill in the art under 10X's proposed claim constructions requiring a separation chamber (a space that is substantially enclosed) and a droplet receiving outlet (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 10X's means plus function construction).

136. For example, Ismagilov 119 discloses that "the plugs can be sorted by their *density* relative to that of the carrier fluid." Ismagilov 119, ¶ 123. This means that, based on the difference in densities between the droplets and the carrier fluid, the droplets are substantially separated from the carrier fluid. Ismagilov 119, ¶ 123. 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. Ismagilov 119, ¶ 123. This is different and

distinct from, for example, the next example in Ismagilov 119 that describes two different groups of plugs that are separated from each other based on the differential property of magnetism. Ismagilov 119, ¶ 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.”). The paragraph 123 disclosure also contrasts with the previous Ismagilov example in which the droplets are described as having a range of sizes, and droplet size is used to separate the droplets from each other. Ismagilov 119, ¶ 123 (“For example, the plugs can also be sorted according to their sizes.”). Thus, this paragraph 123 disclosure from Ismagilov 119 teaches sorting droplets apart from the immiscible fluid (that is, creating a separated fraction of substantially only droplets).

137. This teaching from Ismagilov 119, together with the other teachings of Ismagilov 091 and the knowledge of a person of ordinary skill in the art, would render this limitation obvious to a person of ordinary skill in the art. A person of ordinary skill in the art would already be familiar with the features of a system to sort droplets based on different density between the droplets and the continuous phase—such systems and techniques were already well-known.

138. As described in section VI, the state of the art section above, droplets either float to the top of the immiscible continuous phase (“cream”) or sink to the bottom of the immiscible continuous phase (“sediment”) depending on whether the

droplets have lower density (float) or higher density (sink) than the immiscible continuous phase fluid. This “creaming” or “sedimenting” of droplets would naturally happen whenever droplets were placed in a large enough vessel such that the droplets and the continuous phase liquid could move freely past each other (and provided that the droplets and immiscible fluid had different densities, as Ismagilov expressly teaches, for example in the case of a fluorinated oil continuous phase and aqueous droplets).

139. The paragraph 123 teaching from Ismagilov 119 described a density difference between the carrier fluid and the droplets. Ismagilov 091, incorporated by reference in Ismagilov 119, similarly teaches the use of droplets and immiscible fluids with different densities as described in the section above regarding the state of the art. Based on well-known density measurements, a person of ordinary skill in the art would have known that water-based aqueous solution droplets would float when suspended in a continuous phase of (denser) fluorinated oil. Even without consulting such well-known, readily available density measurements, a person of ordinary skill in the art could have simply observed the droplets in the oil and noticed the aqueous droplets floating to the surface of the heavier (more dense) oil.

140. Following the teachings of paragraph 123 of Ismagilov 119 that “the plugs [or droplets] can be sorted by their density relative to that of the carrier fluid”, a person of ordinary skill in the art would know that all that would be required to

perform such density-based sorting would be a relatively simple chamber with a sufficiently large volume to collect multiple droplets and allow them to move freely through the continuous oil phase to form a separate fraction enriched for droplets (the “cream” of droplets that would float to the top). This would be well-known to a person of ordinary skill in the art based on experience with all sorts of emulsions (which had been studied for decades prior to the 837 patent). A chamber or reservoir would need to extend vertically for the density sorting to occur—because ultimately it is gravity that causes the (denser) fluorinated oil to sink and the (less dense) droplets to float. As a result, a person of ordinary skill in the art would know that the chamber for sorting should be oriented vertically (up and down) to allow the force of gravity to separate the droplets from the immiscible oil.

141. Following the teachings of paragraph 123 of Ismagilov 119 that “the plugs [or droplets] can be sorted by their density relative to that of the carrier fluid”, a person of ordinary skill in the art would also be familiar that once the droplets floated to the top of the oil, that top fraction of the chamber (the fraction containing substantially only droplets that floated to the top of the oil) could be collected or transferred for further use by placing an outlet 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 while the heavier fluorinated oil would remain behind in the separation chamber. The person

of ordinary skill in the art would also in the process make the space of the chamber enclosed except for the inlet and outlet to allow the droplets to be extracted from the top of the chamber. An enclosed chamber first permits the collection of droplets that float. As the droplets rise, the top of the enclosed container will collect them and allow them to pass through the chamber outlet. An enclosed container also keeps the system pressurized. An open container would not be pressurized, and so the liquids would not flow to the next structure in the microfluidic chip.

142. This process of following the paragraph 123 teachings of Ismagilov 119 (together with the teachings of Ismagilov 091) to create a sufficiently large, substantially enclosed chamber with an inlet to allow fluorinated oil to carry aqueous droplets into the chamber such that the droplets could float to the top of the chamber where they could exit the chamber through a droplet receiving outlet while leaving the heavier oil behind amounts to nothing more than a person of ordinary skill in the art combining known elements (e.g., the channels, chambers or reservoirs, and inlets and outlets taught by Ismagilov and known in the art together with the fluorinated oil and aqueous droplets taught by Ismagilov) according to known methods to yield the predictable results that Ismagilov 119 itself specifies (that is, that the droplets can be sorted or separated from the oil based on their differences in relative densities).

143. Moreover, a person of ordinary skill in the art would have recognized that there were only a finite number of places to place an outlet for such a vertical

separation chamber (e.g., the bottom, the top, or somewhere in the middle). Given the person of ordinary skill in the art's knowledge that the droplets would float (based on either looking up the density properties or simply observing the droplets), and the teachings of Ismagilov 119 that it was desirable to collect substantially only the droplets, it was obvious to try to place the outlet at the top of the chamber where the droplets would float up and be collected. It also would be trivial for a person of ordinary skill in the art to test (and obvious to try) alternate configurations that placed the outlet on the bottom of the chamber or somewhere between the top and bottom of the chamber to readily observe that, because the droplets float to the top of the heavier oil, an outlet placed at the top of the chamber would be most effective for collecting the droplets. The outcomes (i.e., which fluids will exit the chamber and in particular which will float to the top and exit first) are predictable, and a person of ordinary skill in the art experimenting with this configuration would be familiar with the principles of fluids of different densities and have a reasonable expectation of success. *E.g.*, Ismagilov 091, 16:54-57, 17:27-30. This 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).

144. 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). Ismagilov 091, 21:48-54, 14:21-29 (“applying continuous pressure to a fluid within the substrate”). A person of ordinary skill in the art 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.

145. 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) or waste. 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.

146. 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.

147. 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.

148. 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 091 describes. Ismagilov 091, 21:48-54, 14:21-29 (“applying continuous pressure to a fluid within the substrate”). A person of ordinary skill in the art 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. In addition to the chamber and outlet described in detail above, Ismagilov's teachings of a droplet well or reservoir to include teaching an inlet to allow the formed droplets to enter, because if there were not such an inlet, there would be no way for the droplets to enter the well or reservoir and, similarly, no way to sort the droplets based on density as Ismagilov 119 teaches.

149. **3b:** Bio-Rad's interpretation of "droplet receiving outlet" is broad enough to include the opening at the top of an open outlet well and Bio-Rad's interpretation of "separation chamber" is also broad enough to encompass an open well. Ismagilov 119 discloses a density sorter with an outlet at the top of the chamber, which is a separation chamber with a droplet receiving outlet at the top. There is no indication that Bio-Rad's interpretations exclude closed structures, like those shown in Figure 38 of the 837 Patent. Thus, Ismagilov 119 describes this limitation under Bio-Rad's interpretations.

c. Grounds 2

150. While Ismagilov 091 describes this limitation, to the extent that Bio-Rad argues otherwise, Ismagilov 091 in combination with Quake renders this limitation obvious under Bio-Rad's interpretation of the claims. The motivation to

combine the wells in Quake with Ismagilov 091 is described in section XI(**Error! Reference source not found.**).

151. For example, Quake provides additional teachings and details describing and showing wells or reservoirs (also disclosed by Ismagilov) as open structures. Figure 6 (reproduced below) shows large wells with inlets from channels. The round circles in the below figure are wells, and the “T” shape connecting them is made up of channels.

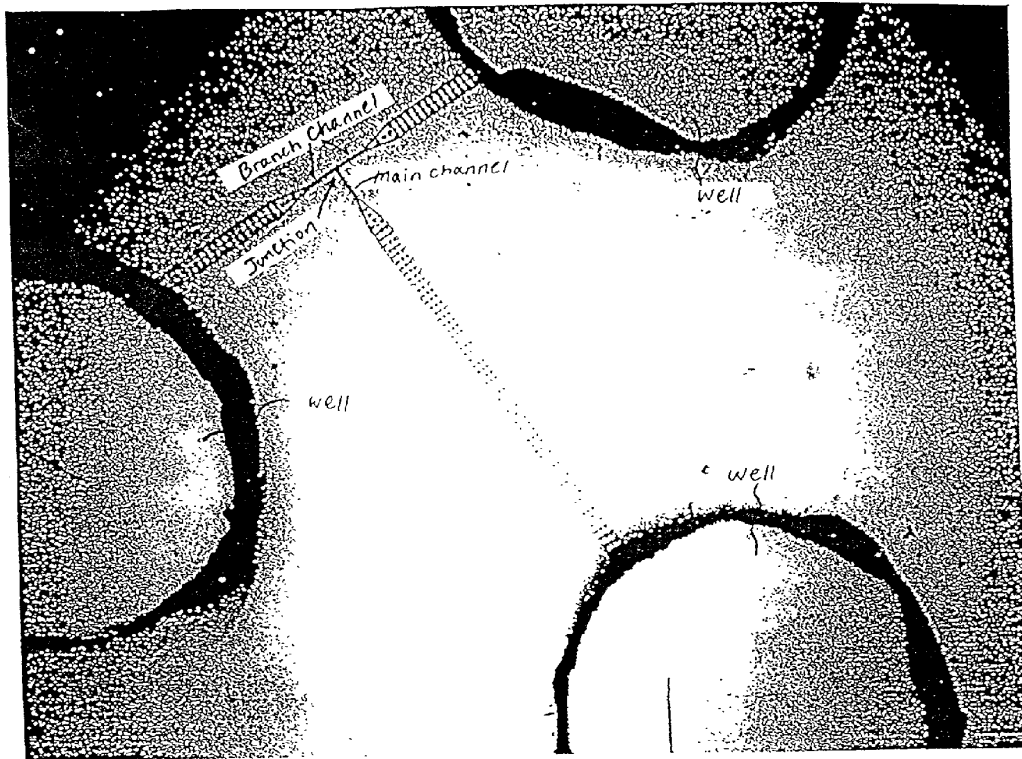


Fig 6

152. Figure 8 (reproduced below) further confirms the wells are open because electrodes are shown inserted into the open wells. Quake also describes both

inserting electrodes and injecting fluids into the wells or reservoirs, and filling the wells or reservoirs with fluid. Quake, ¶¶ 198-200. To be able to do this, the wells or reservoirs would be open. Quake describes that “[t]hree platinum electrodes were each inserted into separate wells.” *Id.*, ¶ 198. Quake also describes that this embodiment was used for sorting, and that “[s]amples of the different colored fluorescent beads, having ratios as indicated below, were injected into the inlet well in 10 to 30 µl aliquots. The collection wells were filled with the same buffer.” *Id.*, ¶ 200. All the wells are shown as the same size in the above two figures (Figures 6 and 8). Thus, the wells of Quake are open.

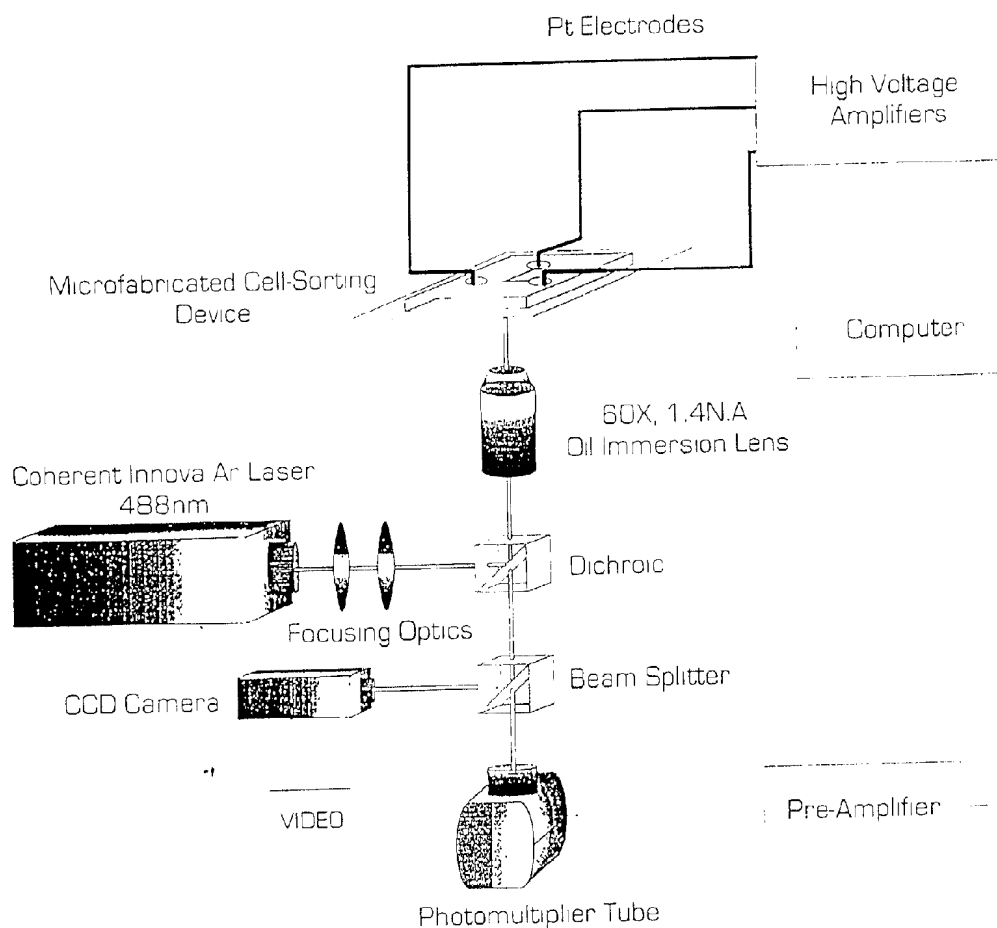


Fig 8

153. Thus, one of ordinary skill would combine the microfluidic configurations, organizations, uses, and chemical compositions from Ismagilov 091 / 119—including placement of wells, reservoirs, or chambers—with the structures disclosed for wells or reservoirs, their inlets and outlets, and channels in Quake. Combining such systems would be well within the grasp of a person of ordinary skill in the art with experience related to systems for handling microfluidic droplets in

which it was desired to collect the sample content from microfluidic channels for subsequent analysis or simply as the output from the system. A person of ordinary skill in the art working with such systems would understand how to combine different microfluidic features, connect microfluidic features, select materials for microfluidic substrates, select fluids, and make many other design and development related choices. There is nothing challenging to a person of ordinary skill in making this combination, which takes a known configuration and modifies parameters of it to be similar to other known organizations. A person of ordinary skill would know how to make such a combined structure with wells. Quake describes that the wells are “incorporated into the elastomer chip.” Quake, ¶ 197. For example, Ismagilov 091 also describes that, after curing, holes may be cut in the PDMS substrate. Ismagilov 091, 16:23-41. Thus, creating wells by cutting holes in a substrate would be one option available to a person of ordinary skill for making wells.

154. In the combination, the well or reservoir would be part of the Ismagilov 091 substrate with the other features described throughout that are disclosed in Ismagilov 091. The fluids used in and compositions of the substrates (e.g., as described in Ismagilov 091 at 16:3-47) would be those of Ismagilov 091. In the combination, the Ismagilov 091 well or reservoir would have the orientation and dimensions of the wells or reservoirs in Quake, and an inlet connected to channels of the dimensions and orientation of those in Quake, through which the droplets of

Ismagilov 091 in the immiscible fluid of Ismagilov 091 would pass. Thus, a droplet receiving chamber inlet was obvious. The structure of the output well of Ground 1 in the combination could have an opening as in Quake, and just as fluids could be added to the Quake well, so too could they be removed through that opening as described by Ismagilov 091, including by micropipette, as Bio-Rad has alleged meets this claim limitation in its infringement contentions. The other portions of this limitation are also rendered obvious by this combination. There is a well (separation chamber) and a droplet receiving chamber inlet through which the droplets enter the well as in Quake.

d. Grounds 4a-5a

155. **4a-5a:** While Ismagilov 119 describes this limitation, to the extent Bio-Rad argues otherwise, Ismagilov 091 119 in combination with Pamula further renders this limitation obvious under 10X's proposed constructions. Additional explanation of why a person of ordinary skill in the art would be motivated to combine the wells in Pamula with Ismagilov is described in section XI(D), the overview of Grounds 4a-5a.

156. While Ismagilov 119 discloses that "the plugs can be sorted by their *density* relative to that of the carrier fluid," Ismagilov 119, ¶ 123, to the extent that it is found that a person of ordinary skill in the art would need additional information regarding that density sorter beyond Ismagilov 119, a person of ordinary skill in the

art 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 IX(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 091:

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]***⁴ ***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***.

Ex. 1018, ¶ 418; Ex. 1007, ¶ 418; Ex. 1025 at 8-9. A person of ordinary skill in the art following Ismagilov's teachings to prepare and collect droplets (as well as

⁴ Pamula 058, the provisional application, refers to a "chip" here while Pamula 238 and Pamula 634 both refer to a "droplet microactuator." In the context of the Pamula references, a person of ordinary skill in the art would understand these to be referring to the same structure.

Ismagilov's teachings at, e.g., Ismagilov 119, ¶ 123 to use density differences between the droplets and the immiscible fluid to do that sorting and collection) would have been motivated to look to Pamula for additional teachings about how to separate those droplets from the immiscible oil for collection based on density. A person of ordinary skill in the art would have been able to apply Pamula's teachings of a density separation chamber with an outlet 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. For example, 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* Ex. 1018, ¶ 385; Ex. 1025, 2 and 12 ("In **some** embodiments, devices of the invention provide a platform technology that avoids continuous-flow microfluidic technologies" and "A segment of liquid can be used to produce a hydraulic force on a filler fluid in a channel."). Alternatively, both Ismagilov and Pamula constrained the movement of droplets. Ismagilov did so with channels. Pamula discloses microactuators with electrodes that form channels for constrained droplets with top and bottom plates. Pamula 634, ¶¶ 378, 380; *see also* Ex. 1018, ¶¶ 378, 380; Ex. 1025, 3, 8, 12, Fig. 5. A person of ordinary skill in the art

understood the similarities between the combined physical and electrical control of droplets in Pamula and the physical, channel-based control in Ismagilov. They were known and recognized alternatives for manipulating aqueous droplets in an oil medium, and one of ordinary skill knew how to apply the teachings known in both methods to the problem of droplet collection and separation from the oil phase. 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 both channel-based and electrowetting approaches).

157. This combination would be a simple substitution of one known element for another (Ismagilov 119 density sorter with Pamula’s vertical structure with an outlet at the top for receiving substantially only droplets floating on the more dense oil) or the application of the known technique in Pamula (a well with an outlet at the top for separating droplets based on density) to the device of Ismagilov 119, which already taught a density sorter and wells and reservoirs. Particularly given the motivation in Ismagilov 119 (e.g., Ismagilov 119, ¶ 123), it would also have been obvious to try what was one of a finite number of identified, predictable solutions (a vertically oriented chamber or a horizontally oriented chamber; an outlet at the top or an outlet at the bottom) with an expectation of success given the known components and properties of the fluids. This was also a combination of known

elements according to known methods of manufacture to yield the predictable result, identified by Ismagilov 119 itself (and confirmed by Pamula), of separating droplets.

158. Thus, a person of ordinary skill in the art 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 like Ismagilov's aqueous droplets in (denser) fluorinated oil (or at the bottom for droplets that sink). It similarly would have been obvious to a person of ordinary skill in the art to place a waste outlet at the opposite end, as taught by Pamula. Ex. 1018, ¶ 418; Pamula 634, ¶ 418; Ex. 1025 at 8-9. Such a waste outlet would permit undesired fluids (such as excess immiscible oil) 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 (not droplets and immiscible oil). This chamber would be enclosed to direct the fluids into the collection or waste containers at the top and bottom of the chamber, as described above and in Ground 2. The chamber of the combination would also necessarily have an inlet to receive droplets, as described in

both Pamula and Ismagilov 119, attached to the channels and droplet generator of the Ismagilov 119 system that generates the droplets.

159. **4b-5b:** Bio-Rad's interpretation of "droplet receiving outlet" is broad enough to include the opening at the top of an open outlet well and Bio-Rad's interpretation of "separation chamber" is also broad enough to encompass an open well. Ismagilov 119 in combination with Pamula discloses a density sorter with an outlet at the top of the chamber, which is a separation chamber with a droplet receiving outlet at the top. There is no indication that Bio-Rad's interpretations exclude closed structures, like those shown in Figure 38 of the 837 Patent. Thus, Bio-Rad's interpretations are also disclosed.

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

a. Ground 1

160. Ismagilov 091 discloses this limitation. The outlet wells or reservoirs of Ismagilov 091 are upright. As I explained for limitation 1.3, wells or reservoirs in Ismagilov 091 "collect" plugs or permit collection by a micropipette. Ismagilov 091, 8:41-44, 9:5-8, 14:36-38, 27:53-58, 28:67-29:5. As I explained for limitation 1.3, Ismagilov 091 describes forming the substrate, closing the channels with a glass coverslip, and placing the glass coverslip down. Based on both of these disclosures, the well or reservoir would extend up and out of the plane of the microchannels. *See* Ismagilov 091, 16:37-41, 30:2-9. When the glass coverslip is placed flat down, the

channels are adjacent to the coverslip. Generally, structures will not extend down through the glass coverslip. Thus, if there is a well, it will be extending upward and out of the plane of the microchannels to permit the collection of multiple droplets and to collect a volume sufficient to be pipetted.

161. The extension of the well or reservoir out of the horizontal plane of the microchannels is further confirmed by the fact that the volume of an outlet well or reservoir in Ismagilov 091 must permit collecting multiple droplets and must be large enough that the fluid can be collected by micropipette. Ismagilov 091, 17:27-30. First, a micropipette can collect down to 0.1 μL . Ex. 1040, Ex. 1041. This is the minimum possible volume to pipette, but in practice larger volumes are typically used. If there is only a small volume or a volume spread across a surface, a micropipette will not be able to collect the liquid because air will enter the micropipette tip instead of liquid. To pipette liquid, the tip of the micropipette must be completely inserted into the liquid volume. There must therefore be a sufficiently deep and wide well for the pipette to enter and then collect the liquid. Thus, the well will need to be larger than the 0.1 μL minimum volume that a micropipette can collect. By contrast, examples of droplets in Ismagilov 091 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 091, 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. Second, a well for collecting droplets would similarly need to extend vertically out of the plane of the microchannels. Ismagilov 091, 8:41-44, 9:5-8, 14:36-38. Thus, the outlet well will necessarily be extending upward and out of the plane of the microchannel because it will not extend down through the glass cover slip and it will need to extend upward to the top of the substrate in order to be an open well (as opposed to a closed cavity or chamber). A person of ordinary skill in the art would understand the disclosure of an outlet “well” to refer to an open-topped, bucket-like structure from which the accumulated droplets could be extracted, e.g., by using a micropipette. Thus, a well to “collect[]” droplets would extend vertically out of the plane of the microchannels to serve the purpose of holding multiple droplets in a vertical volume such that they can then be used downstream.

b. Ground 3a

162. Ismagilov 119 renders this limitation obvious. To allow the droplets to separate from the immiscible phase, there must be a vertical distance through which they can rise or sink. A person of ordinary skill in the art knows that it is gravity that causes the separation of more dense and less dense fluids, and as I explained in section VI on the state of the art, the effects of density separation—creaming (floating) or sedimentation (sinking)—are observed over a vertical distance over

which the droplets can float or sink. Thus, a person of ordinary skill in the art would either know from Ismagilov 119 or find it obvious to have a density sorter with a vertical dimension. Also, because Ismagilov 119 describes forming the substrate and closing the channels with a glass coverslip, the vertical chamber would be upright and extend out of the plane of the microchannel to accommodate the vertical volume of fluid necessary. *See* Ismagilov 091, 16:37-41, 30:2-9. Generally, structures will not extend down through the glass coverslip, and instead structures will extend upward above the glass slide.

c. Grounds 2

163. While Ismagilov 091 describes this limitation, to the extent that Bio-Rad argues otherwise, Ismagilov 091 in combination with Quake renders this limitation obvious. As I explained for limitation 1.3, Quake 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 for limitation 1.3.

164. Quake shows wells or reservoirs that have a large volume that extends upright and above the height of the channels. In Quake, the “wells are 2 mm in diameter” and can hold at least 10 to 30 μl of fluid. *Id.*, ¶¶ 196, 200. One microliter (μl) is equal to 1 cubic millimeter, and so the volume of the wells or reservoirs are at least equal to 10 to 30 mm^3 . To determine the height of the wells, which are shown

in Figure 6 in Quake as cylindrical, the formula for the height of a given cylinder can be used: $\text{height} = \text{Volume} / (\pi r^2)$. The radius of the cylinder is half of the diameter. The equation becomes: $\text{height} = 10 \text{ or } 30 \text{ mm}^3 / (\pi (1\text{mm})^2)$. Thus, the height of the cylinder approximating the well would be approximately 3.2 to 9.5 mm. By contrast, the channels in Quake have a depth of only 4 μm . Thus, the well or reservoir in the combination of Quake and Ismagilov 091 extends upward above the plane of the microchannels (and above the glass coverslip). Thus, in the combination with Quake the well would extend vertically above the plane of the microchannels.

165. The manufacture of substrates in Quake also shows that the wells would extend vertically above the plane of the microchannels. As in Ismagilov, Quake describes the manufactures of the microfluidic chip 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, Fig. 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. Quake, ¶¶ 196-98, Fig.8. Quake also describes that an oil immersion lens is used, *id.*, which is an objective on a microscope that has a drop of oil placed on it, and the oil on the objective is brought into contact with the glass coverslip. This again confirms that the glass would be placed down to permit imaging through the oil of the objective contacting the glass. Thus, the well

or reservoir in the combination is upright, above the glass, and out of the plane of the microchannels.

d. Grounds 4a-5a

166. While Ismagilov 119 describes this limitation, to the extent Bio-Rad argues otherwise, Ismagilov 119 in combination with Pamula renders this limitation obvious. Pamula describes the “vertical configuration” of the structure for density separation. Ex. 1018, ¶ 418; Pamula 634, ¶ 418; Ex. 1025 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 release droplets from the microchannel in the horizontal plane) “at an appropriate point.” Ex. 1018, ¶ 418; Pamula 634, ¶ 418; Ex. 1025 at 8-9. A person of ordinary skill in the art would know that the inlet could be placed at the bottom of the chamber because the droplet channels are formed in the plane of the substrate. Because the channels are formed in the plane of the substrate, a vertical structure would typically extend vertically above the substrate. This means that the inlet to the chamber could be at the bottom of the chamber at the level of the microchannels, and the droplets could either stay on the bottom of the chamber or float to the top of the chamber. 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, a person of ordinary skill in the art would appreciate that Pamula teaches multiple configurations of a chamber that are upright and out of the horizontal plane.

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

a. Ground 1

167. Ismagilov 091 discloses this limitation. Ismagilov 091 discloses microfluidic devices with a pressure-driven flow through the substrate from where the fluids enter (inlet) to where they exit (outlet). Ismagilov 091, 21:48-54, 14:21-29. For example, Ismagilov 091 describes that an aspect of the invention includes “a means for applying continuous pressure to a fluid within the substrate.” Ismagilov 091, 14:21-29. The “inlet port” to “receive[] plug-fluids,” and an “outlet port” to “collect[] or dispense[] the plug-fluid.” Ismagilov 091, 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 091, 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. 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. Ismagilov also describes that the inlet port “receives plug-fluids” and the outlet port “collects or dispenses . . . plugs.” Ismagilov 091, 8:41-42, 9:5-7. Thus, the droplets are formed from the fluids from the inlet and those droplets move through the system to the outlet. Thus, Ismagilov 091 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.

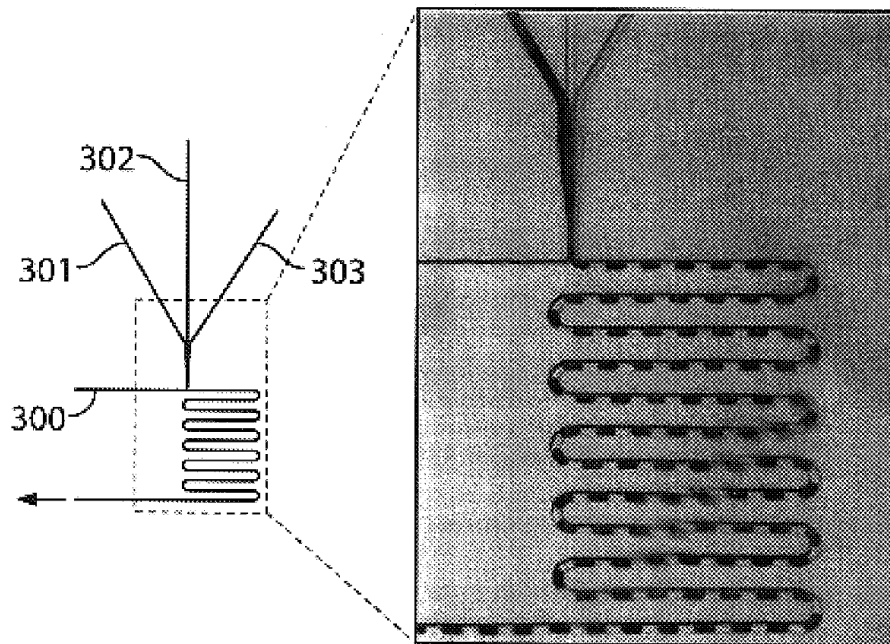


FIG. 3A

b. Grounds 3a-5a

168. Ismagilov 091 in combination with Pamula include structures in which the droplet formation modules described for limitation 1.2 are in communication with separation chamber described for limitation 1.3. For Grounds 3-5, the main structure of the assembly is provided by Ismagilov. Ismagilov 091 describes that the fluids flow through the system under pressure, 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 091 Fig. 3A, provides a fluidic communication for the droplets to pass through to downstream microfluidic features.

c. Grounds 2

169. Ismagilov 091 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 fluids flow through the system under pressure from the inlet to the outlet with the wells, as described in Ground 1.

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

170. Ismagilov 091 discloses this limitation. As described for limitation 1.3, the wells or reservoirs “collect” plugs and permit collection by micropipette.

Ismagilov 091, 8:41-44, 9:5-8, 14:36-38, 17:27-30. Thus, the outlet separation chamber disclosed in Ismagilov 091 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. First, such a structure would not accommodate a micropipette. Pipetting requires pooling droplets in a deep and wide vessel. Second, the terms used to describe the relevant structure were “well” and “reservoir,” not channel, indicating that those structures are different. One way in which a person of ordinary skill would know that they are different is in their dimensions. Third, long, thin structures such as tubing are distinguished in Ismagilov from reservoirs or wells. For example, Ismagilov 091 describes “[a] substrate can be fabricated with a fluid reservoir or well at the inlet port,” and separately describes that the “inlet port may also contain a connector adapted to receive a suitable piece of tubing.” Ismagilov 091, 16:48-59. The well or reservoir was described as different from the tubing. The wells or reservoirs in Ismagilov are therefore wider in cross-section than the microchannels.

b. Grounds 3a-5a

171. Ismagilov 119 renders this limitation obvious. As described for limitations 1.3-1.4, a person of ordinary skill in the art would use a chamber for density separation, whether based on Ismagilov 119 alone or Ismagilov 119 and

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, as was well known in the art.

c. Grounds 2

172. While Ismagilov 119 describes this limitation, to the extent Bio-Rad argues otherwise, Ismagilov 119 discloses or renders obvious this limitation, to the extent that it is found not to be disclosed or rendered obvious, 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 091 and Quake renders this limitation obvious because the output wells of the combination have a wider cross-section (2 mm) than the channels (3-100 μm). The volume of the wells can accumulate a plurality of droplets.

- 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. Grounds 1

173. This limitation is disclosed by Ismagilov 091 under Bio-Rad’s interpretation. As described for limitation 1.6, 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. *E.g.*, Ismagilov 091, Figs. 2-10. Those droplets have a density that is different from the density of the immiscible fluid. 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.

174. 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 091 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 is pooled in the outlet well or reservoir. *See* section VI, State of the Art.

b. Grounds 3a-5a

175. This limitation is rendered obvious by the references identified for each ground. First, Ismagilov 091, or if Bio-Rad disagrees, Ismagilov 091 and Pamula describe separating droplets based on density, and so the volume would be sufficient

to separate the droplets based on density. Because multiple droplets are collected (*see* discussion of limitation 1.6), the chamber under each ground has both a plurality of droplets and a volume of immiscible fluid that separates the droplets. *E.g.*, Ismagilov 091, Figs. 2-10. Thus, the volume will be sufficient to separate droplets from immiscible fluid because this will occur whenever the droplets have a density different from that of the immiscible fluid, as described in section VI, State of the Art.

c. Grounds 2

176. Ismagilov 091 in combination with Quake renders this limitation obvious under Bio-Rad's interpretation. As described for limitation 1.6, 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 091, 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 given that the droplets have a different density from the density of the immiscible fluid. Thus, if Bio-Rad argues this is not explicit, a person of ordinary skill in the art would at least know that the separation will necessarily occur when the droplets are pooled.

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.” (Grounds 1-5a)

177. Claim 2 of the 837 Patent depends from claim 1, and the references describe the limitations of claim 1 as set forth above.

178. Ismagilov 091 / 119 discloses the additional limitation of this dependent claim. As explained for limitation 1.2 and in section VI, Ismagilov 091 / 119 discloses aqueous droplets and segmenting by immiscible fluid at the junction.

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.” (Grounds 3a-5a)

179. Claim 3 of the 837 Patent depends from claim 1, and the references describe the limitations of claim 1 as set forth above.. Claim 3 is only challenged under Grounds 3a-5a.

180. Ismagilov 091 in combination with Pamula renders the additional limitation of this dependent claim obvious for the reasons stated for limitation 1.3. In particular, 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. Such a structure would operate with oils, such as mineral oil, that are less dense than water such that the droplets float. *See* section VI.

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.” (Grounds 1-5a)

181. Claim 4 of the 837 Patent depends from claim 1, and the references describe the limitations of claim 1 as set forth above.

182. Ismagilov 091 / 119 describes the additional limitation of this dependent claim. The droplet receiving outlet is disclosed or obvious on the upper portion of the separation chamber, as described in Claim 1. (Where I refer to Ismagilov 091 / 119, I am referring to Ismagilov 091 for purposes of Grounds 1-2 as well as Ismagilov 119 for purposes of Grounds 3-5).

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

183. Claim 7 of the 837 Patent depends from claim 1, and the references describe the limitations of claim 1 as set forth above. Claim 7 is only challenged under Grounds 2-5a.

1. Ground 3a

184. Ismagilov 119 renders obvious the additional limitation of this dependent claim under either construction. Ismagilov 119 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 091, 17:27-30. A sample tube, such as a standard 1.5 ml centrifuge tube, was a well-known laboratory vessel and component of microfluidic system before the earliest possible filing date

of the asserted patents. It was obvious to combine such an outlet that receives a tube with the density sorter disclosed in Ismagilov. *See* Ismagilov 119, ¶ 123. The sorted droplets would have little immiscible fluid between them, and the purpose of generating such a fraction would be to collect it, as was well-known in the art and described in section VI (State of the Art) for early methods of generating monodisperse emulsions. Ismagilov 119 discloses the ways output droplets could be removed from the chip: tubing, sample tube, or micropipette. Ismagilov 091, 17:27-30. This was a limited set of options, and they were all obvious to try, particularly to a person of ordinary skill in the art who had experience working with such systems. Similarly, a person of ordinary skill in the art would already be familiar with removing droplets from a chip using tubing, sample tube, or micropipette, and would know that attempts to do so would succeed. 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.

185. **3b:** Bio-Rad's interpretation of "coupled" is broad enough to encompass transporting by pipette between an alleged outlet/chamber and vessel.

Ismagilov 119 discloses an outlet coupled to a 1.5 ml centrifuge tube. There is no indication that Bio-Rad's interpretations exclude such joined structures. Thus, Ismagilov 119 describes this limitation under Bio-Rad's interpretations.

2. Grounds 2

186. Ismagilov 119 in combination with Quake renders obvious the additional limitation of this dependent claim for the reasons stated for the preceding section. Additionally, Ismagilov 119 also discloses the additional limitation of this dependent claim under Bio-Rad's interpretation. Under the interpretation that the well is the separation chamber (described above under Ground 1), 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 person of ordinary skill in the art or obvious that the droplets collected from a well by pipette would be transferred to another vessel for downstream use. The droplets would not be pooled, collected by pipette, and thrown away. That would defeat the purpose of the pooling and collecting. Removing the droplets by pipette and transporting them to another vessel meets Bio-Rad's interpretation.

3. Grounds 4a-5a

187. Ismagilov 119 in combination with Pamula renders obvious the additional limitation of this dependent claim under 10X's proposed constructions. Pamula specifically describes that the density sorted droplets can be delivered to a collection well. Consistent with Ismagilov 119's disclosure of an outlet that receives a centrifuge tube (Ismagilov 091, 17:27-30), the choice of a vessel to collect droplets to facilitate downstream use of them was a simple substitution well within the grasp of a person of ordinary skill in the art.

188. **4b-4c:** Bio-Rad's interpretation of "coupled" is broad enough to encompass transporting by pipette between an alleged outlet/chamber and vessel. Ismagilov 119 discloses an outlet coupled to a 1.5 ml centrifuge tube. Thus, Ismagilov 119 describes this limitation under Bio-Rad's interpretations.

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

189. Claim 8 of the 837 Patent depends from claim 7, and the references describe the limitations of claim 7 as set forth above.. Claim 8 is only challenged under Grounds 3a-5a.

1. Grounds 3a-5a

190. 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 091, 17:27-30. A person of ordinary skill in the art would understand that an outlet that is “adapted” to receive the centrifuge tube would seal the tube.

G. Claim 9: “The assembly of claim 7, wherein the vessel is a PCR tube or a test tube.” (Grounds 2-5a)

191. Claim 9 of the 837 Patent depends from claim 7, and the references describe the limitations of claim 7 as set forth above. Claim 9 is only challenged under Grounds 2-5a.

192. Ismagilov 091 / 119 discloses the additional limitation of this dependent claim under 10X’s proposed constructions. 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 091, 17:27-30. This discloses the claimed test tube. For grounds under which the output well is the separation chamber, it would be obvious to use a centrifuge tube or PCR tube, including, as the Examiner said, because substituting vessels was obvious.

193. **3b-5b:** Bio-Rad’s interpretation of “coupled” is broad enough to encompass transporting by pipette between an alleged outlet/chamber and vessel. Ismagilov 119 discloses an outlet coupled to a 1.5 ml centrifuge tube. There is no indication that Bio-Rad’s interpretations exclude such joined structures. Thus, Ismagilov 119 describes this limitation under Bio-Rad’s interpretations.

H. Claim 10: “The assembly of claim 1, wherein the droplet receiving outlet receives substantially one or more droplets.” (Grounds 1-5a)

194. Claim 10 of the 837 Patent depends from claim 1, and the references describe the limitations of claim 1 as set forth above.

195. Ismagilov 091 / 119 describes the additional limitation of this dependent claim. While the grounds are different from each other, 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 10X’s construction or that it receives droplets under Bio-Rad’s interpretation, as described for claim 1.

I. 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.”

196. Claim 11 of the 837 Patent depends from claim 1 and includes all of the same limitations, and the references describe the limitations of claim 1 as set forth above.

197. Ismagilov 091 / 119 discloses the additional limitation of this dependent claim. Ismagilov 091 / 119 also discloses a reagent inlet in fluid communication with the droplet formation module junction or the microchannel.

198. First, Ismagilov 091 discloses a reagent inlet in communication with the junction. Ismagilov 091 describes a “reagent” as “a component of a plug-fluid

that undergoes or participates (e.g, by influencing the rate of a reaction or position of equilibrium) in at least one type of reaction with one or more components of other plug-fluids or a reagent-containing carrier-fluid in the substrate to produce one or more reaction products or intermediates which may undergo a further reaction or series of reactions.” See Ismagilov 091, 10:60-11:7. Figure 4 (below) discloses “**reagents** or solvents comprising the plug-fluids.” Ismagilov 091, 18:49-58. Figure 4 shows five separate plug-fluids in communication with the junction at an inlet, any one or more of which could be reagents. Thus, one or more of the inlets in communication with the junction at which droplets are formed is a reagent inlet.

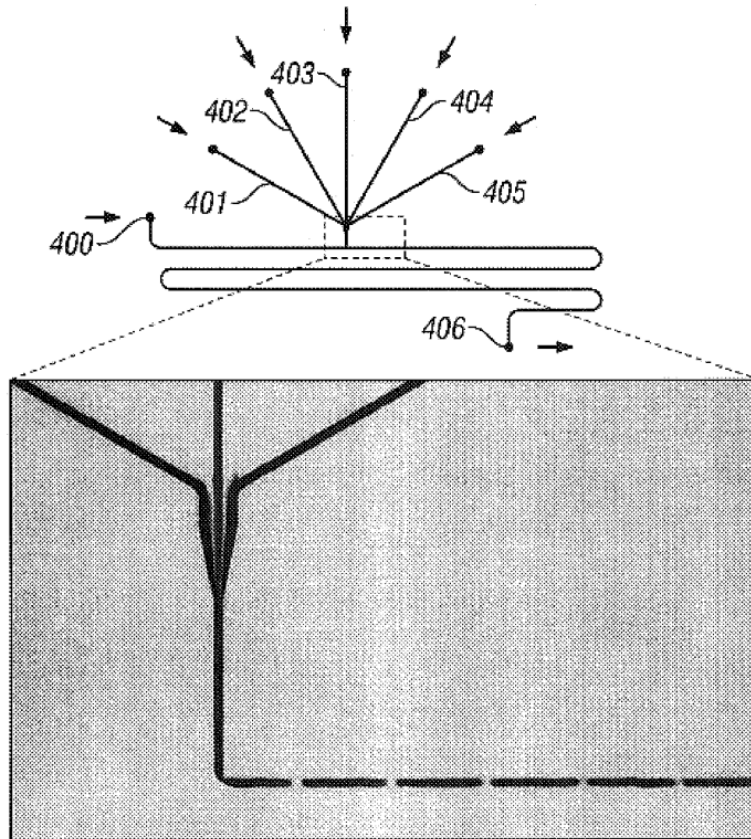


FIG. 4

199. Ismagilov 091 / 119 similarly describes Figure 5 (below) as a microfluidic network “in which several *reagents* can be introduced into the multiple inlets.” Ismagilov 091, 19:5-18. Ismagilov 091 explains that “the reagents A, B, C, and D are introduced into inlet ports 501, 503, 505, and 507, while aqueous streams are introduced into inlet ports 502, 504, 506.” Ismagilov 091, 19:5-18.

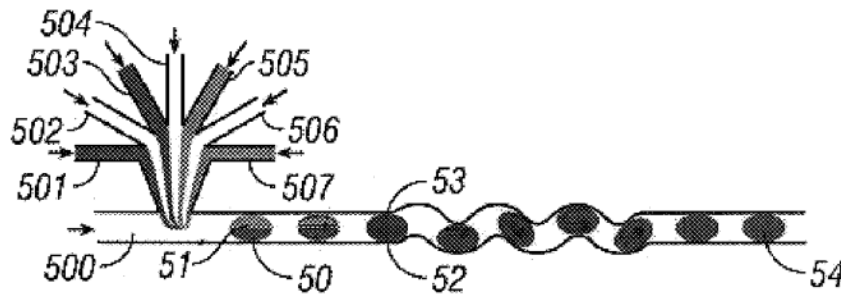


FIG. 5

200. Second, Ismagilov 091 / 119 discloses a reagent inlet in communication with the microchannel. Ismagilov 091 / 119 discloses plugs merged with a “(1) a stream of *reagent*” or “(2) a stream of *reagent plugs*.” Ismagilov 119, ¶¶ 48, 52; Ismagilov 091, 3:14-33 (“The device of the present invention can be used to merge one or more plug fluids. The plug-fluids are introduced either through a single inlet or from multiple inlets....”). Ismagilov discloses devices having “two or more plug-forming regions” with the “first inlet port in communication with the first channel at a first plug-forming region” and “a second inlet port in communication with the first channel at a second plug-forming region.” Ismagilov 091, 15:10-23. A person of ordinary skill in the art would use such a second inlet port to add reagent to the device. Reagent can also be added to the plugs from “a delivery channel in fluid connection with the microchannel.” Ismagilov 119, ¶ 52. The droplets that are formed and merge contain reagents that will be introduced into the merged plugs. Ismagilov 091, 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 (“The reaction can be initiated by forming plugs from each plug-fluid and subsequently merging these different plugs.”). 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 091, 6:48-51, 66:32-42 (introducing “an ester through channel 3701, and an esterase through channel 3703” to cause a “reaction between ester and esterase yield[ing] plugs 3704 that contain a small amount of acid”). 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.

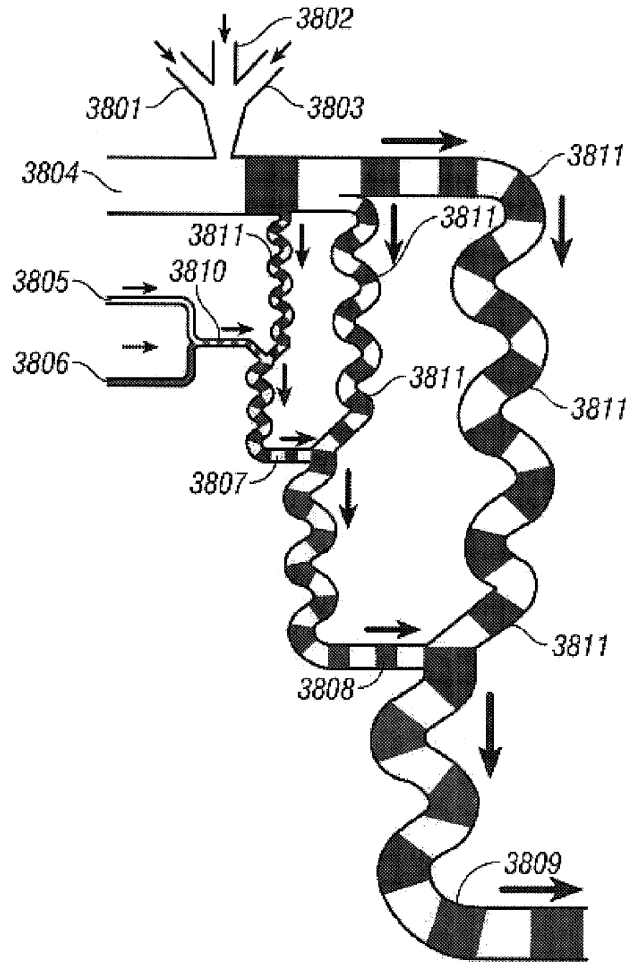


FIG. 38

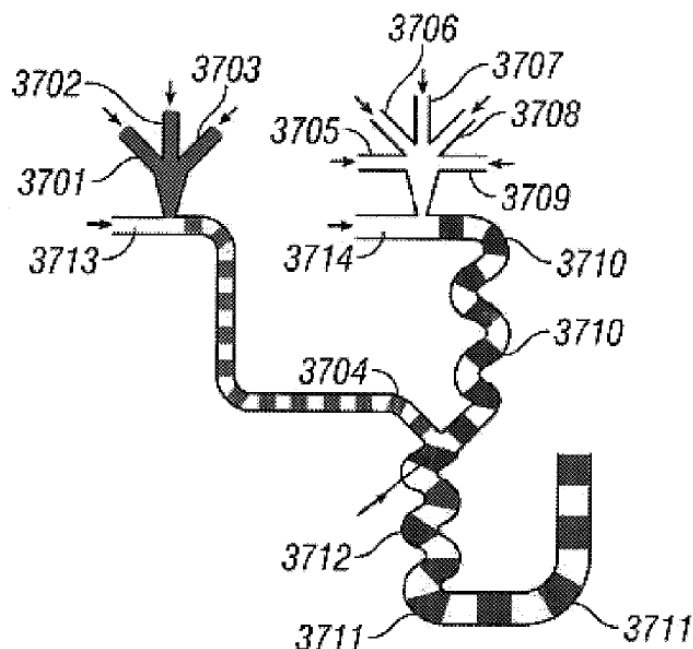


FIG. 37

J. Claim 12: “The assembly of claim 11, wherein the reagent inlet introduces one or more amplification reagents to the junction or the microchannel.” (Grounds 1-5a)

201. Claim 12 of the 837 Patent depends from claim 11, and the references describe the limitations of claim 11 as set forth above.

202. Ismagilov 091 / 119 describes the additional limitation of this dependent claim. Ismagilov 091 / 119 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 091, 45:57-46:5; *see also id.*, 47:22-34.

203. 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 091 / 119 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 091, 47:10-11, 47:59-61. Carrying out autocatalytic reactions like PCR in the invention would involve including the amplification reagents in the disclosed reagent inlets. Thus, Ismagilov 091 / 119 teaches that amplification reagents, including those for PCR, could be introduced through the reagent inlets identified for claim 11.

K. Claim 13: “The assembly of claim 12, wherein the one or more amplification reagents are for a polymerase chain reaction.”(Grounds. 1-5a)

204. Claim 13 of the 837 Patent depends from claim 12, and the references describe the limitations of claim 1 as set forth above. Ismagilov 091 / 119 describes the additional limitation of this dependent claim. As described for claim 12, Ismagilov 091 / 119 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 claim 12, the additional limitation of Claim 13 is described.

205. **3b-5b:** Bio-Rad’s interpretation of “polymerase chain reaction” is broad enough to include any amplification reaction. Ismagilov 119 discloses a PCR,

which is an amplification reaction. Thus, Ismagilov 119 describes this limitation under Bio-Rad's interpretations.

L. 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.”

206. Claim 19 of the 837 Patent depends from claim 1, and the references describe the limitations of claim 1 as set forth above.

1. Ground 1

207. Ismagilov 091 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 091 discloses both detectors and sorting droplets. Ismagilov 091, 15:41-45, 15:46-52, 21:55-59, 31:54-61, 31:20-33:18. For example, Ismagilov 091 describes that “[t]he detector can be any device or method for evaluating a physical characteristic of a fluid as it passes through the detection region. . . .” Ismagilov 091, 31:20-22. Ismagilov also describes that “chemicals present in a plug at a detection region may be sorted into an appropriate branch channel according to a signal produced by the corresponding examination at a detection region.” Ismagilov 091, 32:50-54. Thus, Ismagilov discloses both that there is a detector, and that the information from the detector is used to sort the droplets into a particular channel. 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 091, 9:5-8, 14:36-38.

2. Ground 3a-5a

208. 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. For example, Ismagilov describes that “chemicals present in a plug at a detection region may be sorted into an appropriate branch channel according to a signal produced by the corresponding examination at a detection region.” Ismagilov 091, 32:50-54. It would be obvious to a person of ordinary skill in the art that droplets containing a chemical that produces a signal that is detected at the detector could be sorted into a channel that leads to a density sorter to collect those droplets. As explained for claim 7, a person of ordinary skill in the art would understand that density sorting is advantageous before collection, and so other sorting would be performed first.

3. Ground 2

209. 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.

M. Claim 20: “The assembly of claim 19, wherein the sorting module comprises an apparatus to generate an electric force.” (Grounds 1-5a)

210. Claim 20 of the 837 Patent depends from claim 19, and the references describe the limitations of claim 19 as set forth above.

211. Ismagilov 091 / 119 discloses the additional limitation of this dependent claim. 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 091, 28:35, 29:31-36. Ismagilov 091 / 119 also discloses that “electrodes can be fabricated onto a substrate to control the force fields in a micro fabricated device.” Ismagilov 091, 29:36-39. Thus, Ismagilov 091 / 119 discloses that the sorting module includes an apparatus—electrodes—to generate electrical force, which can move the droplets.

**XIII. SECONDARY CONSIDERATIONS DO NOT SUPPORT
PATENTABILITY WITH RESPECT TO THE OBVIOUSNESS
GROUNDS**

212. Before reaching my opinions regarding obviousness laid out above, I also considered whether there were any secondary considerations of nonobviousness. I understand that the following are considered secondary considerations of nonobviousness: commercial success, long-felt but unmet need, failure of others, praise in the industry and unexpectedly superior results.

213. Considering the information I have reviewed, my general knowledge of the field of microfluidic droplets, and publications within that and related fields, I am not aware of any secondary considerations that might support the patentability of the challenged claims of the 837 Patent.

214. Further, from my review of the file history (Ex. 1002) of the 837 Patent, I did not see that the Patent Owner raised any secondary considerations of nonobviousness during prosecution.

215. In my review, I did not identify nor did I see Bio-Rad identify any evidence that the commercial success of any product has a nexus to the asserted claims; any evidence that the alleged invention claimed met a long-felt but unmet need; that others tried and failed; or that there was either industry praise or skepticism. To the contrary, multiple groups had already shown droplet generation and had identified the principle of density separation as beneficial. There is also no

evidence of unexpected results, nor do I expect that there will be any when the 837 Patent focuses on the long-known principle of density separation.

XIV. PROCEEDINGS ARE NOT DUPLICATIVE OR CUMULATIVE OF PROSECUTION

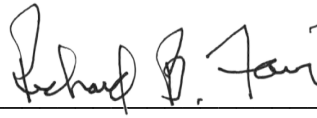
216. The prior art identified in this petition was not addressed by the examiner during prosecution and was not made a basis for a rejection. The prior art identified in this petition is materially different from that considered by the examiner; and is not cumulative of the art actually relied upon during prosecution. For example, during prosecution, the patent owners amended the claims to contain the term “separation chamber” and provide descriptions of its structure, such as having a “volume sufficient to separate.” Ex. 1002, 1165. The patent owner distinguished the art during prosecution because the art contained “merely a junction connecting the fluidic pathways from V6 and channel 66,” not a “separation chamber” with a “volume sufficient to separate.” Ex. 1002, 1168-69. The art cited in this Petition is not duplicative of the art used by the Examiner during the prosecution of the 837 patent because the references in this Petition disclose one or more of the above features that Bio-Rad relied on for an allowance. For example, as discussed above, Ismagilov discloses the “separation chamber” including that it have a “volume sufficient to separate.”

XV. CONCLUSION

217. It is my opinion, as an expert in the field of microfluidic droplet handling, that the 837 patent claims are unpatentable. All elements recited in claims 1-4, 7-13, and 19-20 are anticipated by the prior art, as discussed in Ground 1 above. Further, a person of ordinary skill in the art would have been motivated to combine the art cited in Grounds 2-8 above to arrive at claims 1-4, 7-13, and 19-20 of the 837 patent with a reasonable expectation of success. Also, I have considered potential secondary considerations relating to the 837 patent claims, but I do not believe that there are any secondary considerations that weigh against the obviousness of any claims.

218. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Richard B. Fair", is written above a horizontal line.

Richard B. Fair

Dated: October 25, 2019

Attachment A

RESUME
Richard B. Fair
3414 CAMBRIDGE RD.
DURHAM, NORTH CAROLINA 27707

EDUCATION AND HONORS

BSEE - Duke University, Durham, N.C., 1964, Presbyterian Church Scholarship, 1961.
MSEE - Penn State University, University Park, Pa., 1966, Sylvania Fellow, 9-64/6-66.
Ph.D. - Duke University, Durham, N.C., 1969, NDEA Fellow, 9-66/6-69.

Awards

- (1) Outstanding Paper Award - IEEE Spring Symp., Duke University, 1969.
- (2) "Outstanding Young Men of America" Award, 1973.
- (3) "Outstanding Young Electrical Engineer of the Year" Award, 1974 -National Award from Eta Kappa Nu.
- (4) American Men and Women in Science, 1979 - Present
- (5) Who's Who in Technology Today, 1980, 81.
- (6) Adjunct Professor, Dept. of Electrical Eng., Duke University, 1980-81.
- (7) Who's Who in Frontiers of Science and Technology, 1985, 1986
- (8) Who's Who in the Semiconductor Industry, 1986.
- (9) Fellow Award, IEEE, 1990
- (10) Who's Who in Engineering, 1991, 1993
- [11] Who's Who in America, 1991, 1993
- (12) Fellow Award, Electrochemical Society, 1994
- (13) Professor James F. Gibbons Achievement Award, 4th International Conference on Advanced Thermal Processing, 1996
- (14) Third Millennium Medal, IEEE, 2000
- (15) Solid State Science and Technology Award – The Electrochemical Society, 2003

MEMBERSHIPS / PROFESSIONAL ACTIVITIES

- (1) Member, Sigma Xi
- (2) Fellow, Electrochemical Society
 - a. Session Chairman numerous times, 1975-present
 - b. Symposium Chairman - "Diffusion Processes in Semiconducting Materials," St. Louis, 1980
 - c. Member of Electronics Division Executive Committee, 1987 -
 - d. Organizing Committee - 6th International Symposium on ULSI Science and Technology
 - e. Organizing Committee - 1st Inter. Conf. On ULSI Process Integration - 1999.

- f. Organizing Committee - Joint Electronics/Dielectric General Session - 1997-
- g. Co-chair, Sixth International Symposium on ULSI Science and Technology, Montreal (1997)

(3) Life Fellow- IEEE

- a. Session Chairman at 1977-78 International Electron Device Meetings (IEDM)
- b. Chairman, Solid State Device Committee for 1978 IEDM
- c. Member, Integrated Circuit Technology Subcommittee for 1982 IEDM
- d. Member of Editorial Board - Proceedings of the IEEE - 1988-
- e. Editor, Proceedings of IEEE - 1993- 2001
- f. Associate Editor - Trans. Electron Devices - 1990-1993
- g. Guest Editor, Special Issue on NSF Engineering Research Centers, Proceedings of IEEE, Jan. 1993.
- h. Member, IEEE Publications Board - 1993-

(4) Electronic Materials Committee of AIME - 1985 - 1989

(5) Materials Research Society

- a. Symposium Co-Chairman - "Impurity Diffusion and Gettering in Silicon" - 1984
- b. Member of Editorial Board - Bulletin of Materials Research Society - 1985-1987

(6) Co-chair, 1st International Rapid Thermal Processing Conference, Phoenix (1993).

(7) Co-chair, 2nd International Rapid Thermal Processing Conference, Monterey (1994).

[8] Co-chair, 3rd International Rapid Thermal Processing Conference, Amsterdam (1995).

(9) Co-chair, 4th International Rapid Thermal Processing Conference, Boise (1996).

(10) Co-chair, 5th International Rapid Thermal Processing Conference, New Orleans (1997).

(11) Co-Chair, Fourth International Workshop on Meas., Characterization, and Modeling of Ultra- shallow Doping Profiles in Semiconductors, Research Triangle Park, (1999).

(12) Member of Editorial Advisory Board, Journal Microfluidics and Nanofluidics, (2008-

International Activities

(1) Instructor, CEI Europe - 1985 - present

(2) Member, International Advisory Panel, Microelectronics Systems '91 Conference, Kuala Lumpur, Malaysia

(3) Member, International Advisory Committee, Annual Semiconductor Conference '92-99, Bucharest, Romania

(4) Member, International Advisory Committee, 1993 Symposium on Semiconductor Modeling and Simulation, Taipei, Taiwan

(5) Member, Program Committee, Inter. Symposium on Advanced Microelectronic Devices and Processing - 1993, Sendai, Japan

Employment Experience

Present- - Lord-Chandran Professor of Engineering, Pratt School of Engineering

1993-1994 - Director, Microfabrication Technology and the associated Research Institute of MCNC; Professor, Electrical Engineering, Duke University

1990-1993 - Vice President, MCNC and Executive Director, Center for Microelectronic Systems Technologies; Professor, Electrical Engineering, Duke University

1986-1990 - Vice President, Design Research and Technology, MCNC; Professor, Electrical Engineering, Duke University

10/88-3/89 - Acting President, MCNC; Professor, Electrical Engineering, Duke University

1981-1985 - Vice President, Research Program Management, MCNC; Professor, Electrical Engineering, Duke University

1973-1981 - Supervisor, Bell Laboratories, Reading, PA.

1969-1973 - Member of Technical Staff, Bell Laboratories, Reading, PA.

Board Memberships

1992-1994 - Advanced Technology Applications, Inc.

1993- Microelectronic Technology Corp.

1995- 2014 -Engineering Advisory for the Aurora Fund.

1996- 2010 - Technical Advisory Board, Thunderbird Technologies, Inc.

2003- 2012 - Technical Advisory Board, R.J. Mears, Inc.

2004-2013– Chairman, Scientific Advisory Board, Advanced Liquid Logic

Courses Taught

EE218 (Integrated Circuit Engineering) Spring Semester 1982-present

EE163 (Introduction to Integrated Circuits) Fall/Spring Semester, 1995-99

EE62 (Introduction to Semiconductor Devices), Spring Semester, 1999-present

ECE299 (Biochip Engineering), Fall Semester, 2005-2007

U.S Patents

(1) U.S. Patent 4,033,027 - Dividing Metal Plated Semiconductor Wafers -
July 5, 1977

- (2) U.S. Patent 6,911,132 – Apparatus for Manipulating Droplets by Electrowetting-based Techniques – June 28, 2005
- (3) U.S. Patent 6,989,234 – Method and Apparatus for Non-Contact Electrostatic Actuation of Droplets – January 24, 2006
- (4) U.S. Patent 7,329,545 – Methods for Sampling a Liquid Flow – February 12, 2008
- (5) U.S. Patent 7,439,014 – Droplet-based Surface Modification and Washing – October 21, 2008
- (6) U.S. Patent 7,569,129 – Methods for manipulating droplets by electrowetting-based techniques – August 4, 2009
- (7) U.S. Patent 7,727,723 – Droplet-based pyrosequencing – June 1, 2010.
- (8) U.S. Patent 7,759,132 – Methods for performing microfluidic sampling – July 20, 2010.
- (9) U.S. Patent 8,048,628 – Methods for nucleic acid amplification on a printed circuit board – Nov. 1, 2011
- (10) U.S. Patent 8,147,668 – Apparatus for manipulating droplets – April 3, 2012.
- (11) U.S. Patent 8,221,605 – Apparatus for manipulating droplets – July 17, 2012.
- (12) U.S. Patent 8,287,711 – Apparatus for manipulating droplets – October 16, 2012.
- (13) U.S. Patent 8,313,895 – Droplet-based surface modification and washing – Nov. 20, 2012
- (14) U.S. Patent 8,349,276 – Apparatus and methods for manipulating droplets on a printed circuit board – Jan. 8, 2013.
- (15) U.S. Patent 8,388,909 – Apparatus and methods for manipulating droplets – Mar.5, 2013.
- (16) U.S. Patent 8,389,297 – Droplet-based affinity assay device and system – Mar.5, 2013.
- (17) U.S. Patent 8,394,249 – Methods for manipulating droplets by electrowetting-based techniques – Mar.12, 2013.
- (18) U.S. Patent 8,613,889 – Droplet-based washing – December 24, 2013.
- (19) U.S. Patent 8,541,176 – Droplet-based surface modification and washing – September 24, 2013.
- (20) U.S. Patent 8,524,506 – Methods for sampling a liquid flow – September 3, 2013.
- (21) U.S. Patent 8,492,168 – Droplet-based affinity assays – July 23, 2013.
- (22) U.S. Patent 8,470,606 – Manipulation of beads in droplets and methods for splitting droplets – June 25, 2013.
- (23) U.S. Patent 8,685, 754 – Droplet actuator devices and methods for immunoassays and washing – April 1, 2014.
- (24) U.S. Patent 8,846,414 – Detection of cardiac markers on a droplet actuator – Sept. 30, 2014.
- (25) US Patent 8,871,071, “Droplet manipulation device”, Oct. 28, 2014.
- (26) US Patent 8,906,627, “Apparatuses and methods for manipulating droplets”, Dec. 9, 2014.
- (27) US Patent 8,951,721, “Droplet-based surface modification and washing,” Feb. 10, 2015
- (28) US Patent 8,980,198, “Filler fluids for droplet operations,” Mar. 17, 2015
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- (31) US Patent 9,180,450 “Droplet manipulation system and method,” Nov. 10, 2015.
- (32) US Patent 9,243,282, “Droplet-based pyrosequencing,” Jan. 26, 2016.
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- (35) US Patent 9,638,662, “Apparatuses and methods for manipulating droplets,” May 2, 2017.
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- 2 [20160114320 Droplet Manipulation Device](#)
- 3 [20160108433 SYSTEMS, APPARATUS, AND METHODS FOR DROPLET-BASED MICROFLUIDICS CELL PORATION](#)
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- 5 [20150174577 Filler Fluids for Droplet Operations](#)
- 6 [20150148238 DROPLET-BASED SURFACE MODIFICATION AND WASHING](#)
- 7 [20150060284 Apparatuses and Methods for Manipulating Droplets](#)

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- (11) R. B. Fair, "Optimum Low-Level Injection Efficiency of Silicon Transistors with Shallow Arsenic Emitters," IEEE Trans. Electron Devices, Vol. ED-20, 642 (1973).
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OTHER TALKS AND LECTURES

- (1) "A Machine-Scan Electron Beam Device," 8th Annual Electron and Laser Beam Symposium," University of Michigan, Ann Arbor (1966).
- (2) "High Concentration Arsenic Diffusion in Silicon from Doped Oxide Sources," Electrochemical Society Meeting, Houston (1972).
- (3) "Quantitative Theory of Retarded Base Diffusion in Silicon NPN Structures with Arsenic Emitters," Inter. Electron Device Meeting of IEEE, Washington, DC (1972).
- (4) "Diffusion of Ion-Implanted Boron in High Concentration P, As and Sb-doped Silicon," Electrochemical Society Meeting, Toronto (1975).
- (5) "The Diffusion of Ion-Implanted Arsenic in Silicon," Electrochemical Society Meeting, Dallas (1975).
- (6) "Zener and Avalanche Breakdown in As-Implanted Low Voltage Si N-P Junctions," Inter. Electron Device Meeting of IEEE, Washington, DC (1975).
- (7) "Quantitative Model of Phosphorus Diffusion in Silicon," Electrochemical Society Meeting, Las Vegas (1976).
- (8) "Quantitative Model of the Emitter-Dip Effect," Electrochemical Society Meeting, Las Vegas (1976).
- (9) "Analysis of Phosphorus Profiles," Electrochemical Society Meeting, Atlanta (1977).
- (10) "The Effect of Strain-Induced Bandgap Narrowing on Phosphorus Diffusion and E-Center Concentrations in Silicon," Inter. Conf. on Defects and Radiation Effects in Semicond., Nice (1978).
- (11) "Theory and Direct Measurement of Boron Segregation in SiO₂ During Dry, Near Dry and Wet O₂ Oxidation," Electrochemical Society Meeting, Pittsburgh (1978).
- (12) "Modeling Laser - Induced Diffusion of Implanted Arsenic in Silicon," Electrochemical Society Meeting, Los Angeles (1979).
- (13) "Influence of Strain on Impurity Diffusion in Silicon," Electrochemical Society Meeting, St. Louis (1980).
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- (16) "Dynamic Behavior of the Build-Up of Fixed Charge and Interface States During Hot Carrier Injection in Encapsulated MOSFET's," Electrochemical Society Meeting, Montreal (1982).
- (17) "Modeling Physical Limitations on Junction Scaling for CMOS," Device Research Conference, Burlington, VT (1983).
- (18) "Modeling Rapid Thermal Annealing Processes for Shallow Junction Formation in Silicon," International Electron Device Meeting, Washington, DC (1983).
- (19) "Computer Simulation of Oxygen Precipitation and Denuded Zone Formation," Electrochemical Society Meeting, Cincinnati, OH (1984).
- (20) "Stress Assisted Diffusion of Boron and Arsenic in Silicon," Materials Research Society Meeting, Boston, November 1984.
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- (34) "Modeling the Oxidation of Heavily Doped Silicon in the Thin Regime," R. Ward, H.Z. Massoud and R.B. Fair, Process Simulation Workshop, MCNC, RTP, Nov. 1989.
- (35) "Comparison of Measured and Simulated Two Dimensional P Profiles in Si," R. Subrahmanyam, H.Z. Massoud and R.B. Fair, Process Simulation Workshop, MCNC, RTP, Nov. 1989.
- (36) "A Strategy for 2D Process Simulation," R.B. Fair, Process Simulation Workshop, MCNC, RTP, Nov. 1989.
- (37) "Shallow-Junctions-Modeling the Dominance of Point Defect Charge States During Transient Diffusion," IEDM, Wash., D.C., Dec. 1989.
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- (40) "Modeling The Enhanced Diffusion of Implanted Boron in Silicon," Y. Kim, T.Y. Tan, H.Z. Massoud and R.B. Fair, Electrochem. Soc. Mtg., Montreal, May 1990.

- (41) "The Thermal Oxidation of Heavily Doped Silicon in the Thin-Film Regime: Dopant Behavior and Modeling Growth Kinetics," R.R. Ward, H.Z. Massoud and R.B. Fair, Electrochem. Soc. Mtg., Montreal, May 1990.
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- (43) "The Role of End-of-Range Dislocation Loops as a Diffusion Barrier," Y. Kim, H.Z. Massoud, S. Chevacharoeukul and R.B. Fair, Electrochem. Soc. Mtg., Montreal, May 1990.
- (44) "Technology Transfer Utilizing the Proof-of-Concept Facility," R.B. Fair and J.F. Freedman, Adv. Semicond. Manuf. Conf. & Workshop, Boston, October 1991.
- (45) "Spinoff Strategy for University-Based Applications Effort in Microsystems," Engineering Foundation Conference on Commercialization of Microsystems, Banff, Canada, Sept. 1994.
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Attachment B

List of Materials Considered

Ex/ Doc.	Description
1001	U.S. Patent No. 9,562,837
1002	U.S. Patent No. 9,562,837 Prosecution History
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")
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")
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

Ex/ Doc.	Description
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’s 837 Patent Infringement Contentions, 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.)
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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.)]
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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.)]
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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--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

Ex/ Doc.	Description
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]