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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

10X GENOMICS, INC.

Petitioner,

v.

BIO-RAD LABORATORIES, INC.

Patent Owner.

IPR2018-00302

U.S. Patent No. 9,216,392

PETITION FOR *INTER PARTES* REVIEW

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- 1004 U.S. Published Application 2002/0058332 to Quake et al.
- 1005 U.S. Published Application 2004/0228770 A1 to Gandhi et al.
- 1006 U.S. Patent No. 6,915,679 to Chien et al.
- 1007 U.S. Published Application 2005/0266582 A1 to Modlin et al.
- 1008 U.S. Published Application 2010/0184928 A1 to Kumacheva et al.
- 1009 U.S. Patent No. 6,123,798 to Gandhi et al.
- 1010 U.S. Published Application 2004/0068019 to Higuchi, et al.
- 1011 Anna, et al., *Formation of dispersions using “flow focusing” in microchannels*, Appl. Phys. Lett., 82(3):364-66 (2003)
- 1012 Nisisako and Torii, *Microfluidic large-scale integration on a chip for mass production of monodisperse droplets and particles*, Lab on a Chip, 8:287-93 (2008)
- 1013 U.S. Published Application 2010/0022680 to Karnik, et al.
- 1014 U.S. Published Application 2009/0012187 to Chu, et al.
- 1015 Publication information for Anna, et al., *Formation of dispersions using “flow focusing” in microchannels*, Appl. Phys. Lett., 82(3):364-66 (2003)
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- 1017 U.S. Published Application 2009/0269248 to Falb, et al.

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- 1020 Duffy, et al., *Rapid Prototyping of Microfluidic Systems in Poly(dimethylsiloxane)*, Anal. Chem., 70:4974-84 (1998)
- 1021 U.S. Patent No 6,176,962 to Soane
- 1022 Li and Li, Microfluidic Lab-on-a-Chip (Book Chapter), p. 581-679 (2005)
- 1023 U.S. Published Application 2008/0038810 to Pollack et al.
- 1024 Publication information for Brody, et al. *Biotechnology at Low Reynolds Numbers*, Biophysical Journal, 71:3430-3441 (1996)
- 1025 de Mello and Manz, *Chip technology for micro-separation*, BioMethods 10:129-177 (1999)
- 1026 Brody, et al. *Biotechnology at Low Reynolds Numbers*, Biophysical Journal, 71:3430-3441 (1996)
- 1027 U.S. Published Application No. 2004/0109793 to McNeely, et al.
- 1028 U.S. Provisional Application 60/924,921 to Kumacheva
- 1029 Publication information for Duffy, et al., *Rapid Prototyping of Microfluidic Systems in Poly(dimethylsiloxane)*, Anal. Chem., 70:4974-84 (1998)
- 1030 Publication information for Chien and Parce, *Multiport flow-control system for lab-on-a-chip microfluidic devices*, J. Anal. Chem., 371-106-11 (2001)
- 1031 Galambos, et al., *Precision Alignment Packaging for Microsystems with Multiple Fluid Connections*, Proceedings of 2001 ASME: International Mechanical Engineering Conference and Exposition, November 11-16, 2001. p. 1-8
- 1032 Beer et al., *On-Chip, Real-Time, Single-Copy Polymerase Chain Reaction in Picoliter Droplets*, Anal. Chem. 2007, 79, 8471-8475

- 1033 Publication information for Beer et al., *On-Chip, Real-Time, Single-Copy Polymerase Chain Reaction in Picoliter Droplets*, Anal. Chem. 2007, 79, 8471-8475
- 1034 Whitesides and Strook, Flexible Methods for Microfluidics, Physics Today, June 2001: 42-48
- 1035 Chien and Parce, Multiport flow-control system for lab-on-a-chip microfluidic devices, J. Anal. Chem., 371-106-11 (2001)
- 1036 Publication information for Li and Li, Microfluidic Lab-on-a-Chip (Book Chapter), p. 581-679 (2005)
- 1037 U.S. Published Application 2009/0035770 to Mathies
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- 1039 *Curriculum Vitae* of Dr. Khushroo Gandhi
- 1040 Becker and Gartner, *Polymer microfabrication technologies for microfluidic systems*, Anal. Bioanal. Chem, 390:89-111
- 1041 Publication information for Becker and Gartner, *Polymer microfabrication technologies for microfluidic systems*, Anal. Bioanal. Chem, 390:89-111
- 1042 Complainants' Ground Rule 4 Disclosures, Certain Microfluidic Devices, USITC Inv. No. 337-TA-1068, filed November 17, 2017
- 1043 Kawai, et al., *Mass-Production System of Nearly Monodisperse Diameter Gel Particles Using Droplets formation in a Microchannel*, *Micro Total Analysis Systems*, Micro Total Analysis Systems, 1:368-70 (2002)
- 1044 Declaration of Ruth G. Davila
- 1045 UK Patent Application No. 2097692 to Shaw Stewart
- 1046 U.S. Published Application 2007/0166200 to Zhou, et al.
- 1047 U.S. Published Application 2009/0047713 to Handique
- 1048 Bernouilli Pressure Lowering, <http://hyperphysics> p. 1-4
- 1049 U.S. Published Application 2008/0056948 A1 to Dale and Knight

- 1050 U.S. Patent No. 9,126,160 to Ness et al.
- 1051 Mair, et al., *Injection molded microfluidic chips featuring integrated interconnects, Lab on a Chip*, 6:1346-54 (2006)
- 1052 Publication information for Mair, et al., *Injection molded microfluidic chips featuring integrated interconnects, Lab on a Chip*, 6:1346-54 (2006)

I. INTRODUCTION

Petitioner, 10X Genomics, Inc. (“Petitioner”) respectfully requests *inter partes* review (“IPR”) of claims 1-21 of U.S. Patent No. 9,216,392 (“the ‘392 Patent”, Ex. 1001). For the reasons set forth below, each of the challenged claims is invalid as obvious.

II. MANDATORY NOTICES

A. Real Party-in-Interest

10X Genomics, Inc. is the real party-in-interest.

B. Related Matters

Petitioner is contemporaneously filing two other *inter partes* review petition challenging claims of the ‘392 patent (IPR2018-00300 and IPR2018-00301). The following proceedings would affect or be affected by a decision in this proceeding: *Bio-Rad Laboratories, Inc., et al. v. 10X Genomics, Inc., Case No. 3:17-cv-4339* (N.D. Cal.) and Re: Certain Microfluidic Devices, investigation number 337-TA-1068 (ITC).

C. Designation of Counsel

Lead counsel for Petitioner is Greg H. Gardella (Reg. No. 46,045) of Gardella Grace P.A. Back-up counsel is Dianna DeVore and Sally Brashears of Convergent Law Group.

Lead Counsel	Back-up Counsel
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D. Service Information

Pursuant to 37 C.F.R. § 42.10(b), Powers of Attorney accompany this Petition. Please address all correspondence to lead counsel. Petitioner consents to service of all documents via the following email addresses:

ggardella@gardellagrace.com, ddevore@convergentlaw.com and info@gardellagrace.com.

E. Fees

The undersigned authorizes the PTO to charge the fee set forth in 37 C.F.R. § 42.15(a) for this Petition to Deposit Account No. 601484. Review of claims 1-21 is requested. The undersigned authorizes payment for additional fees that may be due with this petition to be charged to the above-referenced Deposit Account.

III. CERTIFICATION OF GROUNDS FOR STANDING

Petitioner certifies pursuant to Rule 42.104(a) that the patent for which review is sought is available for *inter partes* review and that Petitioner is not barred or estopped from requesting an *inter partes* review challenging the patent claims on the grounds identified in this Petition.

IV. OVERVIEW OF CHALLENGE AND RELIEF REQUESTED

Pursuant to Rules 42.22(a)(1) and 42.104(b)(1)-(2), Petitioner challenges claims 1-21 (“the challenged claims”) of the ’392 Patent and requests each challenged claim be canceled.

A. Grounds for Challenge

This petition, together with the support exhibits including the declaration of Khushroo Gandhi, Ph.D. (“Gandhi Decl.,” Ex. 1003), demonstrates that there is a reasonable likelihood that at least one of the challenged claims is unpatentable for the reasons set forth herein. 35 U.S.C. §314(a).

B. Prior Art Patents and Printed Publications Relied Upon

Petitioner relies upon the following patents and printed publications, the majority of which were before the Examiner during *ex parte* prosecution.

1. U.S. Published Application 2002/0058332 to Quake et al.

U.S. Published Application 2002/0058332 to Quake et al. (“Quake,” Ex. 1004), filed on September 14, 2001, and published on May 16, 2002, is prior art to

the '392 patent under 35 U.S.C. §102(b) because the application was published more than one year before the earliest claimed priority date, September 23, 2008. Quake was one of the four hundred eighty-three (483) references cited during prosecution but was not otherwise mentioned or discussed by the Examiner or the applicants.

2. U.S. Published Application 2004/0228770 to Gandhi et al.

U.S. Published Application 2004/0228770 to Gandhi et al. (“Gandhi,” Ex. 1005), filed on March 3, 2004 and published on November 18, 2004, is prior art to the '392 patent under 35 U.S.C. §102(b) because it was published more than one year before the earliest claimed priority date, September 23, 2008. The lead inventor on the Gandhi reference is Dr. Khushroo Gandhi (hereafter “Dr. Gandhi”), whose declaration is offered in support of this petition. Gandhi was not before the Examiner during prosecution.

3. U.S. Published Application 2008/0166720 to Hsieh et al.

U.S. Published Application 2008/0166720 to Hsieh et al. (“Hsieh,” Ex. 1019), filed on October 5, 2007, and published on July 10, 2008, is prior art to the '392 patent under 35 U.S.C. §102(a) and (e) because it was published and filed, respectively, before the earliest claimed priority date, September 23, 2008. Hsieh was not before the Examiner during prosecution.

4. U.S. Patent 6,176,962 to Soane et al.

U.S. Patent 6,176,962 to Soane et al. (“Soane,” Ex. 1021), issued on January 23, 2001, is prior art to the ’392 patent under 35 U.S.C. §102(b) because it was published more than one year prior to the earliest claimed priority date, September 23, 2008. Soane was not before the Examiner during prosecution.

5. Beer et al., *On-Chip, Real-Time, Single-Copy Polymerase Chain Reaction in Picoliter Droplets*, Anal. Chem. 2007, 79, 8471-8475

Beer et al., *On-Chip, Real-Time, Single-Copy Polymerase Chain Reaction in Picoliter Droplets*, Anal. Chem. 2007, 79, 8471-8475 (“Beer,” Ex. 1032; Ex. 1033), published on July 27, 2001, is prior art to the ’392 patent under 35 U.S.C. §102(b) because it was published more than one year before the earliest claimed priority date, September 23, 2008. Beer’s publication information is submitted herewith as Exhibit 1033.¹ Beer was one of the four hundred eighty-three (483)

¹ Unless otherwise stated, all NPL publication information cited herein is self-authenticating and subject to FRE 803(6), 803(17) and 807. The publication information is also authenticated and shown to be made in the regular course of business (FRE 803(6)) and have circumstantial guarantees of trustworthiness (FRE 807) by the Davila Declaration. (Ex. 1044.)

references cited during *ex parte* prosecution but that publication was not otherwise mentioned or discussed by the Examiner or the applicant.

6. U.S. Published Application 2009/0035770 to Mathies

U.S. Published Application 2009/0035770 to Mathies et al. (“Mathies,” Ex. 1037), filed on October 25, 2007, and published on October Feb. 5, 2009. Mathies is prior art to the ’392 patent under 35 U.S.C. §102(e) because it was filed before the earliest claimed priority date, September 23, 2008. Mathies was one of the four hundred eighty-three (483) references cited during *ex parte* prosecution but that publication was not otherwise mentioned or discussed by the Examiner or the applicant.

C. Relief Requested

Petitioner requests that the Board cancel claims 1-21 on the basis that they are unpatentable under 35 U.S.C. §103.

V. LEVEL OF ORDINARY SKILL IN THE ART AND TECHNICAL BACKGROUND

A person of ordinary skill in the art (POSITA) at the time of the earliest claimed priority date (September 23, 2008) would have had a Ph.D. in chemical engineering, mechanical engineering, biomedical engineering, fluid dynamics, or a related discipline, with two years of work experience in the field of microfluidic devices. (Ex. 1003 ¶53.) Additional training or study could substitute for work

experience and additional work experience or training could substitute for formal education. *Id.*

A. Pressure-Driven Microfluidic Droplet/Emulsion Generators Were Well Known

Microfluidic droplet production is based on the principle that droplets of one fluid, such as water, can be formed within an immiscible carrier fluid, such as oil, at a junction between two microfluidic channels. (Ex. 1003 ¶12.)

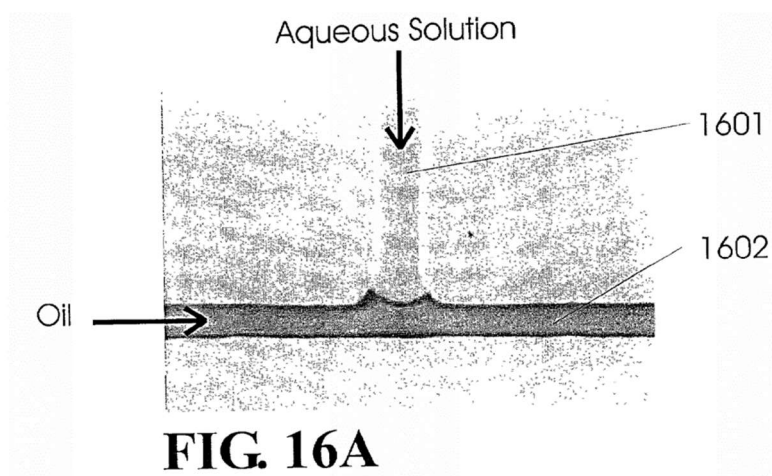
Starting in the 1990s “[t]here [was] a surge of interest in the ‘lab-on-a-chip’ concept, which involves the miniaturization of many chemical processes onto a single silicon chip.” (Ex. 1026 p. 1; Ex. 1024.)² By the beginning of the 2000s, multiple groups had demonstrated use of microreactors to form emulsions³ from

² Unless otherwise stated, all pin cites to page numbers correspond to the exhibit page numbering applied to the bottom of each exhibit (as opposed to the document’s intrinsic page numbering), whereas pin cites to paragraph or column/line numbers refer to the document’s intrinsic numbering.

³ The ‘392 patent broadly defines emulsion as “a composition comprising liquid droplets disposed in an immiscible carrier fluid, which also is liquid.” (Ex. 1001 at 10:11-12.) The term “droplet generator” and “emulsion generator” are used

immiscible fluids for carrying out various analyses, cell sorting operations and biochemical reactions.

For example, in 2000 Quake taught that on-chip wells of aqueous and oil-based solutions feed channel T-junctions at which droplets are formed. (Ex. 1004 ¶¶3, 12, 15, 39, 70, 84, 292.) By adjusting the pressure of the oil and/or the aqueous solution, a pressure difference can be established such that the stream of aqueous solution is sheared off at a regular frequency as it enters the oil stream, thereby forming droplets.

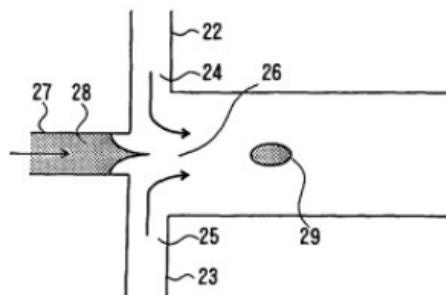


(*Id.*, see also Fig. 16A, ¶¶103, 115, 290-292.) The droplets may each contain a single molecule and the droplets may be analyzed, combined with other droplets (e.g. to react droplet contents) or sorted, as desired. (*Id.* ¶12.)

The following year, Higuchi disclosed a similar T-junction emulsion generator. (Ex. 1010 ¶¶52, 114, 115, Fig. 2.)

interchangeably herein to refer to fluidic junctions which create droplets disposed in an immiscible carrier fluid. (Ex. 1003 ¶12.)

Also in the early 2000s, researchers introduced a “cross junction” approach to forming microfluidic droplets. In contrast to the T-junction, aqueous droplets are formed at two converging flows of the continuous phase that “pinch” off the droplets. This “flow focusing” approach to droplet formation at a cross junction is described, for example, by Higuchi et al. In Higuchi’s flow focusing device, illustrated at right, microdroplets 29 of aqueous dispersion phase 28 are formed by the shear force of the continuous oil phase 24. (Ex. 1010 ¶¶6, 60-63.)



In 2007, Kumacheva disclosed another cross-junction emulsion generator similar to Higuchi and Anna’s. In Kumacheva’s device two immiscible liquids, a droplet phase A, and a continuous phase B, are supplied to the central channel 30 and side channels 32 of the flow-focusing device (FFD) 34. (Ex. 1008 ¶61; Ex. 1028 p. 16.). As shown in Figs. 1 and 2, below, the liquids forced are through a narrow orifice 34 in which a thread of liquid A breaks up and releases droplets 62.

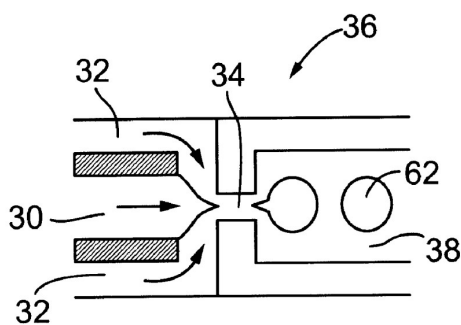


FIG. 1

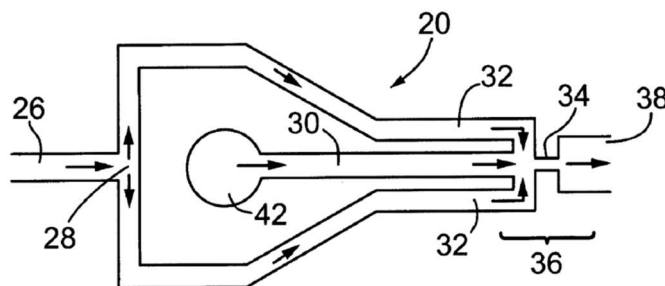
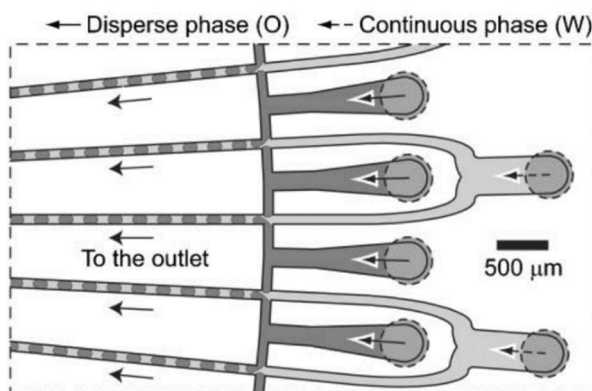


FIG. 2

Kumacheva taught that such microfluidic devices are useful in “DNA separation, parallel PCR assays, detection of enzymatically-generated fluorescence and linear temperature gradients, capillary electrophoresis for immunoassays, and chiral separation.” (Ex. 1008 ¶¶14; Ex. 1028 pp. 9-10.)

In 2008, Nisisako disclosed use of a cross-flow junction for a highly parallelized, high throughput emulsion generator. (Ex. 1012; Ex. 1016.) As shown in Nisisako’s Fig. 1, reproduced at right, shared continuous phase inlets and dispersion phase inlets were used to generate emulsions at cross-junctions. (*Id.* pp. 1-2.)



Still other exemplary emulsion generators were taught by Karnik (Ex. 1013, Fig. 3, ¶¶58, 64, 66) and Chu (Ex. 1014, Fig. 2, ¶¶67-68) in 2007-2008, respectively.

B. Microfluidic Circuits Were Commonly Parallelized to Increase Throughput

It was also known that microfluidic circuits were commonly arranged in parallel to increase throughput. (Ex. 1007 ¶¶151-153, 209-35; Ex. 1046 ¶¶5-13, 26, 49-50, 83; Ex. 1005 ¶¶2, 8-13, 29-35, 44-52; Ex. 1047 at Abstract, ¶¶2, 5, 53, 57, 61, 69, 78; Ex. 1008 ¶¶2, 6-7, 11, 14, 18-21, 54, 46, 61-70, Fig. 2A and 3; Ex. 1028 pp. 7-12, 16-19; Ex. 1017 at Fig. 2A and 3, ¶¶6, 54, 56, 63-65, 68; Ex. 1018

at Fig. 2A, 3, ¶¶5, 51, 53, 60-62, 65; Ex. 1047 ¶5, 65, Figs. 2A and 20; Ex. 1003 ¶¶22-31.)

For example, in 2007 Kumacheva disclosed an approach for improving throughput of microfluidic devices by providing multiple parallel flow paths on a multi-layer microfluidic plate. (Ex. 1008 ¶63-

66; Ex. 1028 p. 16-18.) Droplet are generated at flow focusing devices 20 and the resulting emulsions are sent along outlet channel 38. (Ex. 1008 ¶66; Ex. 1028 p. 18.) Kumacheva taught that such multichannel devices had been used,

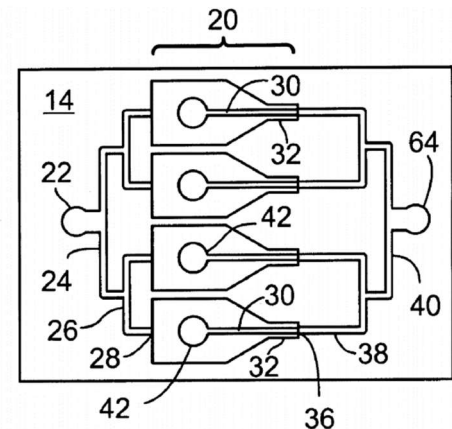


FIG. 4

for instance, to perform parallel PCR assays. (Ex. 1008 ¶14; Ex. 1028 p. 9-10.)

Still other parallelized emulsion generators were taught by Karnik (Ex. 1013, Fig. 3, Fig. 6, ¶¶92, 93, 239), Nissisako (Ex. 1012 p. 2), and Chu (Ex. 1014, Fig. 2, ¶75) in 2007 and 2008, respectively.

C. Microfluidic Chips Could Be Fabricated According to a Variety of Well-Known Techniques

It was generally known that that microfluidic chips could be manufactured according to a variety of well-known processes including casting, injection molding, and compression molding. (Ex. 1017 ¶72; Ex. 1018 ¶72; Ex. 1040 pp. 1, 12; Ex. 1041; Ex. 1021 at 1:34-41; 10:33-39; 4:20-13:64; Ex. 1022 pp. 2-14; Ex.

1036; Ex. 1020 pp. 3-9; Ex. 1029; Ex. 1009 at 4:45-5:3, 7:52-62, 11:48-51; Ex. 1017 ¶72; Ex. 1018 ¶69; Ex. 1040 pp. 1-3, 8, 12-18; Ex. 1041; Ex. 1003 ¶¶32-36.)

VI. OVERVIEW OF THE '392 PATENT

The '392 patent describes the alleged invention as comprising “a plate including an array of emulsion production units” and “a vacuum or pressure source . . . capable of driving a first fluid and a second fluid from respective first and second input wells of such unit and through the droplet generator, for collection as an emulsion in the output well of such units.” (Ex. 1001 at 1:46-58.) Figures 4, 22, 23 and 24 (annotated with arrows below) are illustrative.

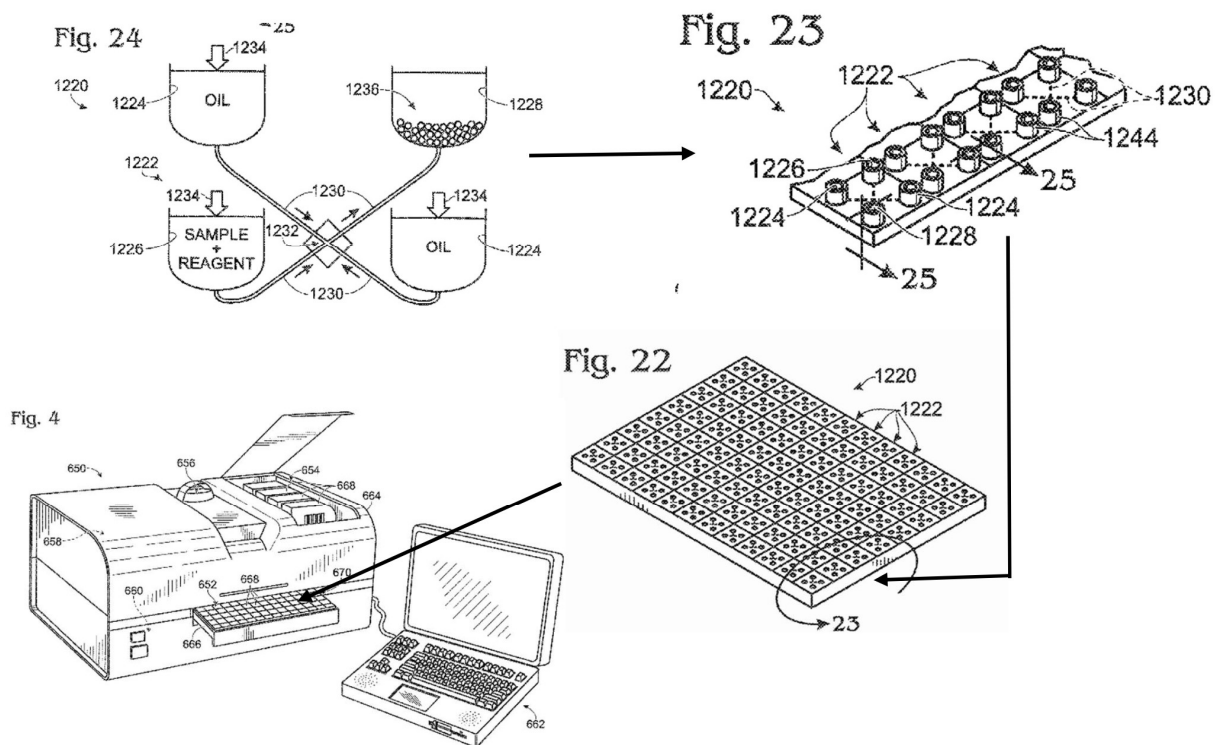


Fig. 4 shows an instrument 650 receives plate 670 that includes reservoirs or wells 668 and a droplet generator. (*Id.* at 20:16-40.) Fig. 22 shows the plate and droplet generators. (*Id.* at 35:24-54.) Figure 23 is a close-up of area 23 of Fig. 22. (*Id.*) Figure 24 illustrates the four-port droplet generator 1222 of plate 1220. (*Id.* at 35:41-55.)

In use, a pressure manifold is aligned with the wells 1224. Pressure 1234 is applied to fluid in the wells to drive the oil, sample and reagent through the channel intersection or junction 1232. (*Id.* at 35:27-55, see also Abstract, 1:46-58, 35:56-36:52.) At the junction 1232 droplets of the sample and reagent are formed in the oil, creating an emulsion which flows to output well 1228. (*Id.* at 35:27-55.)

A. Priority Date of the ‘392 Patent

The ’392 patent claims priority to various provisional applications, the first of which was filed September 23, 2008. In the pending ITC proceeding, Patent Owner identified the priority date to which the claims of the related U.S. Patent 9,126,160 are entitled. Patent Owner alleged that the claims of the ‘160 patent, which correspond closely to those in the ‘392 patent, are entitled to the benefit of date of U.S. Provisional Application No. 61/271,538, filed July 21, 2009. (Ex. 1042 p. 2; Ex. 1050 at claims.)

Because each of the prior art references presented here is prior art even to the ‘392 patent’s earliest claimed priority date, Petitioner does not address whether

the ‘392 patent is entitled to its claimed priority dates. Petitioner reserves the right to challenge the priority claims of the ‘392 patent.

B. Summary of the Prosecution History

During prosecution, the Examiner raised only a single prior-art rejection against the independent claim. The rejection was obviousness based on Pollack et al. 2008/0038810. (Ex. 1002 pp. 253-54). The Examiner noted that Pollack discloses a droplet-based array multiplexed on a multi-well plate that includes the recited input wells and output wells. (*Id.*)

However, Pollack’s droplet generator is neither the T-junction nor the cross-junction described in the Technical Background of this petition. Instead, Pollack teaches that “[d]roplets may be formed by energizing electrodes adjacent to the fluid reservoir causing a ‘finger’ of fluid to be extended from the reservoir. (Ex. 1023 ¶443.) In other words, droplets are formed by applying voltages to electrodes, not by using two pressure driven fluid flows.

Applicant argued, and the Examiner ultimately agreed, that Pollack did not disclose the recited channel junction and vacuum/pressure source. (Ex. 1002 pp. 235-37, 214-16, 143-51.) The Examiner allowed the claims on this basis. (*Id.* pp. 143-51.) The reasons for allowance states:

[T]he prior art fails to teach or fairly suggest a system for forming an array of emulsion that includes at least one input well, a second input well and an output well connected by a set of channels where the

input wells form a channels junction with the output channel extending away from the junction. The prior art further fails to teach or fairly suggest the use of a vacuum or pressure source to create a pressure differential between the input and output wells in order to drive the continuous and dispersed phases where these limitations are in combination with the claim as a whole.

(*Id.* p. 150.)

VII. CLAIM CONSTRUCTION

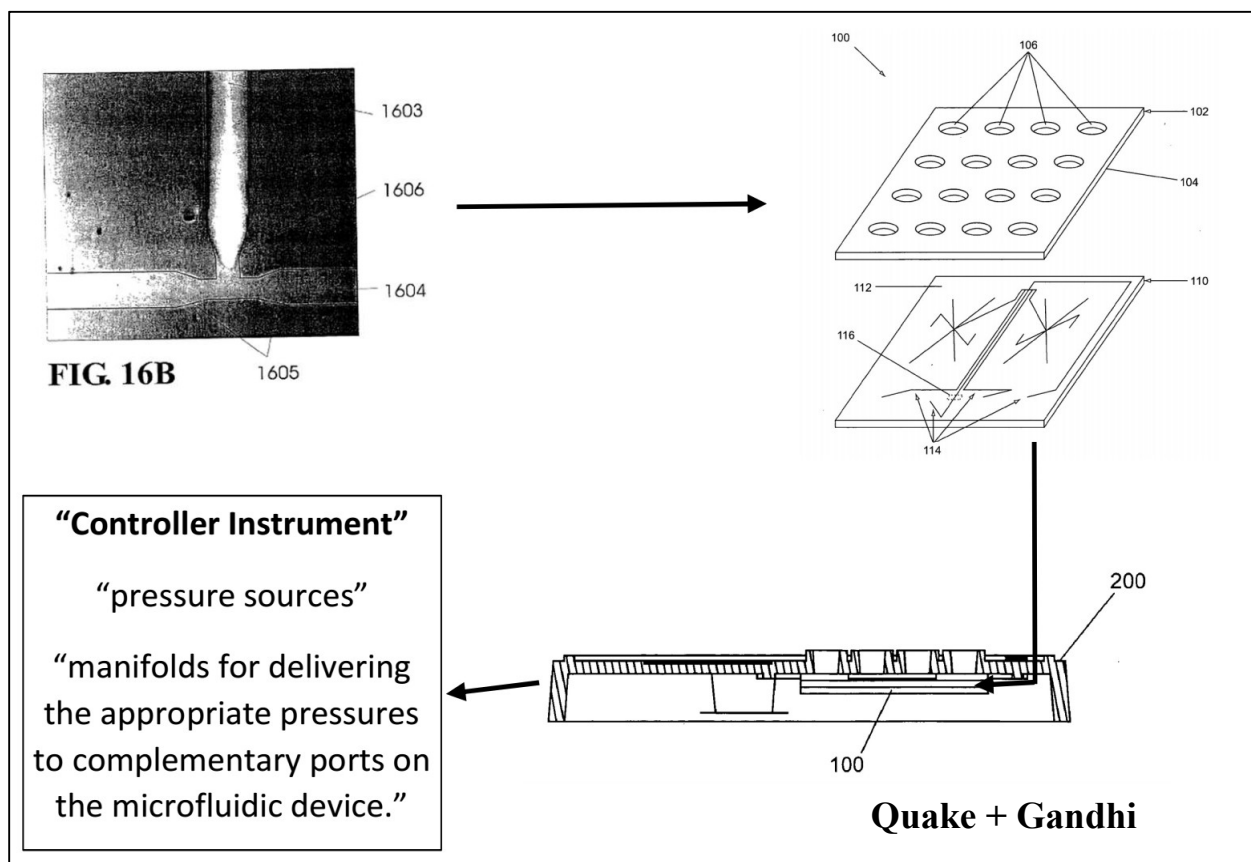
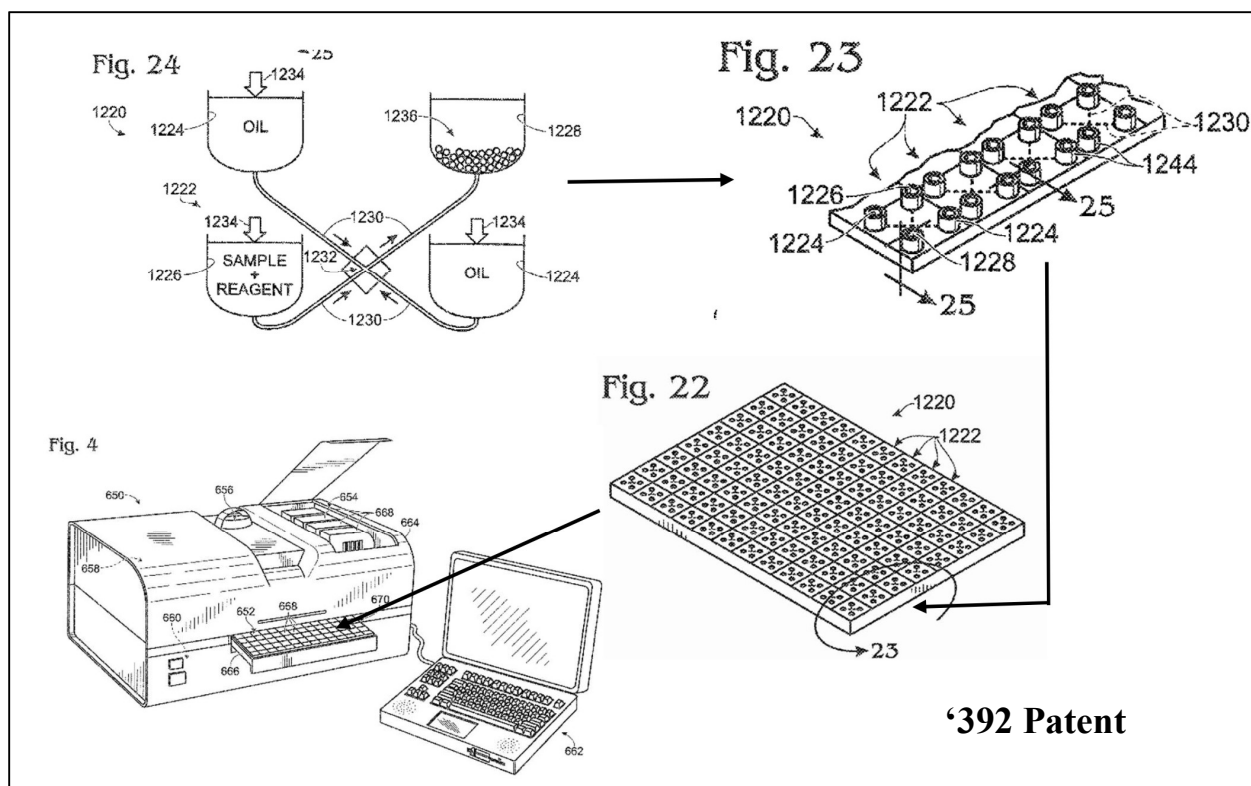
In an *inter partes* review, the terms in the challenged claims are to be given their plain meaning under the broadest reasonable interpretation standard. *Cuozzo Speed Technologies, LLC v. Lee*, 136 S. Ct. 2131, 2139, 2141 (2016). Unless otherwise stated Petitioner adopts that standard for all of the terms set forth in the claims of the ‘392 patent. Petitioner reserves the right to contest any claim construction proffered by Patent Owner in this proceeding.

VIII. GROUNDS FOR FINDING THE CHALLENGED CLAIMS INVALID

Pursuant to Rule 42.104(b)(4)-(5), the grounds for finding the challenged claims invalid are identified below and discussed in the Gandhi Declaration. (Ex. 1003.)

A. Ground 1: Claims 1-6, 8-11 and 21 Are Rendered Obvious by Quake in View of Gandhi

Claims 1-6, 8-11 and 21 are rendered obvious by Quake in View of Gandhi. Quake was one of the four hundred eighty-three (483) references cited during prosecution but was not otherwise mentioned by the Examiner or the applicants. (Ex. 1003 ¶¶39, 54.) Gandhi was not before the Examiner. This Ground presents a new combination of references that has not previously been considered and provides additional evidence that was not before the examiner. The graphic below shows how the preferred embodiment of the '392 patent corresponds to the Combined System of Quake and Gandhi.



1. Independent Claim 1

Quake in view of Gandhi renders claim 1 obvious.

Quake discloses microfluidic emulsion generators. (Ex. 1003 ¶56.) Quake teaches that an emulsion is “a preparation of one liquid distributed in small globules (also referred to herein as drops or droplets) in the body of a second liquid.” (Ex. 1004 ¶75.) Quake generates such droplets using a microfluidic junction having “a main channel, through which a pressurized stream of oil is passed, and at least one sample inlet channel, through which a pressurized stream of aqueous solution is passed.” (*Id.* ¶3) This junction or “droplet extrusion region” “joins the sample inlet channel to the main channel such that the aqueous solution can be introduced to the main channel, e.g., at an angle that is perpendicular to the stream of oil. By adjusting the pressure of the oil and/or the aqueous solution, a pressure difference can be established between the two channels such that the stream of aqueous solution is sheared off at a regular frequency as it enters the oil stream, thereby forming droplets.” (*Id.*) The droplet

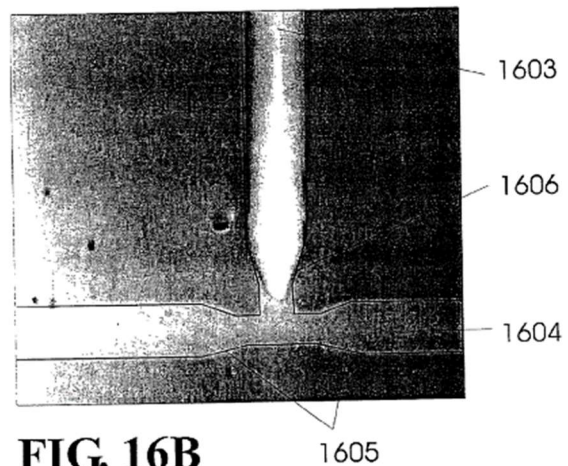
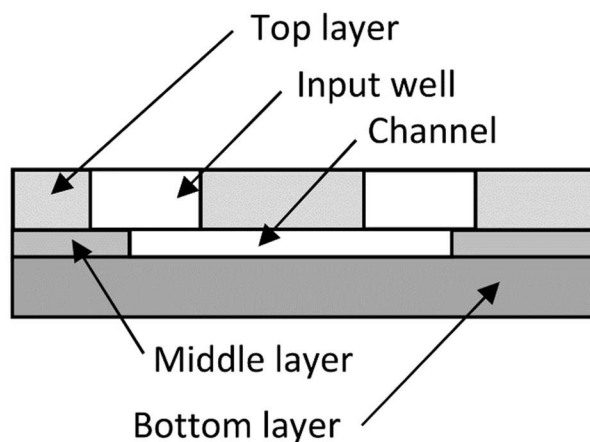


FIG. 16B

extrusion region of Quake is shown in Fig. 16B, depicting a first inlet channel 1603, a second inlet channel (left portion of 1605) and an outlet channel 1604.

Quake's Examples 10-12 teach that the emulsion generators are provided on a microfluidic chip or plate. (Ex. 1003 ¶57.) Example 10 explains that the microfluidic chip or plate is of the plate by sandwiching a stencil-like middle layer between a top layer and a bottom layer, wherein the pattern in middle layer defines the microchannels. (Ex. 1004 ¶¶277-85.)

As shown at right, the input wells are formed by drilling holes into the top layer. (Id. ¶¶278, 284, 288). Fluids are loaded into syringes and tubing is “used to direct the fluids from the syringes for input into their respective input wells of a device.” (Id.)



Quake suggests parallelizing the emulsion production units. (Ex. 1003 ¶58; Ex. 1004 ¶¶79, 80, 293, 294.) Quake teaches that “a plurality of analysis units of the invention may be combined in one device,” and “**linear arrays of channels on a single chip**, *i.e.*, a multiplex system, can simultaneously detect and sort a sample by using an array of photo multiplier tubes (PMT) for **parallel analysis of**

different channels.” (*Id.* ¶79.)⁴ Quake further explains that “[t]his arrangement can be used to **improve throughput** or for successive sample enrichment, and can be adapted to provide a very high throughput to the microfluidic devices that exceeds the capacity permitted by conventional flow sorters.” (*Id.*) Because the droplets produced by the emulsion generators are transmitted to the analysis units (*Id.* ¶¶293-94.), one skilled in the art would have appreciated that high throughput is more readily accomplished using multiple droplet generators to feed the multiple analysis units. (Ex. 1003 ¶58.)

Gandhi also teaches parallelizing microfluidic circuits in an array. (Ex. 1003 ¶59.) As explained in the declaration of Dr. Khushroo Gandhi, the lead inventor of the Gandhi published application, the application (“Gandhi”) teaches that “[m]icrofluidic devices may be used in a variety of applications, including, e.g., the performance of **high throughput** screening assays in drug discovery, immunoassays, diagnostics, genetic analysis, and the like.” (Ex. 1005 ¶29; Ex. 1003 ¶59.) The devices taught by Gandhi thus “will often include multiple sample introduction ports or reservoirs, for the **parallel or serial introduction and analysis** of multiple samples.” (*Id.*) Gandhi teaches that microfluidic devices are

⁴ Throughout this petition all emphasis is added unless otherwise stated.

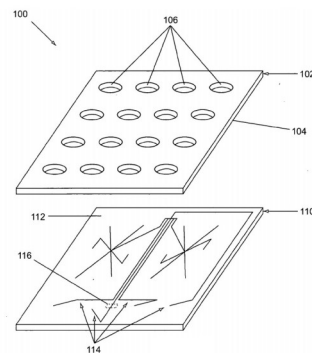
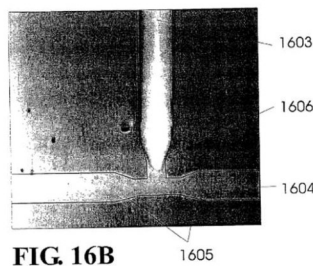
generally miniaturized to “reduce volume, increase the speed of the operation, or **multiplex the particular operation, e.g., incorporate multiple operations within the same unit space occupied by the device.**” (Ex. 1005 ¶38; Ex. 1003 ¶59.) Gandhi thus discloses that microfluidic circuits may be advantageously parallelized to increase throughput. (Ex. 1003 ¶59.)

Quake taken in view of Gandhi renders obvious the provision of multiple droplet generators on a single microfluidic chip, for multiple reasons. (Ex. 1003 ¶60.) *First*, at the time of the earliest claimed priority date it was well known that parallelization of provided higher throughput and enabled multiplexing of different reactions. (See Section V, incorporated herein by reference, Ex. 1005 ¶¶29, 38.). Dale, Kumacheva, Nisisako, Karnik, and Chu all explain that parallelizing microfluidic circuits substantially increases throughput. (Ex. 1049 ¶44; Ex. 1008 ¶20; Ex. 1028 p. 12; Ex. 1012 pp. 1-2; Ex. 1013 ¶¶92-93, 239; Ex. 1014 ¶75, Fig. 2.) Parallelizing Quake merely involved use of a known technique (placing multiple units on a single chip) to improve similar devices (emulsion generators) in the same way (providing increased throughput.). *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 415-421 (2007) (Ex. 1003 ¶¶60-61.)

Second, Quake and Gandhi specifically suggest that providing multiple units on a single chip enables multiplexed processing of different samples, or processing of the same sample by different processes, at the same time. (Ex. 1003 ¶62.)

Quake teaches that “linear arrays of channels on a single chip, i.e., a multiplex system, can simultaneously detect and sort a sample by using an array of photo multiplier tubes (PMT) for parallel analysis of different channels.” (Ex. 1004 ¶79.) Gandhi teaches that the samples reservoirs can perform a “manifolding function” to deliver a single patient sample to multiple reservoirs where, for instance, “a single patient sample may be subject to multiple diagnostic tests.” (Ex. 1005 ¶93.) A skilled artisan would have been motivated to use the technique taught in Gandhi (parallelization) to improve a similar device (Quake’s microfluidic device) in the same way (permit multiplex processing). *KSR*, 550 U.S. at 415-421 (2007) (Ex. 1003 ¶62.)

It was thus obvious that multiple instances of Quake’s droplet generator could be disposed on a single chip as depicted below to increase throughput and enable multiplexed reactions. (Ex. 1003 ¶62.)



Gandhi also teaches that, in the case of pressure-driven fluid flow, it is preferred to mount the chip to a pneumatic manifold that provides air pressure to drive the fluids between fluid reservoirs on the microfluidic chip. (Ex. 1003 ¶63.)

Gandhi explains that the fluids in his microfluidic systems can be driven by either i) pressure or ii) electrokinetic forces. (Ex. 1005 ¶96.) The latter mechanism is used in most of the embodiments described by Gandhi and is discussed at some length throughout Gandhi's specification. However, it is former embodiment – microfluidic systems using pressure-driven flow – relied upon in the instant petition. (Ex. 1003 ¶63.)

Gandhi teaches that “for example, in the case of microfluidic systems employing pressure based fluid flow,” the “**controller instrument** typically includes **pressure sources** as well as appropriate **manifolds** for delivering the appropriate pressures to complementary ports on the microfluidic device.” (Ex. 1005 ¶96.) Gandhi also teaches that either vacuum or positive pressure is applied to the ports to drive the fluids: “[t]he instrument then applies pressure/vacuum . . . directly to fluids, to move those fluids through the channels of the device in a controlled fashion.” (*Id.*)

The instrument manifold mates with the upwardly extending reservoirs (apertures 206 surrounded by ridges 208) of cover layer 200, as depicted in the annotated version of Gandhi's Fig. 3A at right. (Ex. 1005 ¶¶77-90; Ex. 1003 ¶63.)

The ridges 208 “provide[] a barrier between neighboring **reservoirs** in the overall

device and also functions to increase the effective volume of each **reservoir** in the

resulting device.” (Ex. 1005 ¶80, see also

¶¶45-46; Ex. 1003 ¶63.) The

apertures/reservoirs 206 “are positioned

within the cover so as to align with

ports/reservoirs in the body structure of a

microfluidic device.” (Ex. 1004 ¶78; Ex.

1003 ¶63.) This alignment between each

aperture/well 206 and each “**reservoir**

106” in the microfluidic device 100 is illustrated in Figure 2F, a portion of which is

reproduced at right. (Ex. 1005 ¶90, see also ¶¶71, 78; Ex. 1003 ¶63.) The

microfluidic body 100 is adhered or snapped into place underneath the cover 200.

(Ex. 1005 ¶¶ 51-54, 57, 82, 86-87.) The system applies pneumatic (air) pressure to

the fluids in the wells “without contacting the fluid within the reservoir 106.” (Ex.

1005 ¶90; Ex. 1003 ¶63; see also Ex. 1005 at Fig. 4B.)

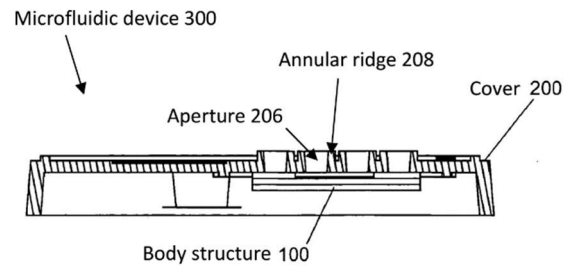


Fig. 3A

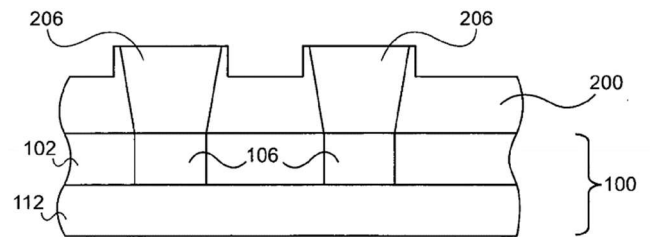


Fig. 2F

*The resulting system, depicted below, is hereafter referred to as the **Combined System**.* In the Combined System, three or more of Quake’s emulsion generation units are provided in a parallel array (as suggested by both Quake and Gandhi) on the microfluidic chip 100 of Gandhi. (Ex. 1003 ¶64.) The microfluidic chip 100 is adhered or snapped into place within the cover 200. (*Id.*) The device or plate 300 is then placed into a controller instrument which applies positive or negative air pressure to each well to drive the fluids as desired from input reservoir, through the emulsion generators, to output reservoirs. (*Id.*)

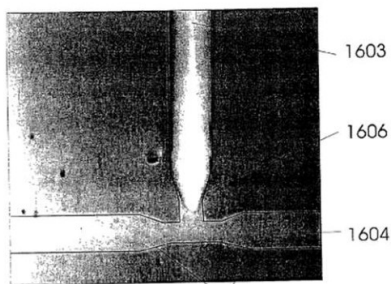
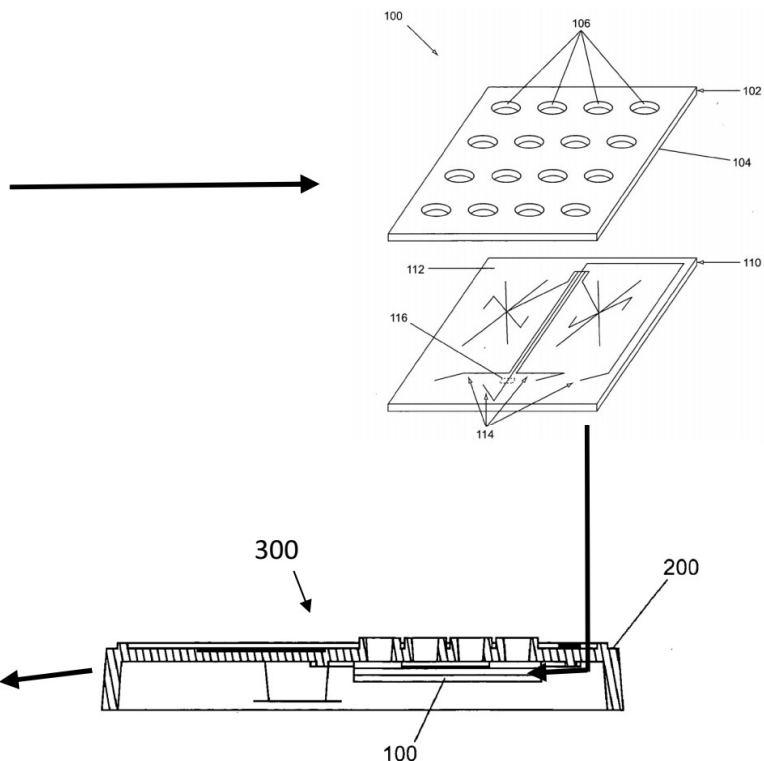


FIG. 16B



“Controller Instrument”
 “pressure sources”
 “manifolds for delivering the appropriate pressures to complementary ports on the microfluidic device.”

The Combined System has input wells (for the oil and aqueous phase fluids) and output wells (to receive the droplets) for each of the emulsion generators. (Ex. 1003 ¶¶65.) Gandhi describes that the reservoirs 106/206 are loaded with fluids which are passed through the microchannels 114 and through a detection region 116. (Ex. 1005 ¶¶27-28). The fluids then pass to an output well (the reservoir above the channel which extends from the detection window). (Ex. 1003 ¶¶65.) In the Combined System, the microfluidic plate 300 is equipped with “multiple sample introduction ports or reservoirs, for the parallel or serial introduction and analysis of multiple samples” as taught by Gandhi. (Ex. 1005 ¶¶29, Ex. 1003 ¶¶65.) The output of the emulsion generators flow into corresponding output wells 106/206. (Ex. 1003 ¶¶65.) In order to achieve the multiplexed, parallelized operation discussed in Gandhi, separate input wells and output wells are provided for each emulsion generator. (*Id.*) This enables the simultaneous processing of multiple different samples or the simultaneous performance of different analyses in parallel. (*Id.*)

The wells of the Combined System each hold the equivalent of over 3,250,000 droplets, about 275 times more than is needed to perform emulsion-based PCR and other useful processes. (Ex. 1003 ¶¶66.) The photomicrographs in Quake (Ex. 1004 ¶¶299-302) show that the droplets are about 30 microns (0.030 millimeters in diameter), resulting in a per-droplet volume of 0.0000141 μl . (Ex.

1003 ¶¶66.) Gandhi teaches that “the volume of the reservoirs of the overall device will typically fall in the range between about 1 and about 200 μl , preferably between about 2 and 100 μl , more preferably between about 5 and about 100 μl , and still more preferably, between about 5 and 50 μl .” Assuming a reservoir volume of 50 μl in the Combined System, the reservoir holds the volume equivalent of 3,536,000 droplets. (*Id.*) Assuming further that there is 3X more continuous phase than droplet or dispersion phase, the output reservoir is sufficient to hold about 880,000 droplets. (*Id.*) This is more than sufficient to perform useful processes such as the PCR reactions discussed in connection with claim 18. (Ex. 1037 ¶¶94 (“In particular, clear production in the lanes showing PCR amplified product produced from 1600 and 3200 droplets . . .”); Ex. 1003 ¶¶66.) Thus, the wells of the Combined System are configured to hold 275 times more continuous phase than perform useful processes such as droplet-based PCR (assuming 3,200 droplets for PCR). (*Id.*)

A skilled artisan would have had at least four reasons to use Gandhi’s microfluidic device 300 and control instrument to drive the fluids through the emulsion productions units of Quake. First, as taught by Gandhi, the cover 200 greatly simplifies the interface of the microfluidic chip 100 to the control instrument. (Ex. 1005 ¶¶6-7; Ex. 1003 ¶¶67.) Gandhi teaches that his system

overcomes the difficulties associated with “user handling, reagent delivery or filtration, and system interfacing of such [miniaturized] devices.” (*Id.*)

Second, Gandhi’s cover provides enhanced fluid reservoir volume. Gandhi teaches that “[t]he cover layer component of the microfluidic devices of the present invention also provides the capability to increase the volume capacity of the reservoirs of those devices.” (Ex. 1005 ¶45; Ex. 1003 ¶67.) The “apertures disposed in the cover layer can increase the total depth of the fluid reservoirs of the device by extending those reservoirs.” (*Id.*)

Third, the Gandhi system facilitates handling while reducing overall cost of manufacturing. (Ex. 1003 ¶67.) Gandhi teaches that his device “combines the advantages of microfluidics with improved material handling characteristics and reduced costs for manufacturing.” (Ex. 1005 ¶8.) The cover 200 provides “ease of handling.” (*Id.* ¶86.) The overall cost is reduced because the cover may be inexpensively fabricated by conventional manufacturing techniques using low cost materials, like injection molding. (Ex. 1005 ¶¶48-50, *see also* ¶¶25-26.)

Fourth, it was known that use of air to control pressure in the headspace above fluid wells was known to improve the precision and reproducibility of the fluidic drive. Chien explains that “the use of external pumps to force liquids directly through microfluidic channels” produces relatively “irreproducible and erratic results.” (Ex. 1035 p. 1; Ex. 1030; *see also* Ex. 1006 at 1:39-47.) “A system

that controls the pressure of a compressible gas at the fluid–air interface directly on top of the wells of the microfluidic device is a more practical design.” (*Id.*) A skilled artisan would thus have seen a strong motivation to modify Quake to incorporate the pneumatic fluid drive technique taught in Gandhi. (Ex. 1003 ¶¶67.)

A skilled artisan thus would have been strongly motivated to combine the teachings of Quake and Gandhi references to arrive at the Combined System. (Ex. 1003 ¶¶67-68.)

Because each of the components of the Combined System was well known at the time of filing (as discussed in Section V, incorporated herein by reference) and could be predictably combined, a skilled artisan would have had a strong expectation that the Combined System could be readily fabricated and would work as intended. (Ex. 1003 ¶¶61, 69.) Significantly, the claims do not limit the size of the plate on which the arrays are disposed. Thus, one could increase the size of the plate to facilitate inclusion of an array of emulsion production units on a single chip. (Ex. 1003 ¶¶61, 69.) Providing an array of Quake’s emulsion production units on a single plate or chip and interfacing that chip with Gandhi’s pneumatic drive system would require no more than routine skill and would lead to predictable results. (*Id.*)

Preamble

The preamble recites “[a] system for forming an array of emulsions, comprising.” To the extent the preamble is limiting, Quake taken alone meets or renders obvious the preamble. Alternatively, the Combined System meets this limitation. (Ex. 1003 ¶¶70-76.)

As discussed above, Quake discloses or renders obvious an array of emulsion generators. Quake’s droplet extrusion region is shown in Fig. 16B, depicting a first inlet channel 1603, a second inlet channel (left portion of 1605) and an outlet channel 1604. (Ex. 1003 ¶¶56, 71; Ex. 1004 ¶292.) Quake suggests that an array of his emulsion generation units can be disposed on a single chip. (Ex. 1004 ¶¶79, 80, 293, 294, Ex. 1003 ¶72.) One skilled in the art would have been strongly motivated to parallelize the Quake emulsion generators as suggested by Gandhi. (Ex. 1005 ¶¶ 25, 38; Ex. 1003 ¶¶73-74.)

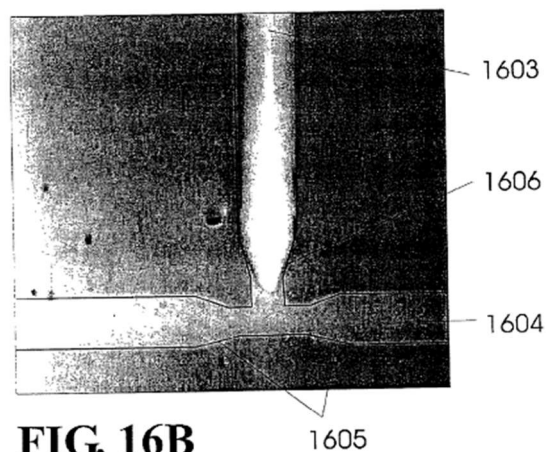
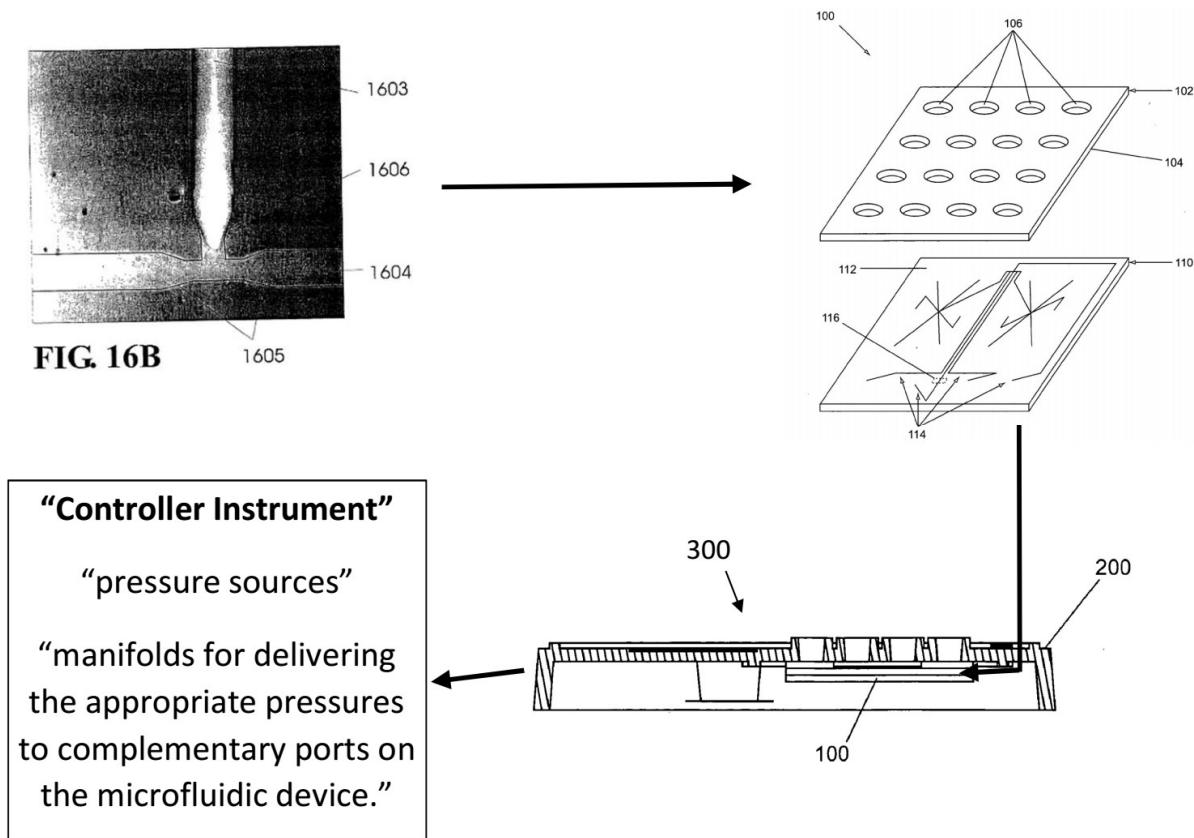


FIG. 16B

The Combined System also includes a plurality of Quake's emulsion generators arrayed in parallel on a single microfluidic plate, thus meeting the preamble. (Ex. 1003 ¶75.) As shown below, three or more of Quake's emulsion generators are arrayed on the microfluidic body 100. (*Id.*) Thus the plate 300 includes an array of emulsion generators. (*Id.*)



Thus, Quake alone or in view of Gandhi renders it obvious to deploy an array of emulsion generators on a single microfluidic chip, meeting the preamble. Ex. 1003 ¶76.)

Element 1[a]

Claim element 1[a] recites “a plate including an array of emulsion production units.”

Quake’s “microfabricated chip” is a plate including an emulsion production unit. (Ex. 1004 ¶¶29-30, 65, 67, 81, 88, 135-136, 271-285, 294, 325; Ex. 1003 ¶78.) “The **planar geometry** of the device allows the use of high numerical aperture optics, thereby increasing the sensitivity of the system.” (Ex. 1004 ¶14.) Quake’s emulsion generation device comprises three layers: a top layer (3-10 mm), a middle layer (30 microns) and a bottom layer (0.5 cm) that were bonded together. (*Id.* ¶¶271-85.) Each layer was produced by depositing a thin layer of material on a silicon wafer. (*Id.* ¶¶277-85.) The layers were bonded together and the resulting device was generally flat and thin, thus meeting the “plate” recitation. (*Id.*; Ex. 1003 ¶¶78.)

The Combined System also includes a plate 300 having an array of droplet generators. (Ex. 1003 ¶¶75, 78-80.) As discussed and depicted above, the plate 300 includes an array of Quake’s emulsion generators. (*Id.*) If the downwardly projecting flanges around the periphery of cover 200 are considered to take the overall structure 300 outside the broadest reasonable interpretation of the term “plate,” then the central portion of cover 200 together with body 100 (*i.e.*, the device 300 without the downwardly extending flanges of the cover 200) may be

considered as being the recited “plate.” The claim is open-ended and does not preclude the addition of flange structures around the periphery of the recited plate. The plate 300 is mated to the control instrument in the Combined System. (*Id.*)

Accordingly, Quake and the Combined System meets this limitation. (Ex. 1003 ¶¶81.)

Element 1[a][i]

Claim element 1[a][i] recites “each unit including at least one first input well⁵ to hold a continuous phase for an emulsion.” The ’392 patent explains that “any of the emulsions disclosed herein may be a water-in-oil (W/O) emulsion (*i.e.*, aqueous droplets in a continuous oil phase).” (Ex. 1001 at 10:51-53.)

⁵ The term “well” does not require that any particular amount of fluid be contained in the structure or that the fluid be contained for any particular period of time. Indeed, an apparatus claim may be distinguished only by the structural limitations of a claim. *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1469 (Fed. Cir. 1990). The intended use of a structure (e.g. to store a large amount fluid for a predetermined period of time) is immaterial if the claim language does not recite a structural difference from the prior art.

The oil of Quake is a continuous phase for an emulsion. As discussed for the preamble, Quake discloses a microfluidic chip in which immiscible fluids are driven via pressure into channel junctions which produce the emulsions. (Ex. 1004 ¶3, *see also* ¶¶ 12, 14, 15, 70, 75, 81-82, 287-301; Ex. 1003 ¶82.) Quake teaches that “a main channel, through which a pressurized stream of **oil** is passed, and at least one sample inlet channel, through which a pressurized stream of **aqueous solution** is passed. ... By adjusting the pressure of the oil and/or the aqueous solution, a pressure difference can be established between the two channels such that the stream of **aqueous solution is sheared off** at a regular frequency as it enters the oil stream, **thereby forming droplets.**” (*Id.* ¶3; *see also* Fig. 16B.) Accordingly, the oil of Quake is a “continuous phase for an emulsion.”

Quake discloses an input well for the continuous phase. Quake discloses this element in describing Examples 10-12, which detail the microfabrication and operation of an illustrative emulsion production unit. (*Id.* ¶¶271-312; Ex. 1003 ¶¶82-84.) In these examples, Quake teaches that “[i]nput wells for the **different fluids, such as water and oil,** were then drilled through the device using a No. 73 drill bit” (Ex. 1004 ¶284.) Furthermore, “Fluids, such as **oil**

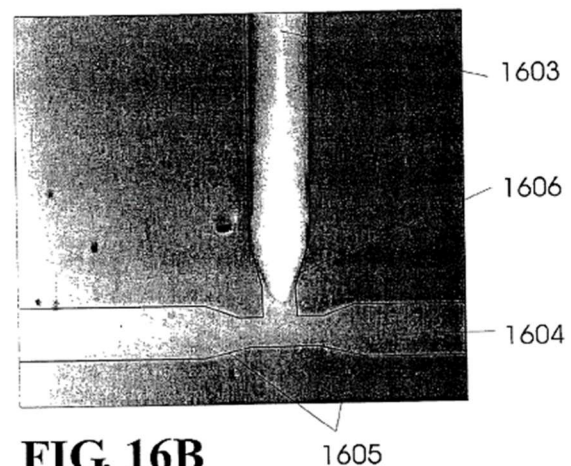


FIG. 16B

and water may be loaded into separate syringes fitted with high-pressure connection fittings ... for **loading** into a microfabricated device of the invention.” (*Id.* ¶288, *see also* ¶300.) “Microline tubing ... can be used to direct the fluids from the syringes for input into their respective **input wells** of a device.” (*Id.* ¶288.) Thus, Quake’s oil input well meets element 1[a][i]. (Ex. 1003 ¶85.)

As discussed above and illustrated below, the plate 300 of the Combined System includes corresponding oil input wells for each emulsion generator. (Id.

¶¶65, 82-84.) The plate 300 of the Combined System includes input wells (reservoirs 106/206) containing the oil phase. Each oil input well is large enough to hold more than 275 times more continuous phase than necessary to perform useful analyses such as PCR (as recited in claim 18). (Id. ¶¶66, 84.)

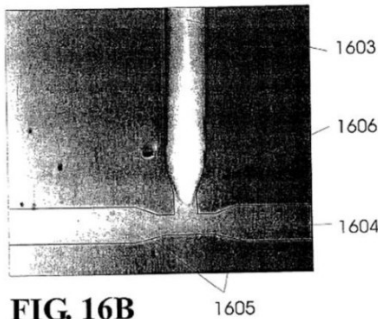
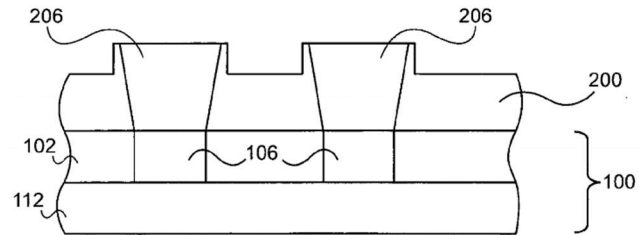
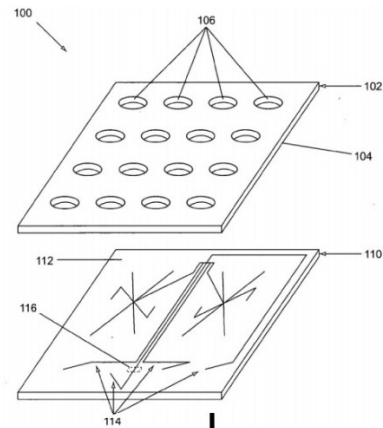
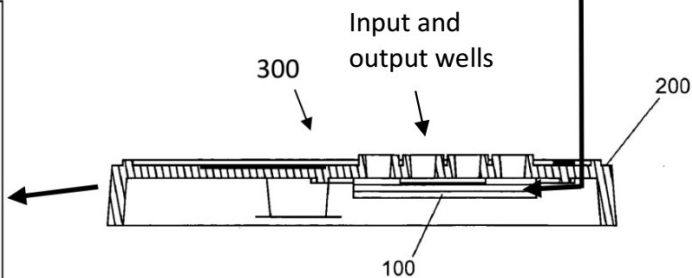


FIG. 16B



“Controller Instrument”
 “pressure sources”
 “manifolds for delivering the appropriate pressures to complementary ports on the microfluidic device.”



Element 1[a][ii]

Claim element 1[a][ii] recites that each emulsion production unit include “a second input well to hold a dispersed phase for an emulsion.” The “dispersed phase” is an aqueous phase. (Ex. 1001 at 10:15-19 “[t]he droplets (e.g., aqueous droplets) are formed by at least one droplet fluid, also termed a foreground fluid, which is a liquid and which forms a droplet phase (which may be termed a dispersed phase or discontinuous phase).”)

Quake discloses an “input well” to hold the dispersed phase. (Ex. 1003 ¶¶86-88.) As discussed for element 1[a][i], input wells on Quake’s chip feed oil into channel 1605 and dispersed phase (aqueous solution) into channel 1603. (Ex. 1004 ¶¶284, 288; *see also* ¶¶3, 39, 65-66, 71, 77, 81-82, 114, 176, 196, 200.)

Quake teaches that “[i]nput wells for the different fluids, such as water and oil, were then drilled through the device using a No. 73 drill bit” (*Id.* ¶284.) Furthermore, “Fluids, such as oil and water may be loaded into separate syringes fitted with high-pressure

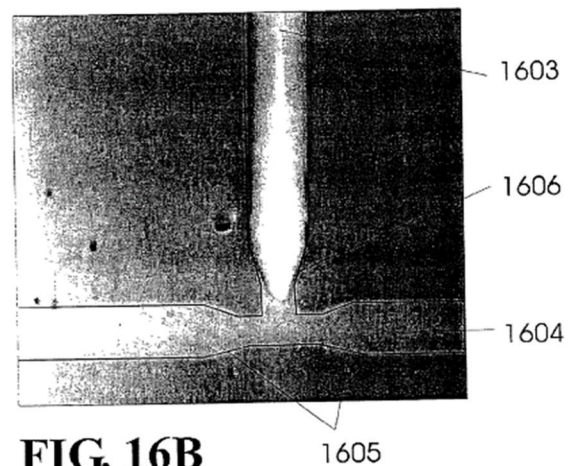


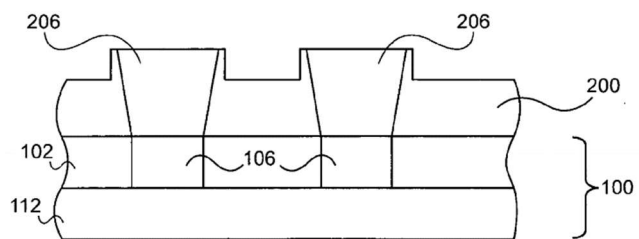
FIG. 16B

connection fittings ... for **loading** into a microfabricated device of the invention.” (*Id.* ¶288, *see also* ¶300.) “Microline tubing ... can be used to direct the fluids

from the syringes for input into their respective **input wells** of a device.” (*Id.*

¶288.) Thus, Quake’s aqueous input well meets element 1[a][ii]. (Ex. 1003 ¶87.)

As discussed above and illustrated below, the plate 300 of the Combined System includes corresponding aqueous phase input wells for each emulsion generator. (Id. ¶¶65, 88.) The plate 300 of the Combined System includes input wells (reservoirs 106/206) containing the aqueous phase for each droplet generator junction. (*Id.*) Each aqueous phase input well is large enough to hold more than 275 times more aqueous phase than necessary to perform useful analyses such as PCR (as recited in claim 18).



(*Id.* ¶66.)

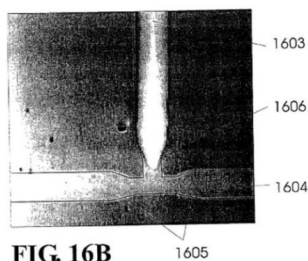
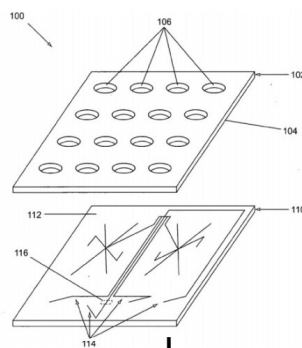
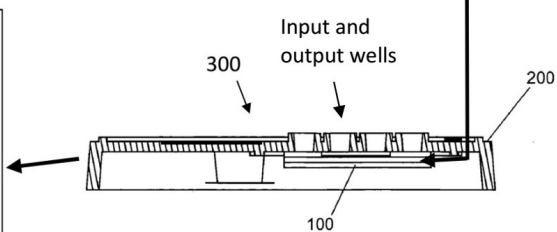


FIG. 16B



“Controller Instrument”
 “pressure sources”
 “manifolds for delivering the appropriate pressures to complementary ports on the microfluidic device.”



Element 1[a][iii]

Claim 1[a][iii] recites “an output well connected to the first and second input wells by a set of channels that form a channel junction, the set of channels including at least two input channels extending separately from the input wells to the channel junction and an output channel extending from the channel junction to the output well.”

Quake discloses the recited “channel junction.” As discussed above for the preamble and elements 1[a][i]-[ii], the droplet extrusion regions of Quake include two input channels (one input channel 1605 for the oil and another input channel 1603 for the aqueous phase) and one output channel (right portion of 1605 and 1604). Quake’s droplet extrusion region is thus the recited “channel junction” element. (Ex. 1003 ¶90.)

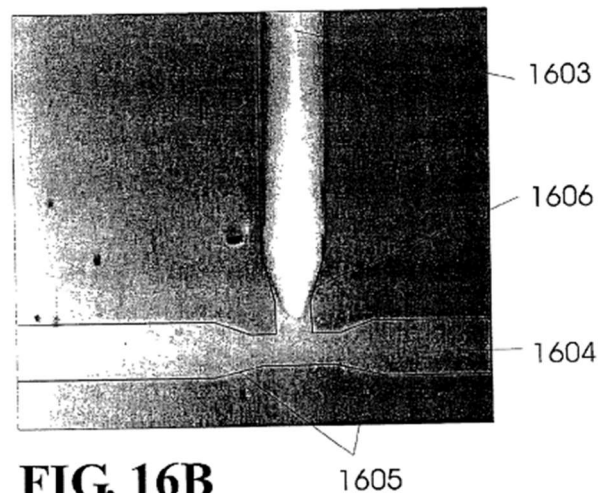


FIG. 16B

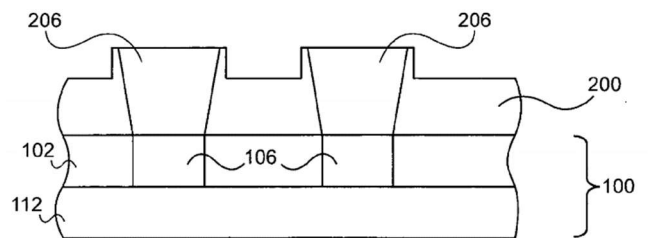
Quake teaches that the input channels extend separately from the respective input wells. Quake teaches that “[i]nput wells for the different fluids, such as water and oil, were then drilled through the device using a No. 73 drill bit” (Ex. 1004 ¶284.) Furthermore, “Fluids, such as oil and water may be loaded

into separate syringes fitted with high-pressure connection fittings ... for loading into a microfabricated device of the invention.” (*Id.* ¶288; *see also* ¶300.) The oil flows from the oil input well through channel 1605 to the “channel junction.” (*Id.* ¶292; Ex. 1003 ¶91.) The water phase flows from the water input well through channel 1603 to the “channel junction.” (*Id.*) Thus, Quake teaches “at least two input channels extending separately from the input wells to the channel junction.” (Ex. 1003 ¶91.)

Quake also discloses “an output channel extending from the channel junction to the output well.” Quake states, regarding Example 12, that droplets can “**flow down the entire length of the channel from the droplet extrusion region to an outlet region**, a distance of approximately 4 cm.” (Ex. 1004 ¶305.) Quake teaches that an “‘outlet region’ is an area of a microfabricated chip that collects or dispenses molecules, cells or virions after detection, measurement or sorting.” (*Id.* at ¶66.) The ‘outlet region,’ in turn, may include an output well to collect the molecules, etc. contained in the droplets. (*Id.* at ¶¶66, 71, 77 (“[a]n outlet region is downstream from a discrimination region, and may contain branch channels or outlet channels . . . a branch channel may also have an outlet region and/or terminate with a **well or reservoir**”), *see also* ¶125; Ex. 1003 ¶92.)

Thus, Quake’s configuration of channels and wells meet element 1[a][iii]. (Ex. 1003 ¶92.)

As discussed above and depicted below, the Combined System includes Quake's arrangement of channels and the recited input and output wells. (Id. ¶¶93.) The plate 300 of the Combined System includes an output well (reservoir 106/206) connected to the first and second input wells (reservoirs 106/206, containing the oil and droplet phases) by a set of channels that form a channel junction (Quake's droplet generator junction), the set of channels including at least two input channels extending separately from the input wells to the channel junction and an output channel extending from the channel junction to the output well (the channels extending between the wells and the droplet generator junction). (Id.)



Each output well is large enough to hold more than 275 times more droplets than necessary to perform useful analyses such as PCR (as recited in claim 18). (Id. ¶¶66, 93.)

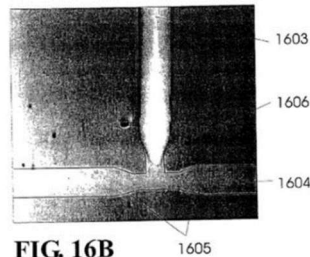
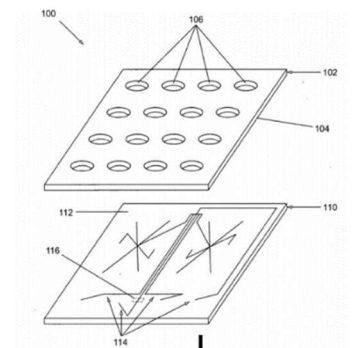
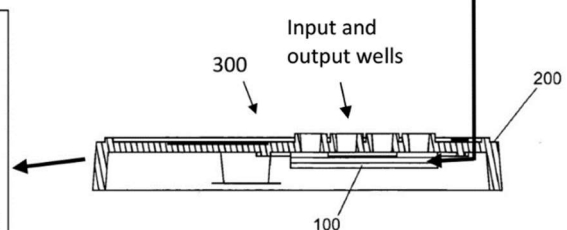


FIG. 16B



"Controller Instrument"
 "pressure sources"
 "manifolds for delivering the appropriate pressures to complementary ports on the microfluidic device."



Accordingly, the Combined System meets element 1[a][iii]. (Ex. 1003 ¶94).

Element 1[a][iv]

Claim 1[a][iv] recites “each channel of the set of channels being circumferentially bounded.”

Quake meets this limitation because its channels are formed by sandwiching a stencil-like layer between a top layer and a bottom layer, which circumferentially bounds the channels. (Ex. 1003 ¶95.) Quake’s channels and droplet generation junctions are formed via a molding process in a middle layer of the chip. (Ex. 1004 ¶¶275-85.) The middle layer serves as a sort of stencil that forms the side walls of the channels while the top layer forms the top wall of the channels. (*Id.*; Ex. 1003 ¶95.) The channels are sealed by adhering the middle layer to a bottom layer. (Ex. 1004 ¶282 “The bottom layer is typically a structural layer used to tightly seal the crossflow channels in the middle layer so that the device can be operated at high pressures (e.g., as high as 40 psi).”). The channels and junctions are thus circumferentially bounded on their sides by the middle, at the top by the top layer and on the bottom by the bottom layer.

The Combined System uses enclosed channels, as in Quake and Gandhi. (Ex. 1003 ¶97.) To use positive and negative pressure to drive the fluids as taught by Quake and Gandhi, the channels in the body structure 100 must be sealed (*i.e.*, circumferentially bounded) and not open on any side. (*Id.*)

For these reasons, the droplet generators (including channels, junctions, and wells) of Quake and in the Combined System meet each of the sub-elements recited in claim 1[a] concerning each of the emulsion production units.

Element 1[b]

Claim 1[b] recites “a vacuum or pressure source configured to be connected operatively to wells of the plate to form a pressure drop between the input wells and the output well of each unit to drive the continuous phase and the dispersed phase from the first and second input wells of the unit to the channel junction, at which droplets of the dispersed phase are generated, and through the output channel for collection in the output well of the unit.”

Gandhi teaches that, in the case of pressure-driven fluid flow, it is preferred to mount the chip to a pneumatic manifold that provides air pressure to drive the fluids between fluid reservoirs on the microfluidic chip. (Ex. 1003 ¶100.) Gandhi teaches that “for example, in the case of microfluidic systems employing pressure based fluid flow,” the “**controller instrument** typically includes **pressure sources** as well as appropriate **manifolds** for delivering the appropriate pressures to complementary ports on the microfluidic device.” (Ex. 1005 ¶96.) Gandhi also teaches that either vacuum or positive pressure is applied to the ports to drive the fluids: “[t]he instrument then applies pressure/vacuum . . .

directly to fluids, to move those fluids through the channels of the device in a controlled fashion.” (*Id.*)

The instrument manifold mates with the upwardly extending reservoirs (apertures 206 surrounded by ridges 208) of cover member 200, as depicted in the annotated version of Gandhi’s Fig. 3A at right. (Ex. 1005 ¶¶77-90; Ex. 1003 ¶101.) The ridges 208 “provide[] a barrier between neighboring **reservoirs** in the overall device and also functions to increase the effective volume of each **reservoir** in the resulting device.” (Ex. 1005 ¶80, see also ¶¶45-46; Ex. 1003 ¶101.) The apertures/reservoirs 206 “are positioned within the cover so as to align with ports/reservoirs in the body structure of a microfluidic device.” (Ex.

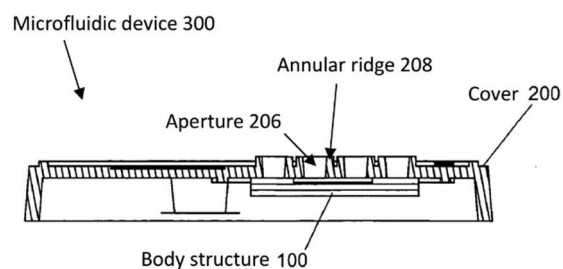


Fig. 3A

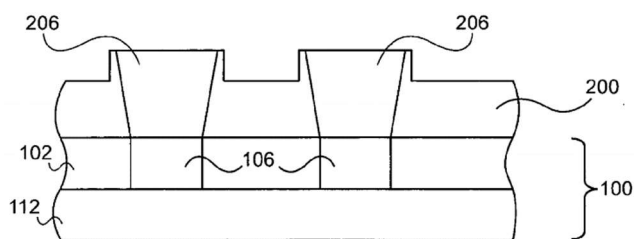


Fig. 2F

206 and each “**reservoir 106**” in the microfluidic device 100 is illustrated in Figure 2F, a portion of which is reproduced at right. (Ex. 1005 ¶90, see also ¶¶71, 78; Ex. 1003 ¶101.) The microfluidic body 100 is adhered or snapped into place underneath the cover 200. (Ex. 1005 ¶¶ 51-54, 57, 82, 86-87.)

The system applies pneumatic (air) pressure to the fluids in the wells to drive the fluids to or from reservoirs 106. (Ex. 1005 ¶90; Ex. 1003 ¶102.)

Gandhi teaches that “[a]pplication of the positive pressure is preferably carried out using an apparatus that sealably fits over the reservoir while not actually contacting the fluid contained therein.” As shown in Fig. 2F, a needle 254 may be “positioned within the ball stopper 256 so as to be able to apply pressure to the reservoir 106, *without contacting the fluid within the reservoir 106.*” (Ex. 1005 ¶90.) The driving force is thus applied is via air pressure. (Ex. 1003 ¶102.) Fig. 4B shows how each reservoir has a headspace in well 308 above the fluid to which the air pressure is applied. (Ex. 1005 ¶53.)

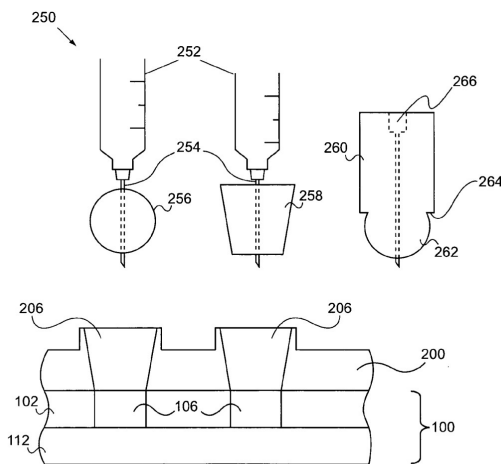


Fig. 2F

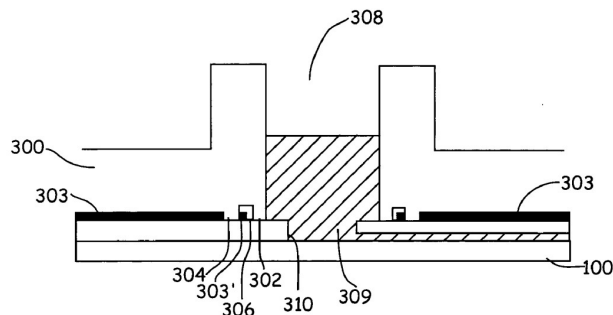


Fig. 4B

To the extent Gandhi is not deemed to expressly disclose use of air pressure, that was obvious in view of the Chien reference for the reasons discussed above in connection with claim 1. (Ex. 1035 pp. 1-6; Ex. 1003 ¶102.) The

advantageousness of using air pressure to drive the fluids among microfluidic wells was known in the art. (Ex. 1035 p. 1.)

As discussed above, the Combined System incorporates the foregoing aspects of Gandhi, and thus meets element 1[b]. (Ex. 1003 ¶103.)

Thus, claim 1 is rendered obvious by Quake taken in view of Gandhi. (Ex. 1003 ¶104.)

2. Dependent Claim 2

Claim 2 depends from claim 1, the analysis of which is incorporated by reference.⁶ Claim 2 recites that “the vacuum or pressure source controls air pressure in wells to which the source is configured to be connected operatively.”

As discussed above in connection with claim 1[b], Gandhi teaches it is preferred to mount the chip to a pneumatic manifold that provides air pressure to drive the fluids between fluid reservoirs on the microfluidic chip. (Ex. 1003 ¶106.)

⁶ Each dependent claim incorporates by reference the analysis for its corresponding base claim throughout this petition.

The advantageousness of using air pressure to drive the fluids among the wells was known in the art. (Ex. 1035 pp. 1-6.) The Combined System utilizes this technique and thus meets claim 2.

3. Dependent Claims 3-4

Claims 3-4 depend from claim 1. Claim 3 recites that “an instrument including the vacuum or pressure source and a manifold, wherein the vacuum or pressure source is configured to be connected operatively to wells of the plate via the manifold.” Claim 4 recites “one or more gaskets that engage the plate and the manifold to form a seal between the manifold and the wells of the plate to which the vacuum or pressure source is configured to be connected operatively.”

As discussed above in connection with claim 1, Gandhi discloses that the fluids are driven among the wells by mating the wells of the cover 200 to a complimentary manifold on a control instrument. Gandhi teaches that “for example, in the case of microfluidic systems employing pressure based fluid flow,” the “**controller instrument** typically includes **pressure sources** as well as appropriate **manifolds** for delivering the appropriate pressures to complementary ports on the microfluidic device.” (Ex. 1005 ¶¶96.) The system applies pneumatic (air) pressure to the fluids in the wells “without contacting the fluid within the reservoir 106.” (Ex. 1005 ¶¶90; Ex. 1003 ¶¶108; see also Ex. 1005 at Fig. 4B.)

Gandhi renders obvious the use of a gaskets to form a seal between the manifold and the wells of the plate to which the vacuum or pressure source. (Ex. 1003 ¶108.) It was of course known that, in order to deliver pressure to wells with a manifold, appropriate seals or gaskets were required. (See, e.g., Ex. 1007 ¶¶153, 202; Ex. 1003 ¶109). Further, Gandhi specifically discloses use of a gasket 314 to seal the microfluidic body 100 to the cover 200. (Ex. 1005 ¶87, see also ¶¶10, 57.) A skilled artisan would have found it obvious to use a gasket to seal the manifold to the wells in the Combined System in order to provide an air-tight seal. (Ex. 1003 ¶109.)

Quake taken in view of Gandhi thus renders obvious claims 3-4. (Ex. 1003 ¶110.)

4. Dependent Claim 5

Claim 5 depends from claim 1 and recites that “the vacuum or pressure source is a vacuum source configured to form a pressure sink at the output wells of the plate when the vacuum source is connected operatively to the output wells.”

As discussed above in connection with claim 1, Gandhi teaches applying vacuum to the wells (via the manifold) to drive the fluids. Gandhi states that either vacuum or positive pressure is applied to the ports to drive the fluids: “[t]he instrument then applies pressure/vacuum . . . directly to fluids, to move those fluids through the channels of the device in a controlled fashion.” (Ex. 1005 ¶96.)

Indeed, at the time of filing it was well known in the art fluids could be driven in microfluidic systems by positive pressure, negative pressure, or both. (Ex. 1007 ¶¶220-35; Ex. 1035 pp.1-5.) Consistent with the foregoing, the Combined System is adapted to apply negative pressure to the output well. (Ex. 1003 ¶111)

For the foregoing reasons one skilled in the art would have considered it obvious to use Gandhi's vacuum technique to drive fluids between the wells and through the microchannels of Quake's emulsion generator (as in the Combined System). (Ex. 1003 ¶¶112-113.)

5. Dependent Claim 6

Claim 6 depends from claim 1 and recites that “the vacuum or pressure source is a pressure source configured to be connected operatively to input wells of the plate.”

The pressure source of Gandhi is configured to be connected operatively to input wells. (Ex. 1003 ¶115.) As discussed above for claim 1[b], Gandhi teaches that the fluids are driven from the input wells to the output wells via a manifold that delivers positive pressure or creates a vacuum in the headspace above the reservoirs of fluid stored in both input wells and output wells. Gandhi explains that “for example, in the case of microfluidic systems employing pressure based fluid flow,” the “**controller instrument** typically includes **pressure sources** as well as appropriate **manifolds** for delivering the appropriate pressures to

complementary ports on the microfluidic device.” (Ex. 1005 ¶¶96.) Gandhi also teaches that either vacuum or positive pressure is applied to the ports to drive the fluids: “[t]he instrument then applies pressure/vacuum . . . directly to fluids, to move those fluids through the channels of the device in a controlled fashion.” (*Id.*)

As explained above for claim 1, one skilled in the art would have considered it obvious to use Gandhi’s technique to drive fluids from the wells and through the microchannels of Quake’s emulsion generator (as in the Combined System). (Ex. 1003 ¶116.)

6. Dependent Claim 8

Claim 8 depends from claim 1 and recites that the “plate includes a linear array of three or more emulsion production units.”

As discussed above in connection with the preamble of claim 1, Quake suggests parallelizing the emulsion production units. (Ex. 1003 ¶¶117-118; Ex. 1004 ¶¶79, 80, 293, 294.)

As also explained above, Gandhi teaches parallelizing microfluidic circuits in an array. (Ex. 1003 ¶120; Ex. 1005 ¶29.) *A person skilled in the art would have been strongly motivated to provide a linear array of four emulsion generators on the microfluidic plate of the Combined System.* (Ex. 1003 ¶121.)

The motivation to provide three or more emulsion generators on the same plate is discussed above in connection with claim 1. In the Combined System the array is

a linear, parallel array of four droplet generation units which corresponds to the input port arrangement provided in Gandhi's cover 206 shown below. (*Id.* ¶122.) For the same reasons discussed below in connection with claims 10-11 (incorporated herein by reference), it would have been obvious to use the smaller ports in columns 1, 2 and 3 as the input ports and the larger ports in column 4 and the output ports. (*Id.*) In the resulting Combined System, a linear array of four droplet generation units are aligned with columns A, B, C and D. (*Id.*)

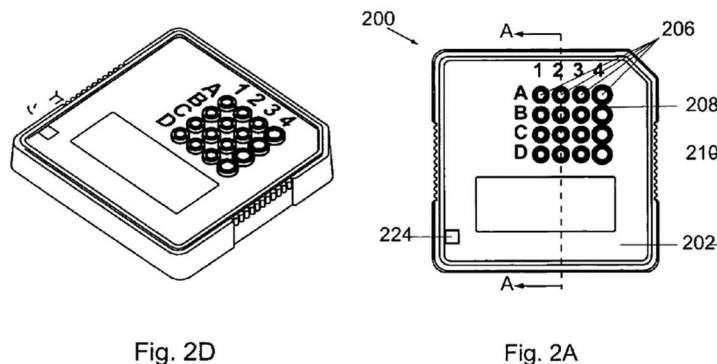


Fig. 2D

Fig. 2A

The Combined System thus meets the recitation of claim 8. (*Id.*)

7. Dependent Claim 9

Claim 9 depends from claim 1 and recites that the “wells of the plate are spaced according to a well spacing of a standard microplate.”

Gandhi teaches that the apertures/reservoirs are spaced according to a standard microplate. (Ex. 1003 ¶125; Ex. 1005 ¶¶79, 80, 93, 94.) As shown in Fig. 2 Gandhi, partially reproduced below, the input ports/reservoirs 106 are “provided in a gridded pattern to match a similar gridded pattern of ports on the

body structure of the device.” (Ex. 1005 ¶79.) “Typically, the gridded arrangement of apertures and ports (collectively, reservoirs) are positioned on regular centers, e.g., 9 mm, 4.5 mm etc., to match the spacing of typical multiwell plates, e.g., 96-well, 384-well, 1536-well, etc.” (*Id.*)

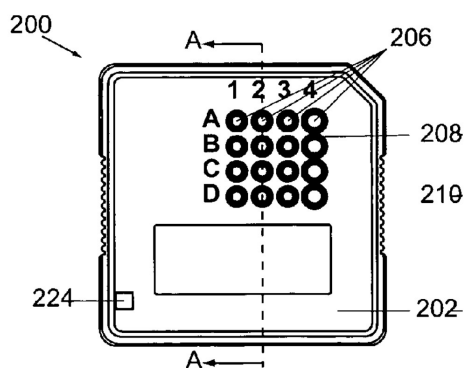


Fig. 2A

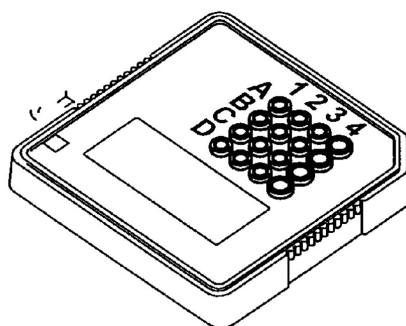


Fig. 2D

As discussed and depicted above in connection with claim 1, the Combined System retains this feature and thus meets the recitation of claim 9. (Ex. 1003 ¶125.)

8. Dependent Claims 10-11

Claim 10 depends from claim 1 and recites that the “second input well of each unit is disposed between the first input well and the output well of such unit.” Claim 11 depends from claim 10 and further recites that “the first input well, the second input well, and the output well of each unit are arranged along a same line.”

Gandhi renders obvious the arrangement in which a second input “port” or well is positioned between and along the same line as a first input well and an output well, thus meeting claims 10-11. As shown in Fig. 2 Gandhi, partially reproduced at right, the input ports/reservoirs 206 are provided in four linear arrays A, B, C and D, with the reservoirs in position 4 being larger than those in columns 1-3. (Ex. 1003 ¶¶127-128, 133.) In the context of the multiplexed and parallelized arrangements described by Gandhi (see discussion above in connection with claim 1), this arrangement of reservoirs would suggest to a skilled artisan that each of the parallel microfluidic circuits could be provided in its own row A/B/C/D with reservoirs 1, 2 and 3 being used for inputs and the larger reservoir 4 being used for output. (*Id.*)

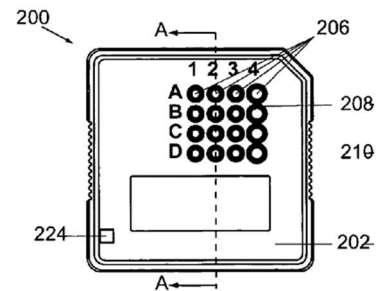


Fig. 2A

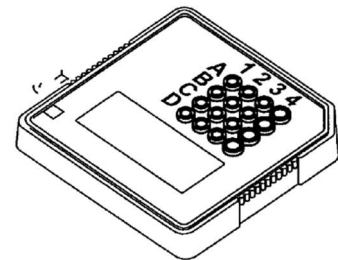
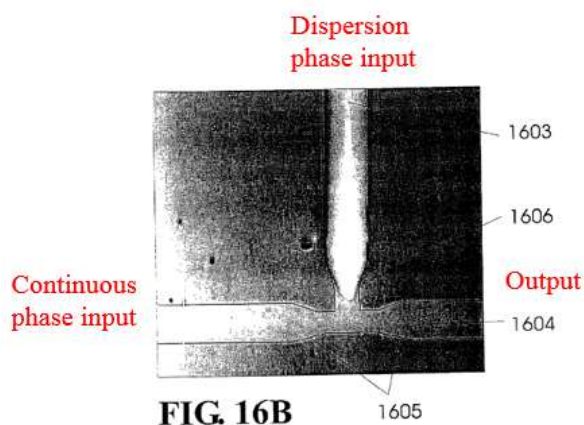


Fig. 2D

One skilled in the art would have been motivated to arrange the inputs to a microfluidic chip in a line, as suggested by Gandhi, such that the dispersion phase input (second well) was positioned between the first input (continuous phase) and the output well. (Ex. 1003 ¶¶129, 134.) Doing so would have facilitated the arrangement of the emulsion generators in the Combined System as suggested by Gandhi. (*Id.*) Given that the input and output wells or ports are substantially larger than the microchannels. (Ex. 1035 pp. 2-3, Ex. 1020 p. 3), the positioning of the input and output wells or ports is the primary factor controlling how closely the microfluidic circuits may be spaced. (*Id.*) Furthermore, in the system of Quake, the continuous phase is injected upstream of the dispersion phase and, accordingly, it is sensible to position the input for the dispersion phase (second input well) in between the input for the continuous phase (first input well) and the output well. (Ex. 1003 ¶¶129, 134.) This can be appreciated from the annotated version of Quake's Fig. 16A, in which the dispersion phase input is positioned between the continuous phase input and the emulsion generator output. For the most compact arrangement, a skilled in the art would locate the dispersion



phase well (second input well) between the continuous phase well (first input well) and the output well, as recited in claims 10-11. (*Id.*)

Thus, claim 10-11 are rendered obvious by Quake taken in view of Gandhi.

9. Dependent Claim 21

Claim 21 depends from claim 1 and recites that “at least one first input well of each emulsion production unit is not shared with other emulsion production units of the plate.”

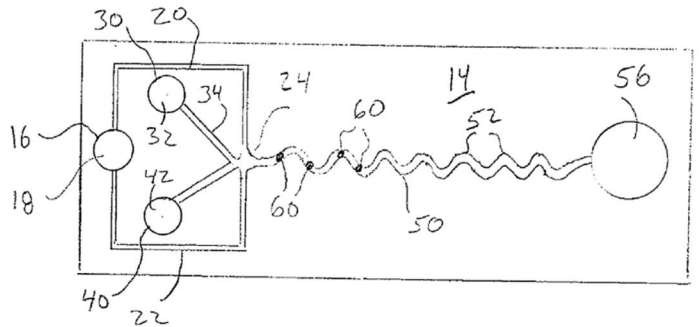
In the Combined System described for claim 1, each of the Quake’s parallelized droplet generators has separate input and output wells, in conformance with claim 21. (Ex. 1003 ¶¶137-139.) As discussed for claim 1, both Quake and Gandhi teach providing an array of parallel microfluidic circuits on a single chip. One skilled in the art would have considered it obvious to parallelize droplet generator of Quake as further suggested by Gandhi. (*Id.* ¶¶138-139.) In the Combined System, each droplet generator has its own input and outputs in order to achieve the multiplexed operation taught by Gandhi. (*Id.* ¶138.) The parallelized emulsion production units thus have input wells that are not shared, meeting claim 21. (*Id.*)

The combination of Quake and Gandhi thus renders obvious claim 21. (Ex. 1003 ¶139.)

B. Ground 2: Claim 7 Is Rendered Obvious by Quake in View of Gandhi and Further in View of Hsieh

Claim 7 depends from claim 1 and recites that the “wells of each unit include only one first input well configured to hold the continuous phase, and wherein a pair of channels of the set of channels of each unit extend separately from one another to the channel junction of such unit from the only one first input well.”

Hsieh’s channels extend separately to a droplet generation junction from one input inlet. Hsieh uses a “flow focusing” droplet generation approach (see Technical Background) in which opposing flows of oil pinch off droplets at a channel junction. Hsieh teaches that “substrate 14 includes a first inlet 16 that is configured to contain a carrier material 18 for the droplets 60.



Generally, the carrier material 18 may include an immiscible continuous phase material such as, for instance, oil.” (Ex. 1019 ¶22.) “The **first inlet 16 is fluidically coupled to two separate channels 20, 22 that terminate in a junction or droplet generation region 24.**” (*Id.*) “[T]he droplet generation region 24 includes a pinch-off area or region that ‘pinches-off’ droplets generated

from the streams flowing from the second inlet 30 and third inlet 40.” (*Id.*)

Accordingly, Hsieh teaches (a) an emulsion production unit having only one first inlet 16 to hold the continuous phase (oil) and (b) a pair of separate channels 20, 22 that extend separately to the junction 24 from the inlet 16.

A skilled artisan would have been strongly motivated to modify the microfluidic circuit of Quake to incorporate Hsieh’s inlet 16 and separate channels 20,22. (Ex. 1003 ¶143.) A skilled artisan would have seen at least two reasons to do so. (*Id.*)

First, it was known in the art that “[i]n comparison with formation of droplets at T-junctions [as in Quake], the flow-focusing mechanism [a cross shaped droplet generator] has higher emulsification efficiency and allows better control over droplet size and size distribution.” (Ex. 1008 ¶17; Ex. 1028 p. 11; Ex. 1003 ¶143.) A skilled artisan would thus understand that using the cross-shaped droplet generation junction described in Hsieh would increase efficiency and improve control over droplet formation. (*Id.*)

Second, it was known that flow focusing devices were an improvement over T-junction droplet generators in that they provide the “advantage in that an emulsion having a size smaller than the width of channels can be readily formed.” (Ex. 1010 ¶98). Droplets can be “in range of hundreds of nanometers,” which of course reduces the amount of reagents used in a chemical or biological reaction

performed in the droplet (relative to reactions performed in micrometer sized droplets). (Ex. 1011 p. 4; Ex. 1003 ¶143.)

A skilled artisan would thus have considered it obvious to use Hsieh's flow focusing droplet generator to improve a similar system (Quake's droplet generator) in the same way (providing enhanced size and distribution control). *KSR*, 550 U.S. at 415-421 (2007) (Ex. 1003 ¶143.)

In light of the level of skill of art described in Section V, which is incorporated by reference, a skilled artisan would have found it routine to make the foregoing combination (yielding the claimed limitation). (Ex. 1003 ¶144.)

C. Ground 3: Claims 12-17 and 19-20 are Rendered Obvious by Quake in View of Gandhi and further in view of Soane

Claims 12-17 and 19-20, which depend directly or indirectly from claim 1, are rendered obvious by Quake in view of Gandhi further in view of Soane.

Soane teaches “[m]ethods for fabricating enclosed microchannel structures.” (Ex. 1021 at Title.) “The microchannel structures are constructed of a base plate and a cover . . . [these microchannels] are enclosed by bonding the planar surfaces of the cover and the base plate together.” (*Id.* Abstract.) Shown in Fig. 6 (right) is “an assembled microchannel device 10 made

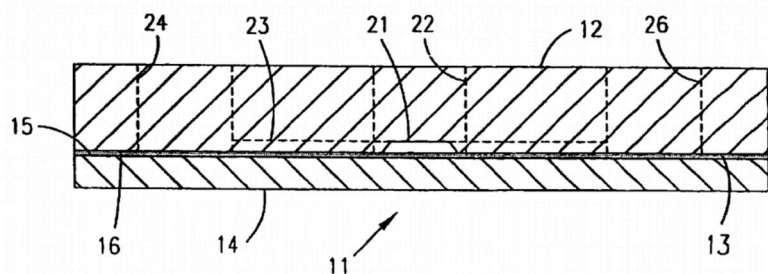


FIG. 6

by bonding a base plate 12 . . . to a cover 14.” (*Id.* 5:35-38.) “Base 12 has a planar surface 13 in which a microchannel structure is formed, including intersecting linear microchannels 21, 23. At the ends of the channels holes 22, 24, 26, 28 are bored through, to provide reservoirs for fluids to be moved within the channels.” (*Id.* 5:45-49.) “Cover 11 has a generally planar surface 15, apposable onto the channel-bearing surface 13 of base plate 12, onto which a thin film 16 of a bonding material is applied. Microchannel device 10 is formed by opposing the surfaces 13, 15 with the bonding material between them. As a result, the microchannels 21, 23 are closed, having three walls formed in the base plate surface 13, and a fourth wall formed by the cover 11, with the bonding material film 16 constituting the surface of the fourth microchannel wall.” (*Id.* 5:55-64.) Reservoirs formed as described above are open on a surface of the base plate opposite the surface apposed to the cover.” (*Id.* at 5:65-67.)

A skilled artisan would have been motivated to fabricate the Quake/Gandhi parallel droplet generation devices using Soane’s methods.

First, Soane specifically teaches that his techniques are applicable to making “microchannel structures . . . for chemical and biochemical assays,” the same application proposed by Quake. (Ex. 1004 ¶95; Ex. 1021 at 1:25-33.)

Second, Soane teaches that his injection-molding based methods “would be much more economical, and therefore desirable” than those based on other methods such

as photolithography. (Ex. 1021 at 2:7-10.) Soane explains that “microchannel structures . . . are typically produced by injection molding using various thermoplastic polymers. Injection molding is an economical process, and a variety of thermoplastics having good optical and mechanical properties can be processed by injection molding to form the desired structures.” (*Id.* at 1:27-38.)

Third, Soane demonstrated his methods created “polymeric microchannel structures . . . [w]ithout deformation, partial or complete clogging of the enclosed microchannels.” (*Id.* at 13:42-49.) Accordingly, Soane permits the realization of the benefits of injection molding without any disadvantage which would preclude its use in the context of a microfluidic assay. (Ex. 1003 ¶146.)

One skilled in the art would have had a reasonable expectation of success using the Soane method to fabricate Combined System of Quake and Gandhi.

(Ex. 1003 ¶147.) Soane provides various working examples which could be directly applied to fabricate the Quake/Gandhi system. (*Id.*) Moreover, the claims cover microfluidic systems using an arbitrarily low fluid pressure, which further simplifies the fabrication of the microfluidic plate. (*Id.*) In light of the level of skill of art described in Section V, which is incorporated by reference, a skilled artisan would have found it routine to make the foregoing combination and would fully expect that the combination (yielding the claimed limitation) would work as expected. (*Id.*)

1. Dependent Claim 12

Claim 12 depends from claim 1 and recites that “each channel of the set of channels of each unit extends to the channel junction of such unit from a bottom region of a well and not a top region of the well.”

Soane teaches channels that extend to a channel junction from a bottom region of a well. As shown in Fig. 6 (right), “[b]ase 12 has a planar surface 13 in which a microchannel structure is formed, including intersecting linear microchannels 21, 23. At the ends of the channels holes 22, 24, 26, 28 are bored through, to provide reservoirs for fluids to be moved within the channels.” (Ex. 5:45-49, *see also* 5:50-67.) As depicted

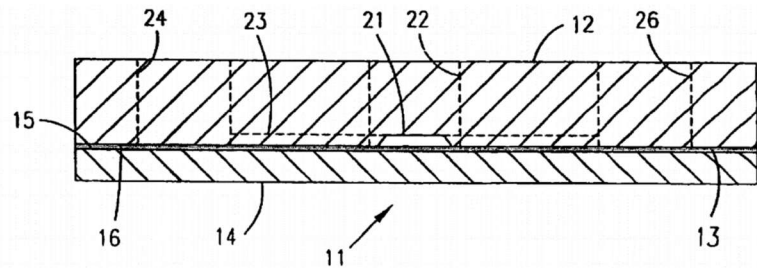


FIG. 6

in Fig. 6, these microchannels 21, 23 extend from the bottom (not top) regions of these reservoirs 22, 24, 26, thus meeting the recitations of claim 12. (Ex. 1003 ¶¶151, 153.)

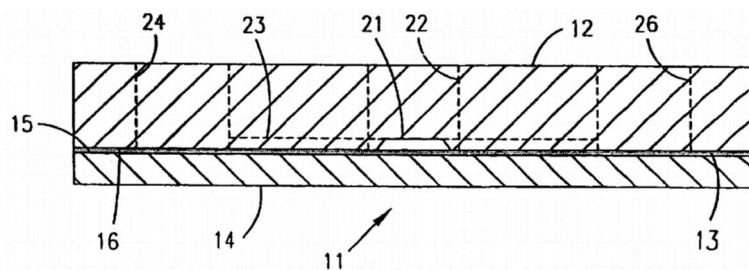
2. Dependent Claim 13

Claim 13 depends from claim 1 and recites that “wherein the plate includes an upper member attached to a lower member, wherein the upper member forms side walls of the wells of each unit and also forms top and side walls of each channel of the set of channels of each unit, and wherein the lower member extends

under each well and channel of the unit to form a bottom wall of such well and channel.”

Soane teaches an upper member (base plate 12) forms side walls of the wells (holes 24, 26) of each unit and also forms top and side walls of each channel (channels 21/23) and the lower member (film 16 or, alternatively, film 16 and cover 14) extending under each well and channel of the unit to form a bottom wall of such well and channel. (Ex. 1003 ¶155.) “Cover 11 has a

generally planar surface 15, apposable onto the channel-bearing surface 13 of base plate 12, onto which a thin film 16 of a bonding material is applied.



Microchannel device 10 is formed by apposing the surfaces 13, 15 with the bonding material between them.” (Ex. 1021 at 5:55-60.) “As a result, the microchannels 21, 23 are closed, having **three walls formed in the base plate surface 13, and a fourth wall formed by the cover 11, with the bonding material film constituting the surface of the fourth microchannel wall.**” (Ex. 1021 5:55-64, see also Examples 1-8 at 9:65-13:7.) The Soane structure thus meets claim 13. (Ex. 1003 ¶¶155, 157.)

Quake also teaches the recited structure. As explained above for claim 1, Quake teaches the channels and droplet generation or “cross flow” junctions are formed via a molding process in middle layer of the chip. (Ex. 1004 ¶¶275-285.) Quake’s top layer and middle layer is the recited “upper member” and Quake’s bottom layer is the “lower member” that extends under each well and channel of the unit to form a bottom wall of such well and channel. (Ex. 1003 ¶156.)

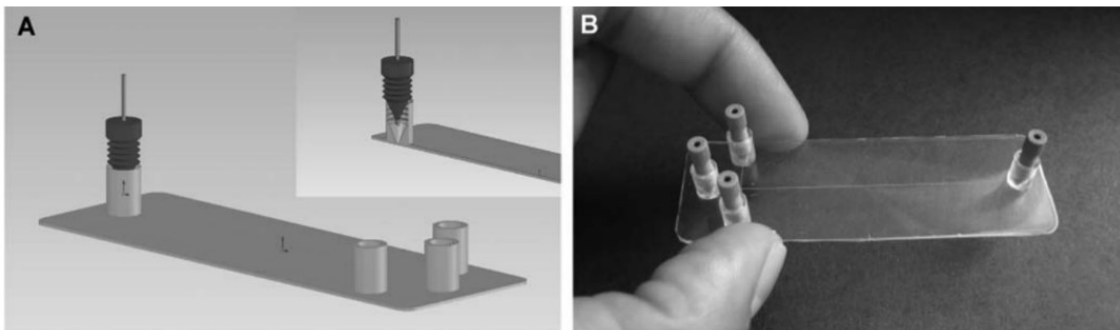
3. Dependent Claim 14

Claims 14 depends from claims 1 and 13 and recites that “the upper member is formed of an injection-molded polymer.”

The specification does not identify any difficulty or unexpected result associated with fabrication by injection molding. To the contrary, the specification states that the upper member “may be manufactured by any suitable method, such as by injection molding a thermoplastic material.” (Ex. 1001 at 60:28-29.)

Soane teaches an upper member (base plate 12) formed of an injection molded polymer. “Microchannel structures . . . are typically produced by injection molding using various thermoplastic polymers.” (Ex. 1021 at 1:27-35.) “[I]njection molding techniques were used to prepare a microchannel base plate of an acrylic polymer (AtoHaas, PlexiglasTMV825NA-100).” (Ex. 1021 at 10:36-40, see also 11:27-31, 12:7-13:7.) The Soane base plate 12 thus meets claim 14. (Ex. 1003 ¶¶158-159.)

A skilled artisan would have considered it routine to fabricate the body 100 and cover 200 of the Combined System in a single piece by injection molding at the time of filing. (Ex. 1003 ¶¶158-159.) Soane provides various working examples which could be directly applied to fabricate the Quake/Gandhi system. (*Id.*) Such structures were commonly integrally formed by injection molding at the time of filing. (Ex. 1017 ¶72; , see also Ex. 1018 ¶69; Ex. 1040 p. 12, Ex. 1003 ¶158.) For instance, in 2008 BioScale filed an application directed to a microfluidic plate with input wells 332 and output wells 342, and explained that the entire body could be formed by injection molding. (Ex. 1017 ¶72; *see also* Ex. 1018 at ¶69.) In 2006 Mair explained that the microfluidic chip shown below (including the upwardly extending inlets) was integrally molded from a single piece of plastic (excluding, of course, the threaded inserts). (Ex. 1050 p. 6, Fig. 5; Ex. 1051; Ex. 1017 ¶72; Ex. 1018 ¶69.)



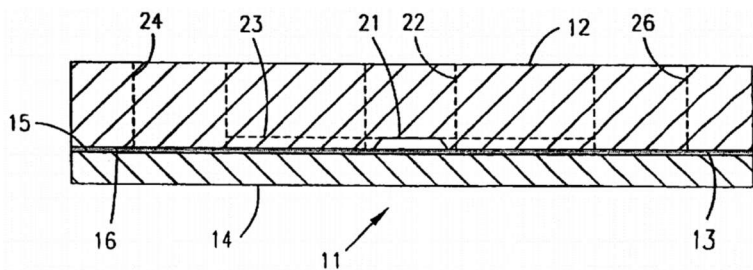
In light of the level of skill of art (including that described in Section V, which is incorporated by reference) a skilled artisan would have found it routine to

make the foregoing combination and would fully expect that the combination (yielding the claimed limitation) would work as expected. (Ex. 1003 ¶159.)

4. Dependent Claim 15

Claims 15 depends from claim 14 and recites that “each of the upper and lower members is formed by a respective, continuous piece of material.”

Soane discloses that each of the base plate 12 (the upper member) and the bonding material film 16 (the lower member) is formed by a continuous piece of material. “In general, the microchannel structures according to the invention are constructed of two parts, each having at least one generally planar surface, sealed together so that the generally planar surfaces are apposed. One part is referred to as a base plate, and the other is referred to as a cover.” (Ex.



1021 at 4:59-66.) The base plate 12 is formed by injection molding, which results in a plate made from a single, continuous piece of material. (Ex. 1021 at 10:37-40, see also 11:27-31, 12:7-13:7; Ex. 1003 ¶160.) “The cover [11] may be a more or less rigid plate, or it may be a film . . . [and] may be fabricated from a single material or be fabricated as a composite material.” (Ex. 1021 at 4:66-5:7.) In Example 2, for instance, the cover 11 is a continuous Mylar film coated with an

adhesive such that the adhesive layer may be considered the lower member. (*Id.* at 10:29-57; see also 5:55-64.) In Fig. 6, the lower member is depicted as “bonding material film 16.” (*Id.* at 5:55-64, 6:8-12.) The base plate 12 and bonding material film 16 of Soane are each made of a continuous piece of material and thus meet claim 15. (Ex. 1003 ¶161.)

5. Dependent Claim 16

Claim 16 depends from claim 1 and recites “wherein the plate includes an upper member attached to a lower member, wherein the upper member includes upper and lower surfaces, wherein the upper member defines through-holes corresponding to the wells of each unit and extending from the upper surface to the lower surface and also defines grooves corresponding to the set of channels of each unit and formed in the lower surface, and wherein the lower member is attached to the upper member at the lower surface to form a bottom wall below each through-hole and groove.”

Soane includes an upper member (base plate 12) having an upper surface defining through-holes (22, 24, 26) corresponding to the wells extending to its lower surface which has grooves (21,23) corresponding to the set of channels, and a

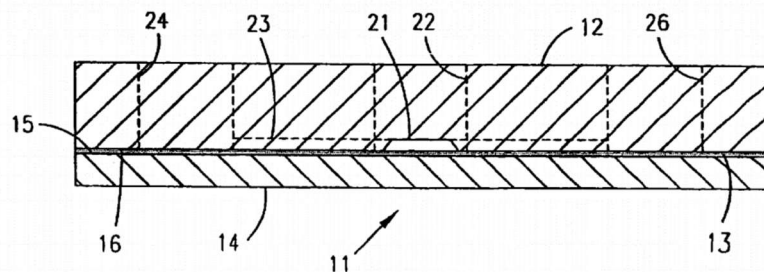


FIG. 6

lower member (film 16) that forms a bottom wall below each through-hole and groove. (Ex. 1003 ¶164.) “Base 12 has a planar surface 13 in which a microchannel structure is formed, including intersecting linear microchannel 21, 23. At the ends of the channels holes 22, 24, 26, 28 are bored through, to provide reservoirs for fluids to be moved within the channels.” (Ex. 1021 at 5:45-49.) “Cover 11 has a generally planar surface 15, appposable onto the channel-bearing surface 13 of base plate 12, onto which a thin film 16 of a bonding material is applied. Microchannel device 10 is formed by apposing the surfaces 13, 15 with the bonding material between them. As a result, the microchannels 21, 23 are closed, having three walls formed in the base plate surface 13, and a fourth wall formed by the cover 11, with the bonding material film constituting the surface of the fourth microchannel wall.” (*Id.* 5:45-64, see also Examples 1-8 at 9:64-13:7.) The base plate 12 and bonding material film 16 of Soane thus meet claim 16. (Ex. 1003 ¶¶164-165.)

6. Dependent Claim 17

Claim 17 depends from claim 16 and recites that “the lower member is a sheet of material that is substantially thinner than the upper member.”

Soane teaches that the lower member (film 16 or, alternatively, film 16 and cover 14) can be a sheet of material that is substantially thinner than the upper member (base 12). In Fig. 5-6 of Soane, the bonding material film (lower

member) is depicted as being substantially thinner than the base plate 12. (Ex. 1021 at 4:47- 6:30; Ex. 1003 ¶167.)

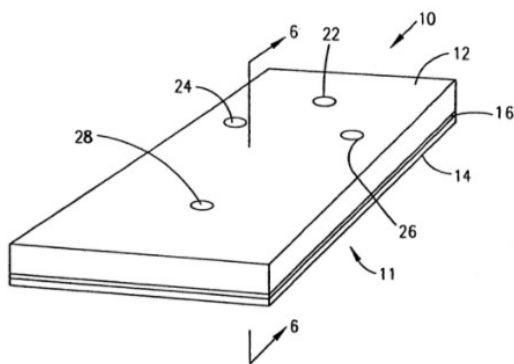


FIG. 5

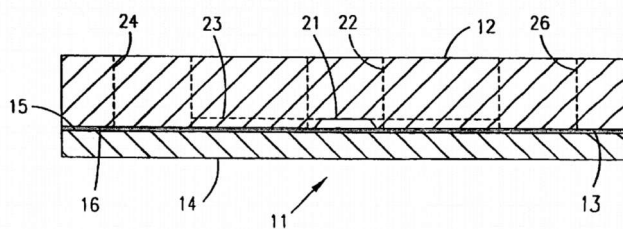


FIG. 6

As to the lower member (bonding material 16) Soane teaches that “[i]n practice, generally, the bonding material usually is applied to a thickness at least about 0.5 μm , in some embodiments at least about 1 μm , and in still other embodiments at least about 2 μm .” (Ex. 1021 at 6:26-30.) As to the base plate 12 into which the channels are formed, Soane teaches that “the thickness of the polymeric material [in which the channels are formed] will be at least about 1 μm , usually at least about 5 μm , and more usually at least about 50 μm , where the thickness may be as great as 5 mm or greater.” (Ex. 1021 at 4:47-51.) Soane thus teaches that the bonding material 16 is usually on the order of 1 μm whereas the base plate 12 is usually on the order of at least 50 μm .

In the alternative, if bonding material 16 and cover 14 are together considered the lower member, Example 2 teaches that the cover 14 may be a 2 mil

(50.8 micron) sheet of Mylar. (Ex. 1021 at 10:45-50.) The lower member would thus be 51 μm and Soane teaches that the base plate 12 (upper member) would be 5 mm (5,000 μm) or greater.

Under either approach, Soane thus meets the recitations of claim 17.

7. Dependent Claim 19

Claim 19 depends from claim 1 and recites that “the plate includes an upper member attached to a lower member to form an array of emulsion production units each configured to produce a separate emulsion, and wherein the lower member has an upper surface that is flat and that abuts a lower surface of the upper member to form a bottom wall of openings formed in the lower surface and corresponding to the wells and the channels of each unit.”

This claim recites features duplicative to those recited in claims 13 and 16 except that 19 further recites that each emulsion production unit is “configured to produce a separate emulsion.” The discussion of claims 13 and 16 is incorporated by reference.

In the Combined System described in connection with claim 1, each of the Quake’s parallelized droplet generators is “configured to produce a separate emulsion.” (Ex. 1003 ¶¶169-172.) As discussed in connection with claim 1, As discussed for claim 1, both Quake and Gandhi teach providing an array of parallel microfluidic circuits on a single chip. One skilled in the art would have considered

it obvious to parallelize droplet generator of Quake as further suggested by Gandhi. (*Id.* ¶¶62, 65.) In the Combined System, each droplet generator has its own input and outputs in order to achieve the multiplexed operation taught by Gandhi. (*Id.* ¶65.) The parallelized emulsion production units thus produce separate emulsions, meeting claim 19. (*Id.* ¶173.)

8. Dependent Claim 20

Claim 20 depends from claims 1 and 19 and recites that “each of the upper and lower members is formed by a respective, continuous piece of material.”

The discussion of claim 15 is incorporated herein by reference. As explained therein, it would have been obvious to fabricate the upper and lower members of a respective, continuous piece of material.

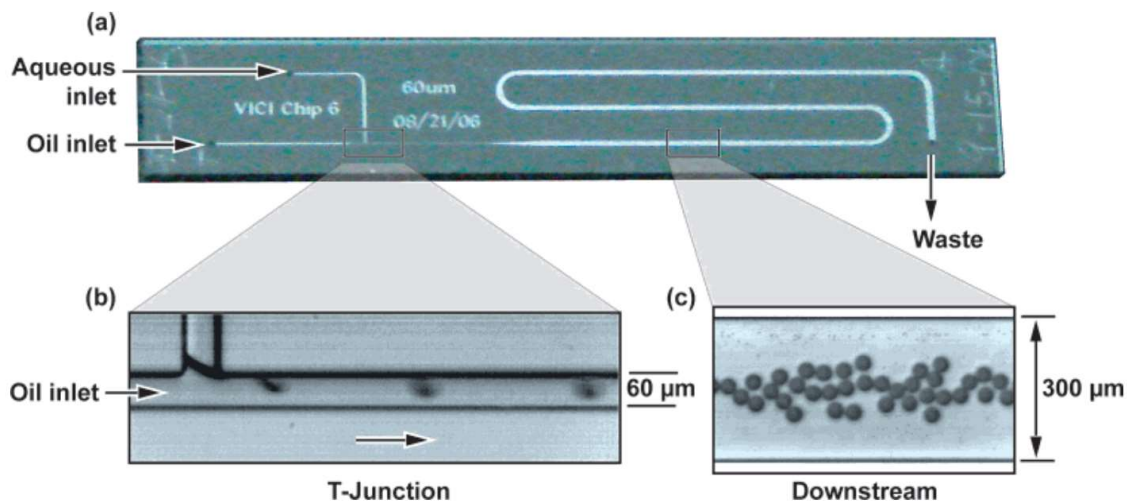
For the foregoing reasons claims 12-17 and 19-20 are thus rendered obvious when Quake in view of Gandhi are taken further in view of Soane. (Ex. 1003 ¶¶145-175.)

D. Ground 4: Claim 18 Is Rendered Obvious by Quake in View of Gandhi and Further in View of Beer

Claim 18 depends from claim 1 and recites that “the first input well of a unit contains a nonaqueous continuous phase, wherein the second input well of such unit contains an aqueous phase configured for PCR amplification, and wherein the

output well of such unit contains an emulsion including droplets of the aqueous phase disposed in the nonaqueous continuous phase.”

Beer’s PCR method as performed on the Quake/Gandhi device meets claim 18. Beer teaches performing PCR in droplets formed with microfluidic emulsion generators. “To generate **water-in-oil (w/o) microdroplets**, we utilized a chip (Figure 1a) with hydrophobic channel surfaces and a shearing cross-flow T junction.” (Ex. 1032 p. 2.) “Two infusion syringe pumps (KD Scientific) independently drove the **aqueous and oil (M8662, Sigma-Aldrich) streams** at predetermined flow rates of 2.3 and 0.3 mL/h, respectively.” (*Id.*) “A **mixture of nucleic acid sample and PCR reagents was injected into the aqueous stream** and delivered to the chip.” (*Id.*)



When the Combined System is used to perform PCR as taught by Beer the Combined System meets claim 18. (Ex. 1003 ¶¶177-178.)) Oil is added to the first input well, aqueous PCR reagents are added to the second input well, and the

resulting emulsion is collected in the output well of the Combined System, thus meeting claim 18. (*Id.*)

One skilled in the art would have been motivated to use the Quake/Gandhi system to perform PCR as taught by Beer. Quake specifically suggests that PCR could be performed on his microfluidic chips (Ex. 1004 ¶80), which is an express suggestion to modify the Quake device as taught by other art relating to microfluidic PCR. (Ex. 1003 ¶178.) Making the proposed modification would, as taught by Beer, provide the high-throughput system of Quake/Gandhi system “a level of control over microdroplet compartmentalization not achievable by ‘shake-and-bake’ methods.” (Ex. 1032 p. 2; Ex. 1003 ¶178.) Beer also teaches that use of his method will allow “detection of a single copy of nucleic acid at significantly reduced cycle thresholds and will benefit from the high-throughput and low reagent usage architecture that on-chip processes provide.” Making the proposed modification thus would provide this functionality on an even higher throughput, parallelized platform. (Ex. 1003 ¶178.) Accordingly, a skilled artisan would have been motivated to use the technique taught in Beer (PCR in picoliter sized droplets) to improve a similar device (the Quake/Gandhi device) in the same way (providing improved control and detection). *KSR*, 550 U.S. at 415-421 (2007) (Ex. 1003 ¶178.)

In light of the level of skill of art described in Section V, which is incorporated by reference, a skilled artisan would have found it routine to make the foregoing combination, yielding the claimed limitation. (Ex. 1003 ¶179.)

IX. SECONDARY CONSIDERATIONS OF NONOBVIOUSNESS CANNOT OVERCOME THE OBVIOUSNESS GROUNDS

Petitioner is unaware of any objective indicia of nonobviousness, let alone any that could overcome the obviousness grounds set forth above. Petitioner is not aware of any industry praise of the subject matter recited in the challenged claims. Neither Patent Owner's website nor its complaint in *Bio-Rad Laboratories, Inc., et al. v. 10X Genomics, Inc.*, Case No. 3:17-cv-4339 (N.D. Cal.) assert that the '392 patent was praised in the industry. Nor does Patent Owner therein allege commercial success, copying, failure of others, unexpected results, long-felt need or industry acquiescence, much less attempt to establish any nexus between such objective indicia and any novel aspect of the claimed subject matter. *Novartis AG v. Torrent Pharmaceuticals Ltd.*, 853 F. 3d 1316, 1331 (Fed.Cir. 2017).

X. CONCLUSION

For the foregoing reasons, claims 1-21 of the '392 patent recite subject matter that would have been considered obvious by a skilled artisan at the time of filing. Petitioner requests institution of an *inter partes* review to cancel those claims.

Respectfully submitted,

Date: December 14, 2017

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WORD COUNT CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing petition for *inter partes* review complies with 37 C.F.R. § 42.24 because it contains 13,759 words as measured by the word processing software used to prepare the document, including footnotes and the reproduction of the claim language but excluding the table of contents, mandatory notices under §42.8, certificate of service or word count, and appendix of exhibits.

Respectfully submitted,

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CERTIFICATE OF SERVICE

The undersigned certifies service pursuant to 37 C.F.R. §§42.6(e) and 42.105(b) on the Patent Owner by USPS Priority Mail Express of a copy of this Petition for *Inter Partes* Review and supporting materials at the correspondence address of record for the '392 patent to:

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Dated: December 14, 2017

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