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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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10X GENOMICS, INC.

Petitioner,

v.

BIO-RAD LABORATORIES, INC.

Patent Owner.

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IPR2018-00301

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

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PETITION FOR *INTER PARTES* REVIEW

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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.

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 petitions challenging claims of the '392 patent (IPR2018-00300 and IPR2018-00302). 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 (Reg. No. 42,484) and Sally Brashears (Reg. No. 38,087) of Convergent Law Group.

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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>U.S. Published Application 2002/0058332 to Quake et al.</u>

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 2008/0056948 to Dale et al.

U.S. Published Application 2008/0056948 to Dale et al. (“Dale,” Ex. 1005), filed on September 5, 2007, and published on Mar. 6, 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. Dale was not before the Examiner during prosecution.

3. U.S. Patent No. 6,915,679 to Chien et al. (“Chien I”)

U.S. Patent No. 6,915,679 to Chien et al. (“Chien I,” Ex. 1006), filed on February 23, 2001, and published on July 12, 2005, 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. Chien was not before the Examiner during prosecution.

4. Chien et al., *Multiport flow-control system for lab-on-a-chip microfluidic devices*, Fresenius J Anal Chem (2001) 371:106–111 ("Chien II")

Chien et al., *Multiport flow-control system for lab-on-a-chip microfluidic devices*, Fresenius J Anal Chem (2001) 371 :106–111 ("Chien II," Ex. 1035), 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. Chien II is the journal article corresponding to Chien I and is cited on the face of that patent. (*See* Ex. 1006 at "Other Publications".) Chien's publication information is attached as Ex. 1030, which is self-authenticating and subject to FRE 803(6), 803 (17) and 807.[1] Chien II was not before the Examiner during prosecution.

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[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.)

5. 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.

6. U.S. Published Application 2005/0266582 to Modlin et al.

U.S. Published Application 2005/0266582 to Modlin et al. ("Modlin," Ex. 1007), filed on April 14, 2005, and published on December 1, 2005, is prior art to the '392 patent under 35 U.S.C. §102(b) and (e) because it was published and filed, respectively, before the earliest claimed priority date, September 23, 2008. Modlin was applied by Examiner only to two dependent claims for its disclosure of a manifold sealably mounted to a chip with a gasket. (*See* Section VI.B.)

7. 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.

8. 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 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.

9. 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 ¶56.) Additional training or study could substitute for work experience and additional work experience or training could substitute for formal education. *Id.*

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.

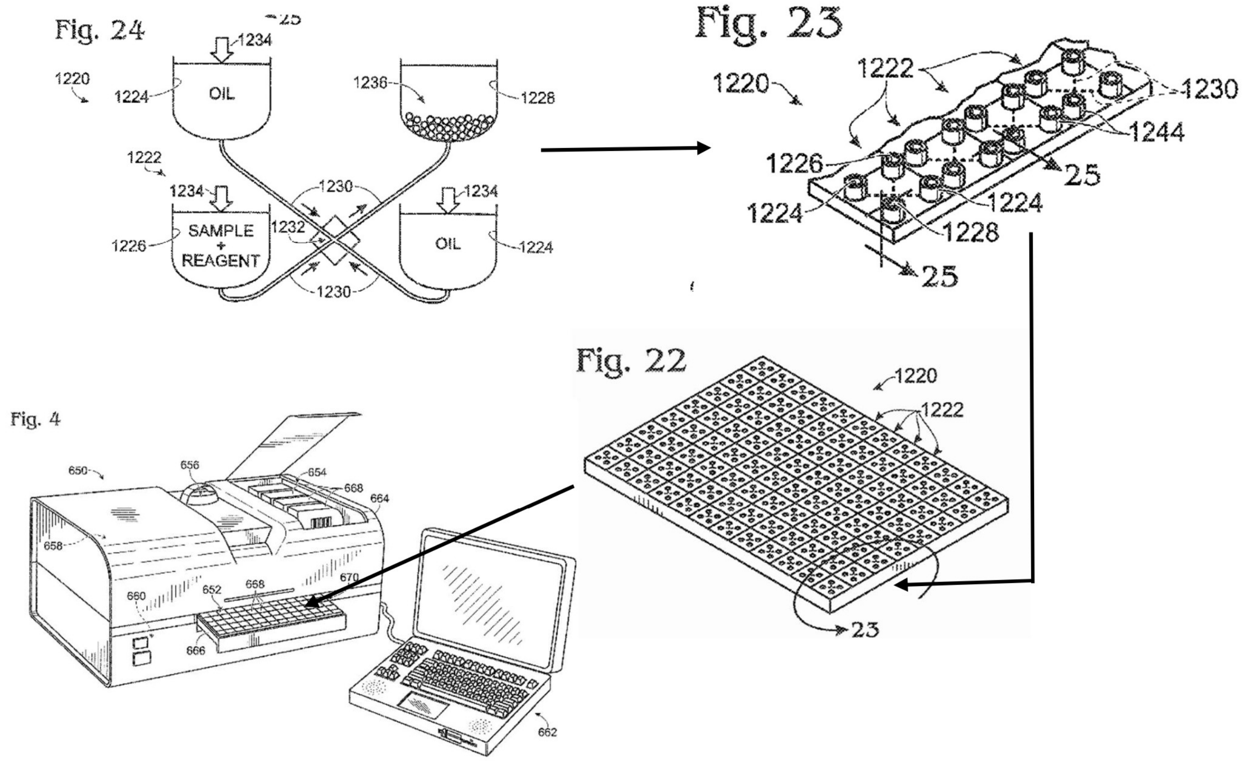


Fig. 4 shows an instrument 650 receives plate 670 that includes reservoirs or wells 668 and a droplet generator. (*Id.* at 20:16-40.) Fig. 22 shows the plate and droplet generators. (*Id.* at 35:24-54.) Figure 23 is a close-up of area 23 of Fig. 22. (*Id.*) Figure 24 illustrates the four-port droplet 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. 1049 at claims.)

Because each of the prior art references presented herein 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, 10-11, and 21 Are Rendered Obvious by Quake in View of Dale, Chien I, and Chien II

Claims 1-6, 8, 10-11, and 21 are rendered obvious by Quake in view of Dale, Chien I, and Chien II. 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.) Dale, Chien I and Chien II were 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, Dale and Chien.

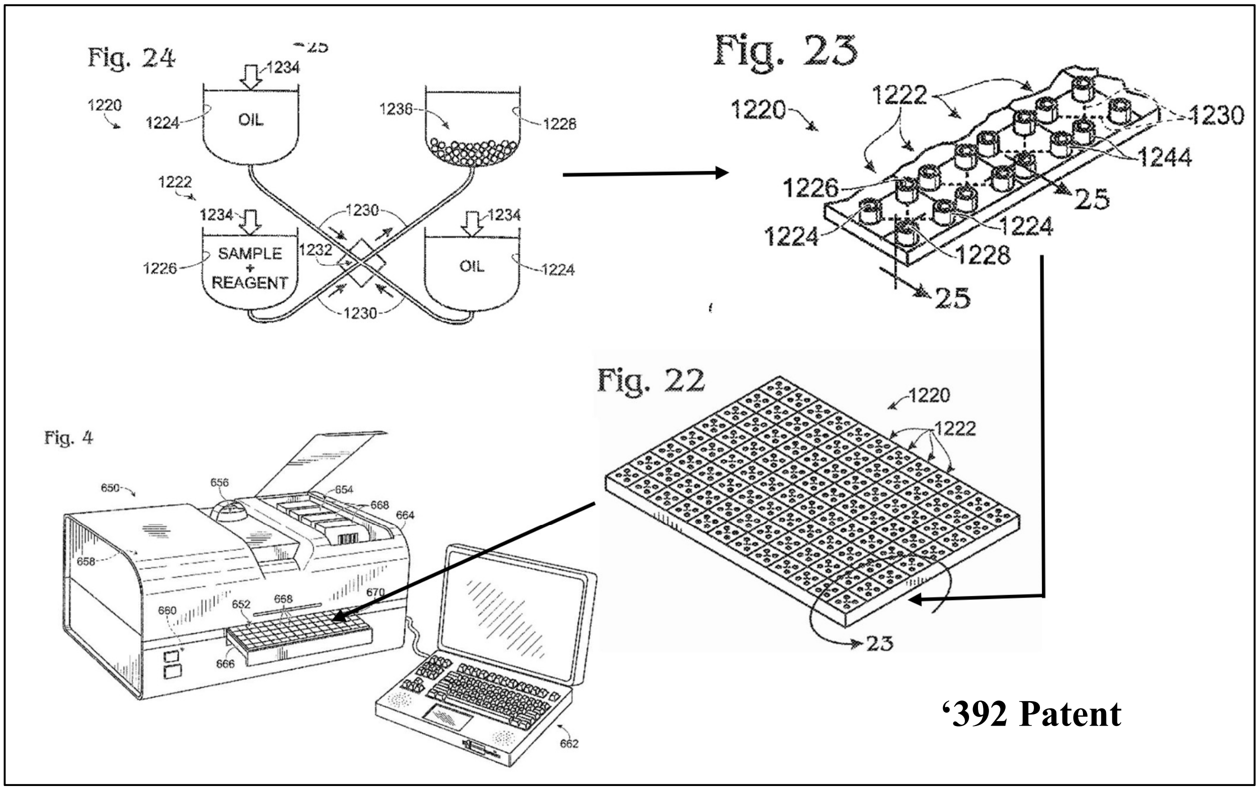


Fig. 24
OIL
SAMPLE + REAGENT
OIL
Fig. 23
Fig. 22
Fig. 4
'392 Patent

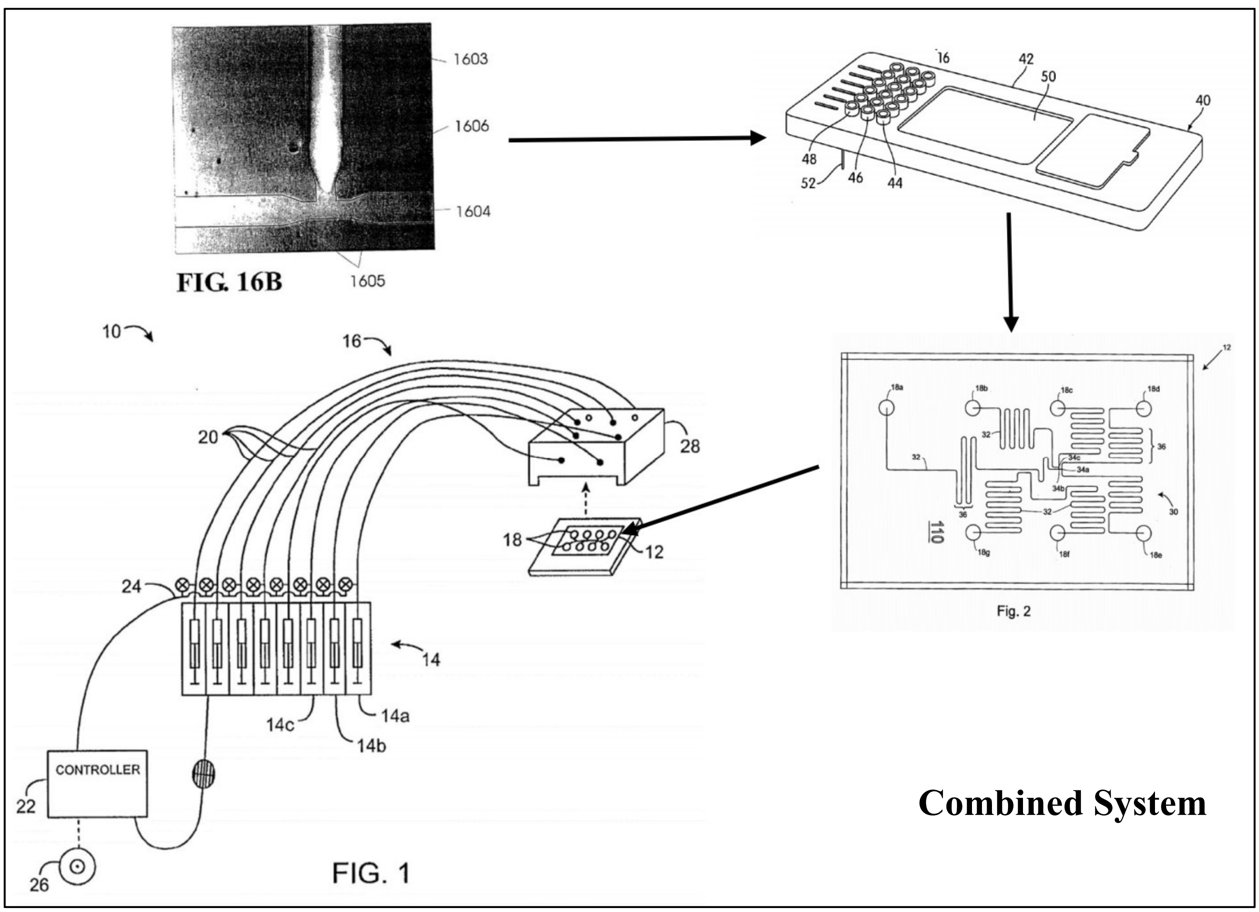


FIG. 16B
CONTROLLER
FIG. 1
Fig. 2
Combined System

1. <u>Independent Claim 1</u>

Quake in view of Dale, Chien I, and Chien II renders claim 1 obvious.

Quake discloses microfluidic emulsion generators. (Ex. 1003 ¶58.) 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 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.

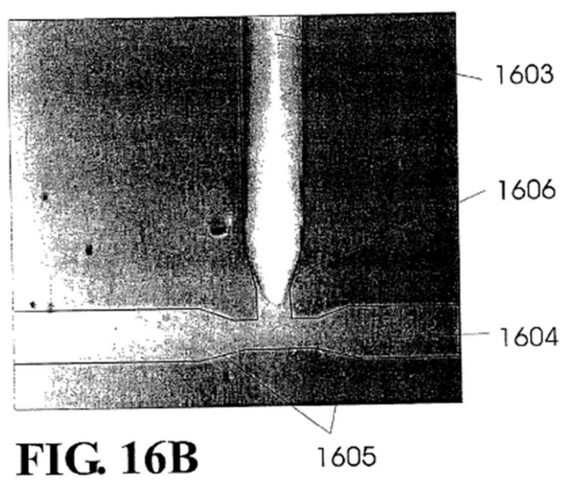
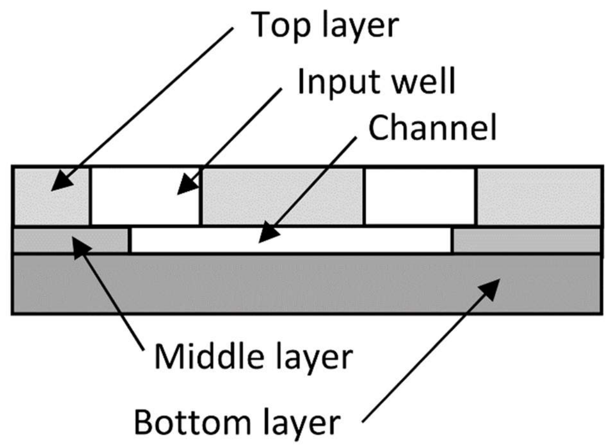


FIG. 16B

Quake's Examples 10-12 teach that the emulsion generators are provided on a microfluidic chip or plate. (Ex. 1003 ¶59.) 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 ¶60; 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**." (Ex. 1004 ¶79.)[2] Quake further explains that "[t]his

[2] Throughout this petition all emphasis is added unless otherwise stated.

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 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. (Ex. 1003 ¶60.)

Dale also teaches parallelizing microfluidic circuits in an array. (Ex. 1003 ¶61.) Dale teaches an array of **parallelized** microfluidic reactors "whereby discrete assays are performed within droplets of DNA or other sample material contained within the micro-channels." (Ex. 1005 ¶39, *see also* ¶¶40-44 ("[t]his arrangement allows increased parallel processing throughput.")) The droplet microfluidic reactor of Dale is shown in Figs. 1a and 3, below:

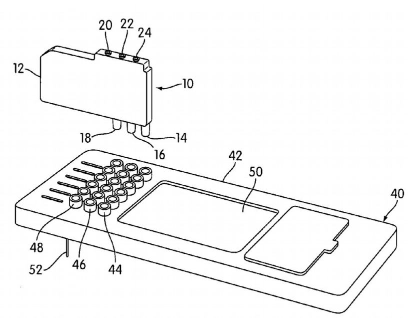


FIG. 1a

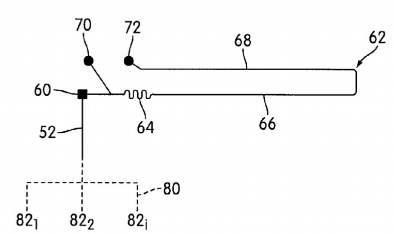


FIG. 3

The Dale system includes a microfluidic chip 40 with access ports 44, 46, and 48 that are in communication with micro-channels 62 formed within the microfluidic chip 40. (*Id.* at ¶¶32-33, 35.) The micro-channel 62 "is associated with each column of access ports within the rows 44, 46, 48 of access ports of micro-fluidic chip 40. Accordingly, in the embodiment shown in FIG. 1a, micro-fluidic chip 40 would **include six micro-channels, one associated with each of the six columns of access ports**." (*Id*. ¶35.) Fluids are drawn through the system by applying a vacuum at port 24. (*Id*. ¶¶29, 48, 50-52.) Dale thus teaches a microfluidic chip 40 having a linear array of parallel microfluidic channels 62 in which droplet reactions such as PCR are performed. (Ex. 1003 ¶61.)

Quake taken in view of Dale renders obvious the provision of multiple droplet generators on a single microfluidic chip, for multiple reasons*.** (Ex. 1003 ¶62.) ***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. (Ex. 1003 ¶¶22-31.) Dale, Kumacheva, Nisisako, Karnik, and Chu all explain that parallelizing microfluidic circuits substantially increases throughput. (Ex. 1005 ¶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 ¶62.)

Second, Quake specifically suggests 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 ¶¶60, 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.) A skilled artisan would have been motivated to use the technique taught in Dale (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 ¶¶60-65.)

It was thus obvious that multiple instances of Quake's droplet generator should be disposed on a single chip as depicted below to increase throughput and enable multiplexed reactions. (Ex. 1003 ¶66.)

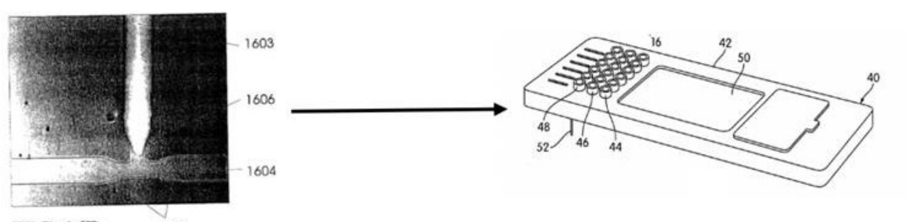


FIG. 16B

Chien I and Chien II teach that, to drive fluids through microfluidic circuits, it is preferred to mount the chip to a pneumatic manifold that provides air pressure to drive the fluids between the wells. (Ex. 1003 ¶67.)

Chien II is an article that describes the same embodiment as that shown in Figs. 1-8 of Chien I. *(Id.)* Chien II is relied upon in addition to Chien I primarily because Chien II includes additional detail concerning i) the benefits of using pressurized gas to drive the fluids positioned in the plate wells, and ii) certain claimed features such as gaskets (which are instead described in Chien I more generically as seals). (*Id.*)

Chien II explains that the flow of fluids can be controlled more precisely on microfluidic chips such as those described in Quake via a pressure delivery system that "controls the pressure of a compressible gas at the fluid–air interface directly on top of the wells of the microfluidic device." (Ex. 1035 p. 1, see also Ex. 1006 8:24-10:33.) Chien II explains that this is superior to the use of external pumps (as used Quake) or the "incorporation of mechanical micropumps and valves within a microfluidic device." (*Id.*, *see also* Ex. 1006 at 1:39-47.) Chien II teaches the use of a compressed gas to drive the fluids in the wells avoids the "irreproducible and erratic results" yielded by off-chip and on-chip fluidic pumps. (*Id.*)

Chien I and Chien II describe the same microfluidic system to drive fluids through the wells of the device. (Ex. 1006 at 8:24-10:33, Ex. 1035 pp. 1-4; Ex. 1003 ¶68.) For convenience, the following discussion will refer preferentially to the disclosure in the patent (Chien I), although Petitioner expressly relies on both references. A bank of pumps 14 supply compressed gas to the pressure manifold 28, the openings of which are sealably mated to the microfluidic chip 12. (Ex. 1006 9:42-10:56; Ex. 1035 pp. 1-3.) The pumps provide positive pressure or vacuum to headspace above the fluids in reservoirs 18 on the microfluidic chip 12 in order to drive the fluids between and among the wells as desired. (Ex. 1006 11:65-13:5; Ex. 1035 pp. 3-6.)

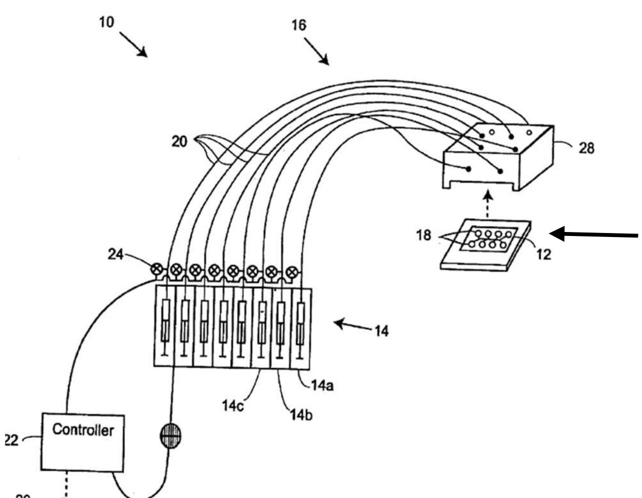


Fig. 1

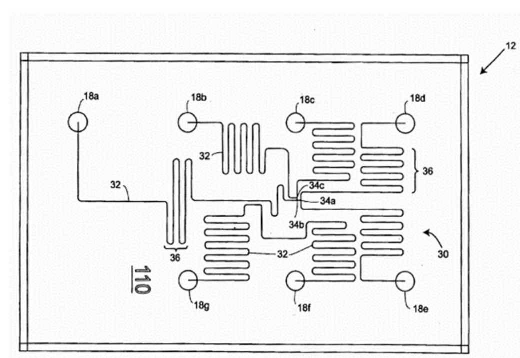
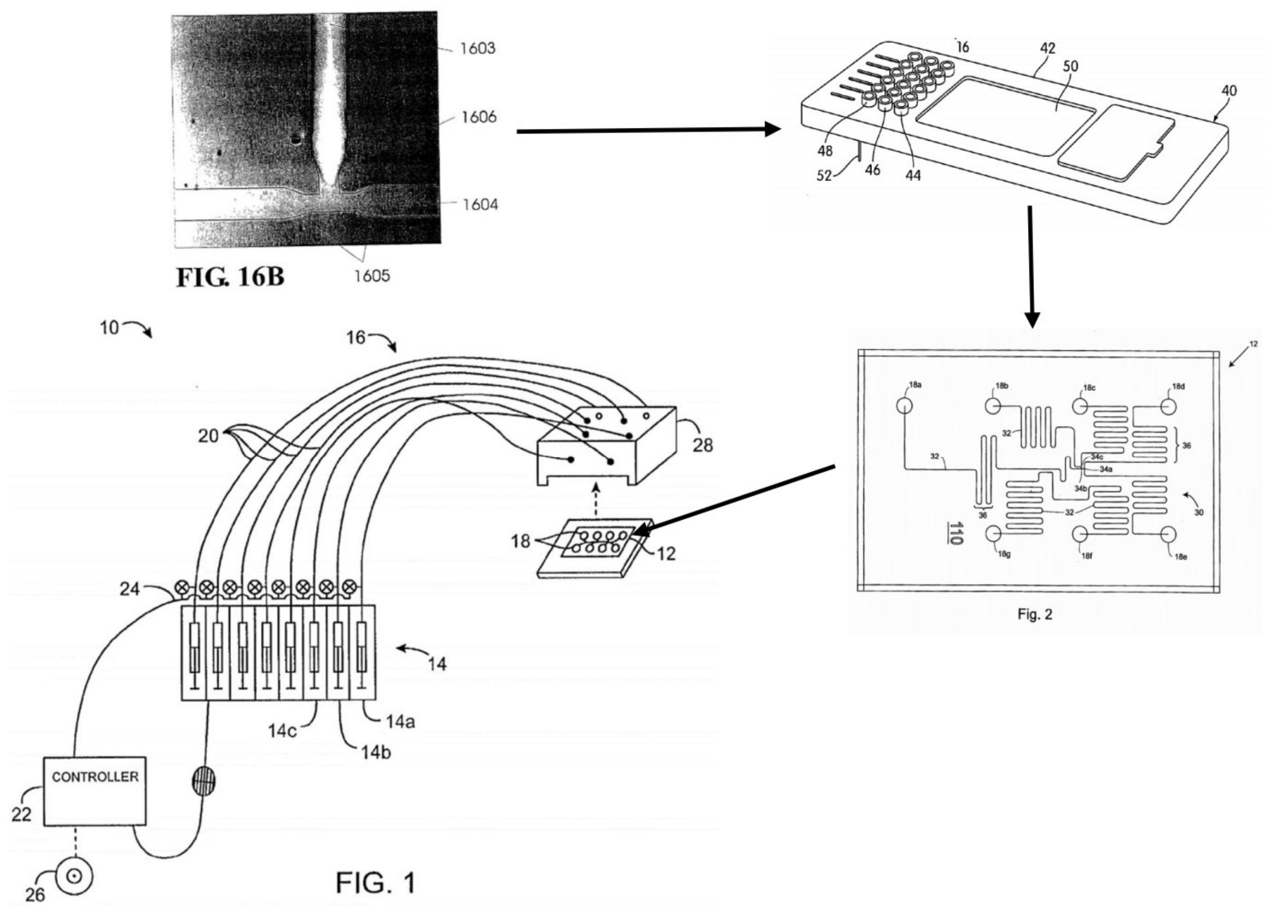


Fig. 2

In light of Chien's teaching that pressurized gas should be used to control the flow of fluids among wells on a microfluidic fluidic device, a skilled artisan would have considered it obvious to use Chien's system to drive the fluids

through a parallelized array of Quake's emulsion generators. (Ex. 1003 ¶69). As discussed above, the benefits of parallelization of microfluidic circuits were well known at the time of filing and discussed in both Quake and Dale. (*Id.*) Chien II explains that the use of a compressed gas to drive the fluids in the wells provides more precise control and more consistent and reproducible results. (Ex. 1035 p. 1, 3.) The resulting system, depicted below, is hereafter referred to as the Combined System.



The Combined System has input wells and output wells. (Ex. 1003 ¶70.) Chien I describes a microfluidic device 12 that "includes an array of **reservoirs 18a, 18b**, . . . coupled together by microscale channels defining a microfluidic network 30." (Ex. 1006 at 10:35-38.) Chien I teaches that "[a] steady flow can be directed toward **reservoir 18a** by applying initial pressure on **wells 18**. (Ex. 1006 at 19:22-23; *see also* 21:13-16 ("a steady-state flow is induced from capillary 176, a substrate reservoir 180a, and/or an enzyme reservoir 180b toward a **vacuum reservoir or waste well 180c** along a channel 182").) As apparent in these passages, Chien I uses the terms "reservoir" and "well" interchangeably.

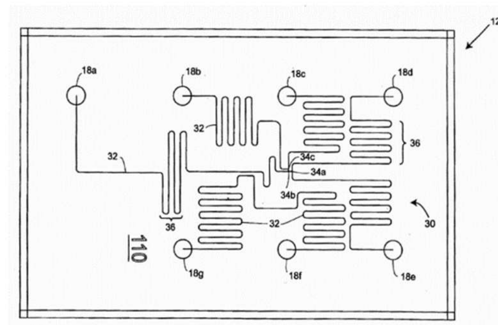
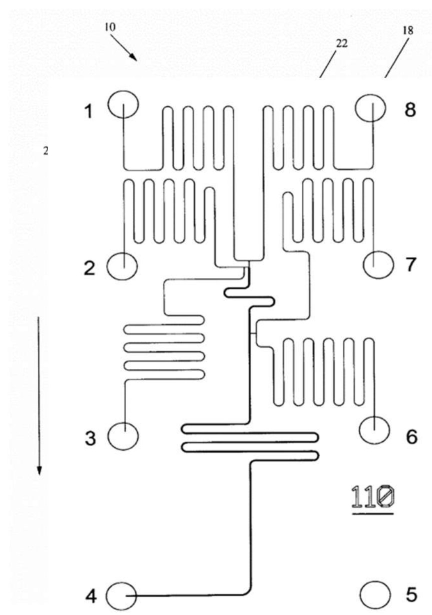


Fig. 2

Chien II further clarifies that the reservoirs are provided for **input wells and output wells**. "The chip [at right] has the pair-well design suitable for dilution and enzymatic studies." (Ex. 1035 p. 3.) "In a typical arrangement, the enzyme is placed in well 7 and the substrate is placed in both wells 1 and 3 to increase the dynamic range. Assay buffer is placed in the remaining wells. … The diluted enzyme and substrate then



flow into the main channel. The incubation time is controlled by the vacuum applied to the **waste well** [well 4]." (*Id*. p. 5.)

The "waste well" is an output well. The '392 patent does not define "output." However, dependent claim 18 recites the performance of a PCR reaction on the device, after which the droplets would typically be optically analyzed (also on the device) and then discarded. Indeed, if the analytical test of interest has already been performed on the droplets before they arrive at the output well, an in Chien I and Chien II, then the droplets may be discarded. (Ex. 1006 at 21:13-38, 23:30-35, Ex. 1035 p. 5; Ex. 1003 ¶72.)

The wells of the Combined System each hold the equivalent of over 2,000,000 droplets, about 170 times more than is needed to perform emulsion-based PCR and other useful processes. (Ex. 1003 ¶73.) Quake's top layer is up to 10 mm thick (Ex. 1004 ¶278.) and the wells are 0.6096 mm diameter (Ex. 1038), resulting in a total volume of 2.92 cubic millimeters. (Ex. 1003 ¶73.) 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 cubic millimeters. (Ex. 1003 ¶73.)   Each input well thus holds the volume equivalent of 2.92 mm^3 / 0.0000141 mm^3 = 207,092 droplets. (*Id*.) Moreover, the wells taught in Chien are about three times as wide (2 mm) at the same top plate thickness would have held over 2,225,000 droplets. (*Id*.) A skilled artisan would be motivated to use Chien's larger well sizes because Chien teaches that the fluids should be provided on-chip rather than being brought from an off-chip source. (Ex. 1035 p. 1.) Assuming that there is 3X more continuous phase than droplet or dispersion phase, this amount of continuous phase (oil) is sufficient to generate over 550,000 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 ¶73.) Thus, the wells of the Combined System are configured to hold 170 times more continuous phase than perform useful processes such as droplet-based PCR (assuming 3,000 droplets for PCR). (*Id.*)

***A skilled artisan would have seen at least three reasons to use Chien's multi-reservoir plate and pressure control system to drive the fluids through the emulsion productions units of Quake*.** **First**, Chien II teaches 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 II explains that "the use of external pumps to force liquids directly through microfluidic channels" produces relatively "irreproducible and erratic results." (Ex. 1035 p. 1.) "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 fluid drive technique taught in Chien I and Chien II. (Ex. 1003 ¶74.)

Second, Chien's fluid drive technique simplifies the bench-top instrument and reduces the risk of contamination. (Ex. 1003 ¶75.) The bench-top instrument need only include air pumps, meaning that it may omit fluid reservoirs or pumps which are both expensive and need periodic cleaning. (*Id.*) Omission of these parts greatly reduces the risk of contamination due to improper cleaning. *(Id.)*

Third, the syringe pumps, tubing and wells of the Chien device were configured in a similar manner to Quake's. In both systems, the wells were formed by drilling holes into a planar substrate and connected to syringe pumps with tubing. (Ex. 1004 ¶288; Ex. 1035 pp. 2-3; Ex. 1006 10:20-34, 14:5-13; Ex. 1003 ¶77.) A skilled artisan would thus have been strongly inclined to improve the Quake device with the readily compatible techniques taught by Chien, which is uses similar equipment. (Ex. 1003 ¶77.)

A skilled artisan thus would have been strongly motivated to combine the teachings of Quake, Dale, Chien I and Chien II references to arrive at the Combined System. (Ex. 1003 ¶78.)

Because each of the components of the Combined System was well known at the time of filing 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 ¶¶22-37, 78.) 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 ¶63, 78.) Providing an array of Quake's emulsion production units on a single plate or chip and interfacing that chip with Chien's pneumatic drive system would require no more than routine skill and would lead to predictable results. (*Id*. ¶¶69, 78.) A skilled artisan would thus have had an expectation of success in arriving at the Combined System. (Ex. 1003 ¶78.)

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 ¶¶79-86.)

As discussed above, Quake renders 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 ¶¶58, 80; 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 ¶81.) One skilled in the art would have been strongly motivated to parallelize the Quake emulsion generators as suggested by Dale. (Ex. 1005 ¶39, *see also* ¶¶40- 44; Ex. 1003 ¶84.)

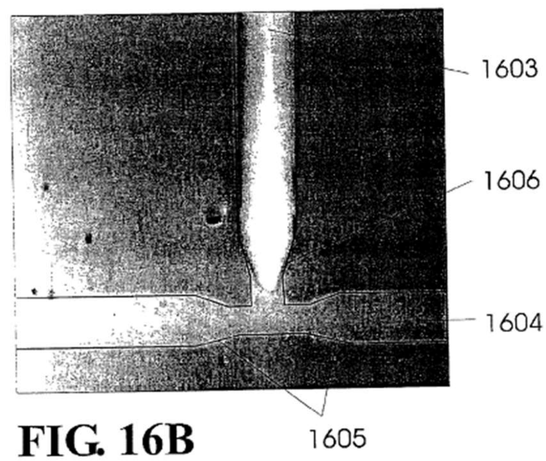
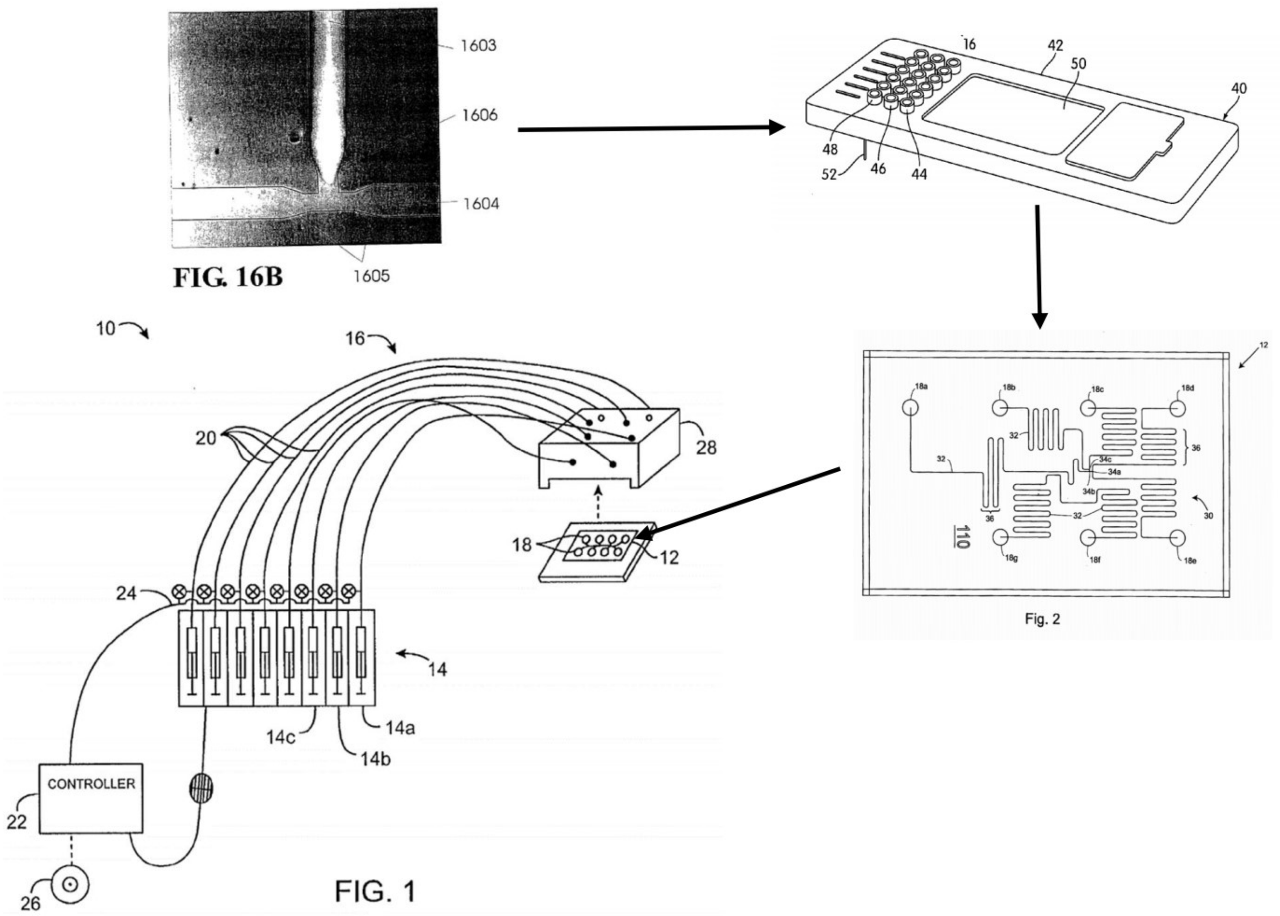


FIG. 16B

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 ¶85.) As shown below, a plurality of Quake's emulsion generators are arrayed on the microfluidic chip 12.



Thus, Quake alone or in view of Dale renders it obvious to deploy an array of emulsion generators on a single microfluidic chip, meeting the preamble. (Ex. 1003 ¶86.)

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 ¶87.) "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 ¶87-88.)

The Combined System also includes a plate 12 having an array of droplet generators. (Ex. 1003 ¶¶89-90.) As discussed and depicted above, the microfluidic chip takes the form of plate 12 having an array of Quake's emulsion generators. (*Id*.) The microfluidic plate is mated to the pneumatic drive device 16 in the Combined System. (*Id*.)

Accordingly, Quake and the Combined System meets this limitation. (Ex. 1003 ¶91.)

Element 1[a][i]

Claim element 1[a][i] recites "each unit including at least one first input well[3] 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.)

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 ¶92.) Quake teaches that "a main channel, through which a pressurized stream of **oil** is passed, and at

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[3] 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) (an apparatus claim may only be distinguished by the recited structure, not its intended use). 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.

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 ¶93.) 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 …." (*Id.* ¶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.) "Microline tubing … can be used to direct the fluids from the syringes for input into their respective **input wells** of a device." (*Id.* ¶288.)

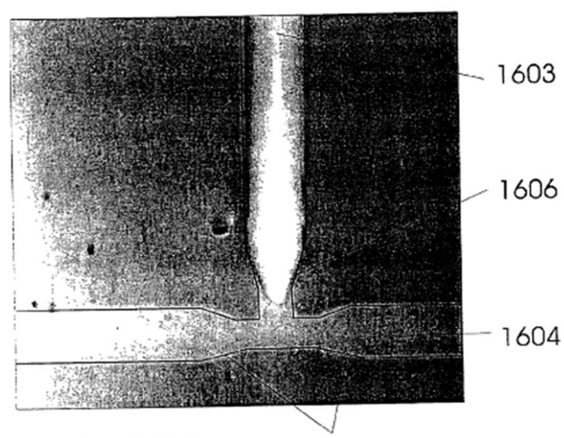


FIG. 16B

Thus, Quake's oil input well meets element 1[a][i]. (Ex. 1003 ¶95.) As discussed above, the Combined System uses the larger wells of Chien because Chien teaches that all fluids for the process should be provided on-chip (as opposed to being provided from an off-chip source). (Id. ¶73.)

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 ¶¶97-98.) 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.)

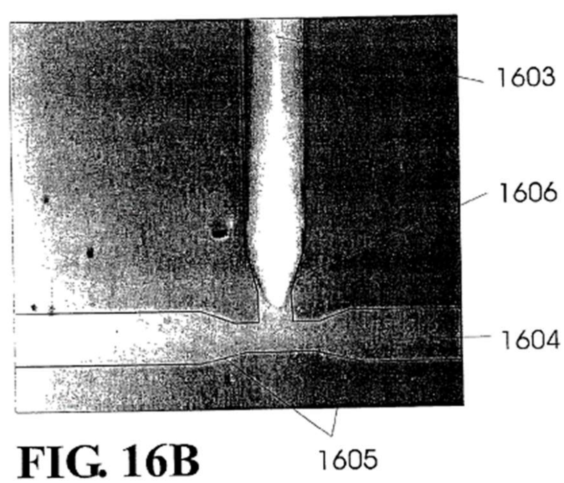


FIG. 16B

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.) “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 ¶¶96-99.) As discussed above, the Combined System uses the larger wells of Chien because Chien teaches that all fluids for the process should be provided on-chip (as opposed to being provided from an off-chip source). (Id. ¶73.)

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 ¶100.)

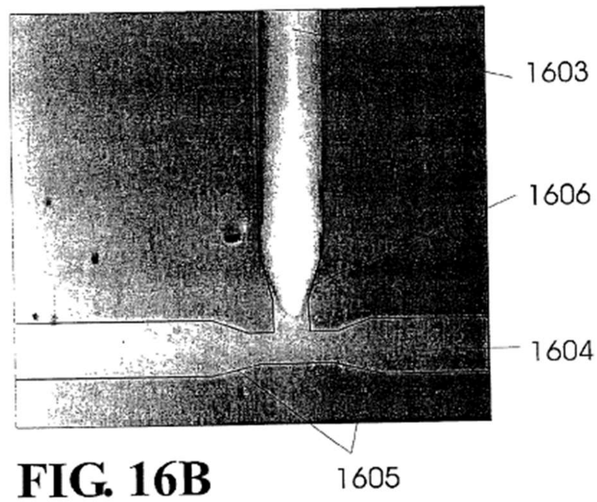


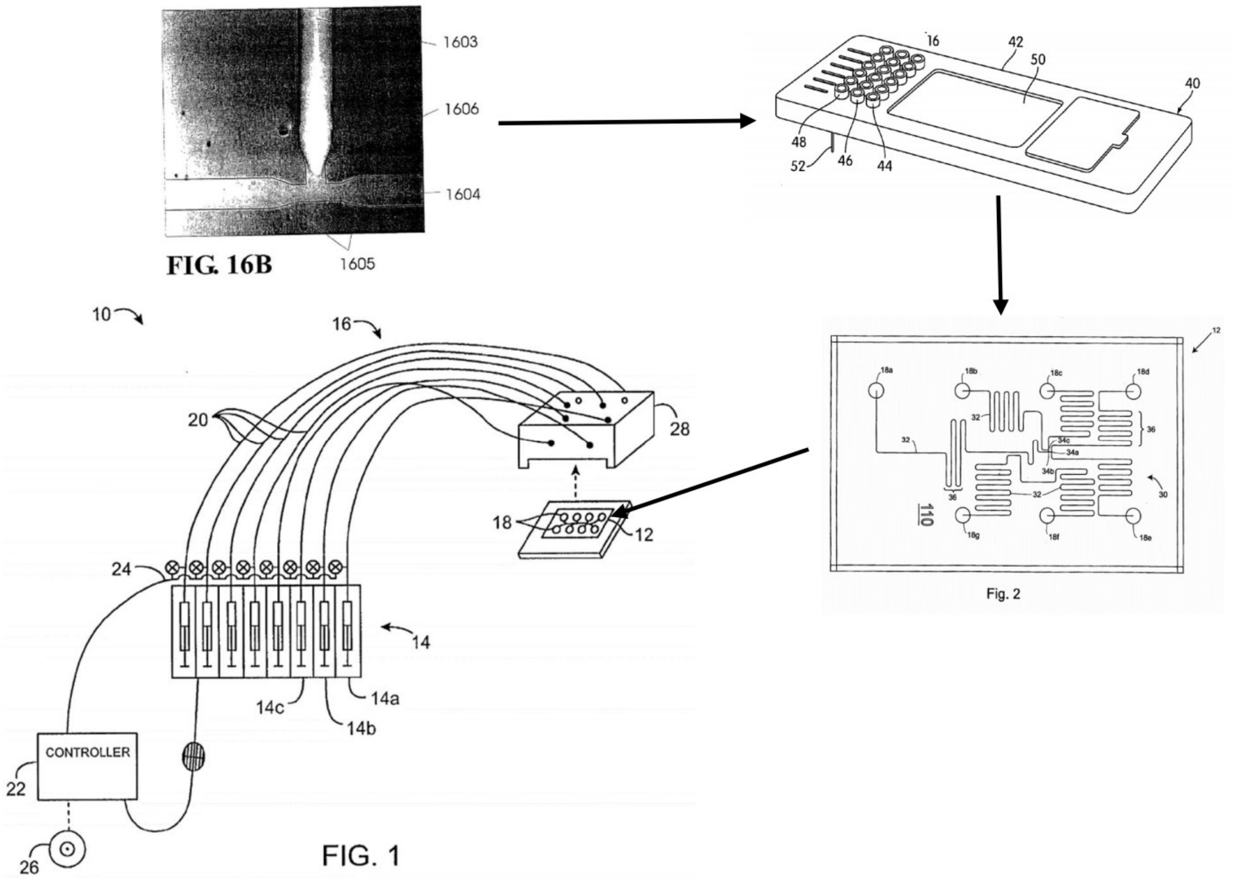
FIG. 16B

***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 ¶101.) The water phase flows from the water input well through channel 1603 to the "channel junction." (Ex. 1004 ¶292; Ex. 1003 ¶101.) Thus, Quake teaches "at least two input channels extending separately from the input wells to the channel junction." (Ex. 1003 ¶101.)

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 at ¶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 ¶102.)

Thus, Quake's configuration of channels and wells meet element 1[a][iii]. (Ex. 1003 ¶112.)

As discussed above and depicted below, the Combined System includes Quake's arrangement of channels and the recited input and output wells. (Id. ¶100-102, 111.) Again, the Combined System uses the larger wells of Chien because Chien teaches that all fluids for the process should be provided on-chip (as opposed to being provided from an off-chip source). (Id. ¶¶73, 104-111.)



Accordingly, the Combined System meets element 1[a][iii]. (Ex. 1003 ¶112).

<u>Element 1[a][iv]</u>

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 ¶113.) 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 ¶113.) 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. (Ex. 1003 ¶¶114-115.) To use positive and negative pressure to drive the fluids as taught by Chien, the channels must be sealed (*i.e.*, circumferentially bounded) and not open on any side. (Ex. 1003 ¶115.)

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."

Chien I and Chien II disclose the recited vacuum or pressure source for forming a pressure drop between input and output wells. Chien I discloses using "a **multi-reservoir pressure controller** coupled to a plurality of independently variable pressure modulators to effect movement of fluids within microfluidic networks. By **selectively controlling and changing the pressure applied to the reservoirs of a microfluidic device, hydrodynamic flow at very low flow rates may be accurately controlled within intersecting microfluidic channels**." (Ex. 1006 at 8:21-28.)

Chien I teaches that, "[t]o accurately apply the pressure within [a] microfluidic network," one can use "a pressure transmission system having relatively large lumens **coupling the pressure modulators to the reservoirs** of the microfluidic device, with the pressure transmission lumens ideally containing a **compressible gas**." (Ex. 1006 at 9:3-8.) The pressure transmission system 16 (Fig. 1, above) includes a manifold 28, which forms a seal with wells/reservoirs of a microfluidic chip. (*Id*. at 10:10-14 ("Manifold 28 releasably seals the lumen of each tube 20 with an associated reservoir 18 of microfluidic device 12.").)

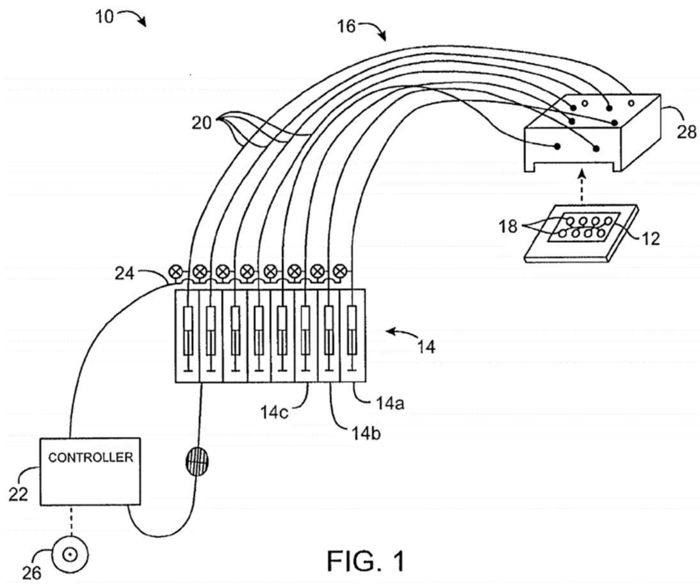


FIG. 1

Chien II describes the same system and discloses the recited vacuum or pressure source for forming a pressure drop between input and output wells. (Ex. 1035 pp. 1-3 ("For a **pressure drop between reservoirs** of approximately 2 psig, this chip will provide a mixing time of approximately 6 s and a reaction time of approximately 20 s.") Chien II also makes clear that air pressure is provided through the pressure manifold. (*Id*. p. 1 ("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.”).)

Chien I and Chien II disclose forming a pressure drop between the input wells and the output well to drive fluid flow in microfluidic channels. (Ex. 1003 ¶¶119-122.) Chien I gives numerous examples of using pressure applied to wells to induce fluid flow in a microfluidic channel network interconnecting input and output wells. For example, Chien I teaches that a “steady state flow can be directed toward reservoir 18a by applying initial pressures on wells 18.” (Ex. 1006 at 19:22-23.) “A steady-state flow is induced from capillary 176, a **substrate reservoir 180a**, and/or an **enzyme reservoir 180b** toward a **vacuum reservoir or waste well 180c** along a channel 182 ….” (*Id.* 21:13-16; *see also* claim 1, reciting a microfluidic system comprising … a plurality of pressure transmission lumens, the lumens **transmitting the pressures from the pressure modulators to the reservoirs so as to induce a desired flow within the channel**.)

Chien I also describes a model for “[d]etermination of reservoir pressures so as to provide a desired flow rate,” wherein flow resistances are used to obtain flow rates through the microfluidic network. (*Id.* 15:15-27. (“Flow resistances are obtained 74 as described above, and the input flow rate propagates through the network to obtain flow rates for each branch 76. The **pressure drop** of each branch is then determined using the network resistance circuit 78. These pressure branches are then allowed to propagate through the network to obtain reservoir pressures 80 so as to effect the desired flow.”).)

Chien II describes the same system and also expressly discloses the pressure drop between the input and output wells. (Ex. 1035 pp. 1-3 (“For a pressure drop between reservoirs of approximately 2 psig, this chip will provide a mixing time of approximately 6 s and a reaction time of approximately 20 s.”).

As discussed above, the Combined System incorporates the foregoing aspects of Chien, and thus meets element 1[b]. (Ex. 1003 ¶¶123-125.)

Thus, claim 1 is rendered obvious by Quake taken in view of Dale, Chien I, and Chien II. (Ex. 1003 ¶126.)

2. Dependent Claim 2

Claim 2 depends from claim 1, the analysis of which is incorporated by reference.[4] Claim 2 recites that “the vacuum or pressure source controls air pressure in wells to which the source is configured to be connected operatively.”

The syringe pumps and manifold of Chien I and Chien II meet the recited vacuum or pressure source. As discussed for claim 1, both Chien I and Chien II

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

teach that it is preferable to drive fluids through microfluidic chips with **syringe pumps** connected to a **manifold** that delivers **air pressure to the headspace above the reservoir of fluid stored in on-chip wells**. (Ex. 1035 pp 1-6; Ex. 1006 at 2:57-3:39, 6:16-23, 10:20-34, 14:5-13.) Chien's pumps and manifold thus meet the recitation of claim 2. (Ex. 1003 ¶129.)

As explained for claim 1, one skilled in the art would have considered it obvious to use this technique to drive fluids from the wells and through the microchannels of Quake's chip (as in the Combined System) because, among other things, that improves and makes more reproducible the microfluidic control. (Ex. 1035 p. 1; Ex. 1006 at2:57-61; Ex. 1003 ¶¶130-131.)

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."

Chien I's "microfluidic system 10" or alternatively Chien II's "universal multiport system" teach these manifold and gasket limitations. Chien I illustrates in Figure 1a "a microfluidic system 10 includes a microfluidic device 12 coupled to a bank of pressure modulators 14 by a pressure transmission system 16. (Ex. 1006 at 9:43-46.) Chien I teaches that "[i]n addition to tubing 20, pressure transmission system 16 includes a manifold 28. **Manifold 28 releasably seals the lumen of each tube 20 with an associated reservoir 18** of microfluidic device 12." (Ex. 1006 at 10:10-13.) Several different designs of chip interface manifold were tested. Figure 1 shows a **universal manifold** suitable for either electrokinetic or hydrodynamic control or a combination of both." (Ex. 1035 p. 3; Ex. 1006 at 10:10-19, 12:33-13:4.) Chien II describes the same structure and refers to the seal as a gasket. (Ex. 1035 p. 3 ("A piece of **rubber gasket with eight holes was glued to the bottom of the block to make vacuum seal as the manifold** was screwed down on to the mounting plate.".) (*Id.*)

As explained for claim 1, one skilled in the art would have considered it obvious to use the technique of Chien I and Chien II to drive fluids from the wells and through the microchannels of Quake's chip (as in the Combined System). (Ex. 1003 ¶¶132-133.)

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."

Chien II teaches a vacuum source configured to form a pressure sink at the output well. (Ex. 1003 ¶¶136-137.) Chien II teaches that it is preferable drive fluids through microfluidic chips via a manifold that delivers positive pressure or creates a vacuum in the headspace above the reservoir of fluid stored in on-chip wells. Specifically: "A home-made eight-syringe pump system is used as our pressure or **vacuum** source. . . The incubation time is controlled by the **vacuum** applied to the **waste well**." (Ex. 1035 pp. 2, 5.) As discussed in connection with claim 1[a][iii], the "waste well" of Chien satisfies the "output wells" of the claim.

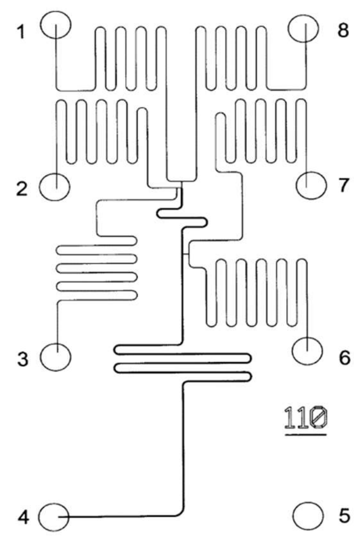
As explained for claim 1, one skilled in the art would have considered it obvious to use Chien's technique to drive fluids between the wells and through the microchannels of Quake's chip (as in the Combined System). (Ex. 1003 ¶138.)

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 manifold of Chien II is a pressure source configured to be connected operatively to input wells. (Ex. 1003 ¶141.) As discussed above for claim 1[b], Chien II teaches that it is preferable drive fluids through microfluidic chips 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. (Ex.

1035 pp. 1-6.) "To perform a dilution using wells 1 and 8, a script of **pressure settings** was generated automatically to set the **relative flow of dye from well 1** from –4% to +44%, with 10% step size, of the total flow. The negative flow means the fluid was directed in opposite direction, flowing back into the reagent well. The **flow from well 8** was correspondingly changed from +44% to –4% of the total flow, to represent 0 to 100% mixing between pair-wells 1 and 8." (Ex. 1035 p. 4.) **Wells 1 and 8 are input wells (*i.e.*, for reagents)** and well 4 is a waste or output well. (*Id.* pp. 2-6.) Chien II thus teaches using a pressure source (syringe pump and pressure manifold) operatively connected to the input wells of a microfluidic chip.



As explained above for claim 1, one skilled in the art would have considered it obvious to use Chien's technique to drive fluids from the wells and through the microchannels of Quake's chip (as in the Combined System). (Ex. 1003 ¶142.)

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."

Dale's parallel microanalysis channels teach a linear array of three or more emulsion production units and the Combined System incorporates this

feature**.** (Ex. 1003 ¶¶144-146.) As explained above for the preamble of claim 1, Dale teaches a **parallelized** microfluidic reactor "whereby discrete assays are performed within droplets of DNA or other sample material contained within the micro-channels." (Ex. 1005 ¶39, see also ¶¶40-42.) "[I]n the embodiment shown in FIG. 1A, **micro-fluidic chip 40 would include six micro-channels,** one associated with each of the six columns of access ports." (*Id*. ¶35.) Dale thus teaches a microfluidic chip 40 having a linear array of three or more (six) parallel microfluidic channels 62 in which droplet reactions such as PCR are performed. (Ex. 1003 ¶146.) As discussed above for the preamble, a person skilled in the art would have been strongly motivated to parallelize the Quake emulsion generators in this manner, thus meeting the recitation of claim 8. (Ex. 1003 ¶¶147-149.)

7. <u>Dependent Claims 10-11</u>

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." Dale renders obvious this limitation. 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."

Dale teaches that 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 Figs. 1a, 8, and 9, each of the micro-channels of Dale includes three ports: input port A and B, and output port C.

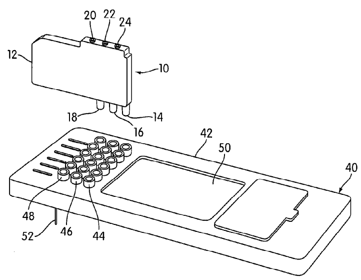


FIG. 1a

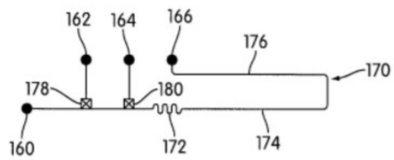


FIG. 8

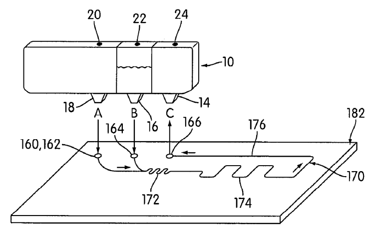


FIG. 9

Here, "a mixture of DNA sample material and buffer solution contained within the cartridge 10 is injected into the micro-channel 170 through port A," and "[n]ozzle 16 of the cartridge 10 communicates with input port B, which corresponds to input port 164 of FIG. 8 [reagent input]." (Ex. 1005 ¶¶47-48.) "Nozzle 14 of the cartridge 10 communicates with port C of the microfluidic chip 182 which corresponds with exit port 166 shown in FIG. 9. To draw the DNA sample material and reagents, as well as buffer solution, through the micro-channel 170 and into the waste compartment of cartridge 10, a vacuum source is connected to the cartridge 10 at vacuum port 24." (*Id.*) The ports A, B, and C are depicted in Fig. 1a as corresponding to access ports 48, 46, and 44, respectively. (*Id.* ¶¶32-33.) Here, the second input port B is disposed between the first input port A and the output port C as recited by claim 10. The first and second input ports A and B and output (or exit) port C are arranged in a line as recited by claim 11.

Moreover, the ports of the Dale device correspond closely to the wells 1274-78 of the '392 patent preferred embodiment. As shown in the side-by-side comparison below, Dale's access ports 44/46/48 have a similar configuration as the wells 1274-1278 of the '392 patent, Fig. 27.

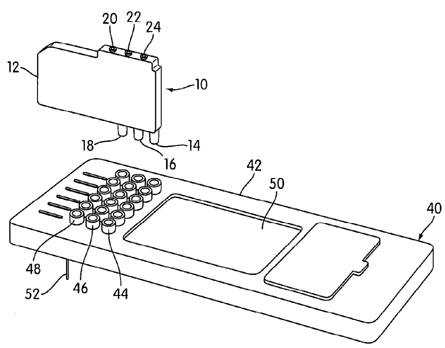
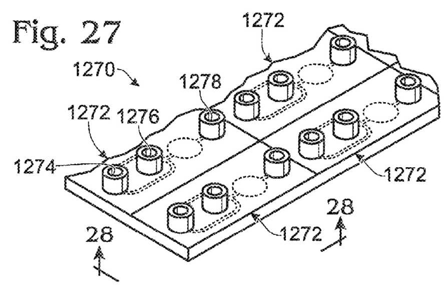


FIG. 1a

Dale



'392 patent

The access ports 44/46/48 of Dale are "wells" within the meaning of the '392 patent. *Hewlett-Packard*, 909 F.2d at 1469 (an apparatus claim may only be distinguished by the recited structure, not its intended use).

One skilled in the art would have been motivated to arrange the inputs to a microfluidic chip in a line, as suggested by Dale, such that the dispersion phase input (second well) was positioned between the first input (continuous phase) and the output well. (Ex. 1003 ¶¶150-159.) Doing so would have facilitated the arrangement of the emulsion generators in the Combined System (of Quake, Dale and Chien) in a parallel array as suggested by Dale. (*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 ¶153.) 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.* ¶¶150-159.)

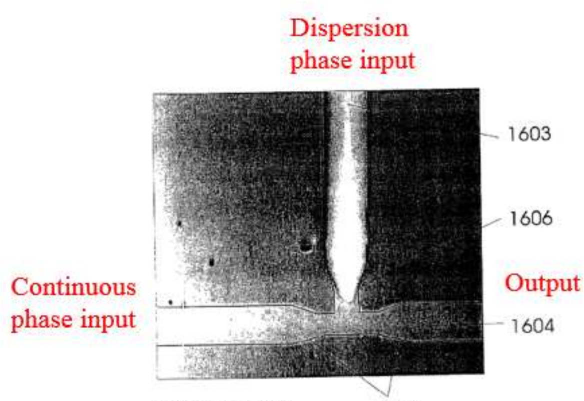


FIG. 16B

Thus, claim 10-11 are rendered obvious by Quake taken in view of Dale, Chien I and Chien II.

8. 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 ¶¶160-164.) As discussed for claim 1, Dale teaches an array of six parallel microfluidic circuits and one skilled in the art would have considered it obvious to parallelize droplet generator of Quake according to the teachings of Dale. (*Id*. ¶160-161.) In the Combined System, each droplet generator has its own input and outputs, as taught in Figs. 1a and 3 of Dale. (*Id*. ¶¶162-163.) These parallelized emulsion production units thus have input wells that are not shared, meeting claim 21. (*Id*. ¶164.)

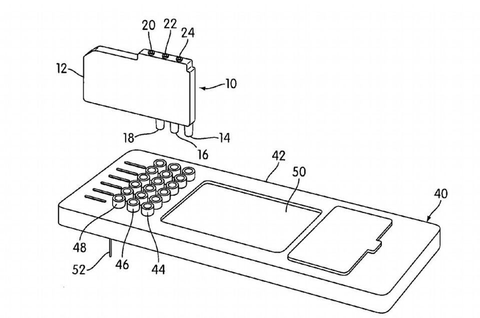


FIG. 1a

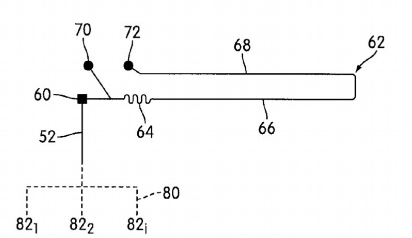


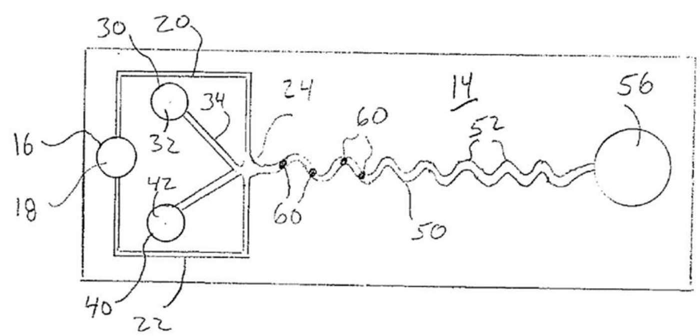
FIG. 3

The combination of Quake, Dale, Chien I and Chien II thus renders obvious claim 21. (Ex. 1003 ¶144.)

B. Ground 2: Claim 7 Is Rendered Obvious by Quake in View of Dale, Chien I and Chien II 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 fluidicially 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 ¶168.) 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 ¶168.) 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. (Ex. 1003 ¶168.)

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 ¶168.)

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 ¶168.)

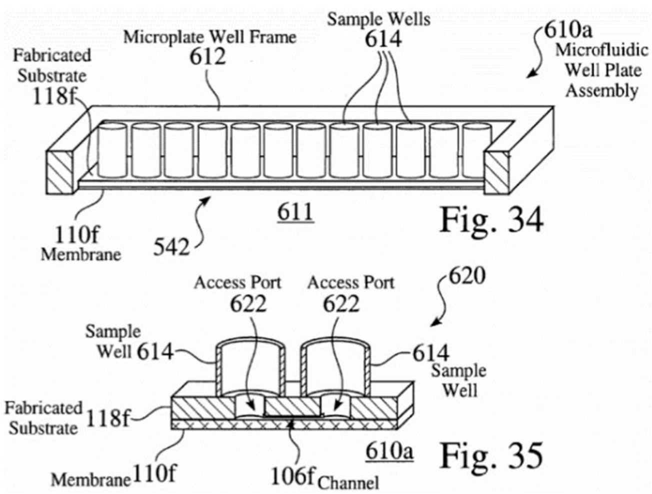
In light of the level of skill of art, a skilled artisan would have found it routine to make the foregoing combination (yielding the claimed limitation). (Ex. 1003 ¶¶22-37, 169.)

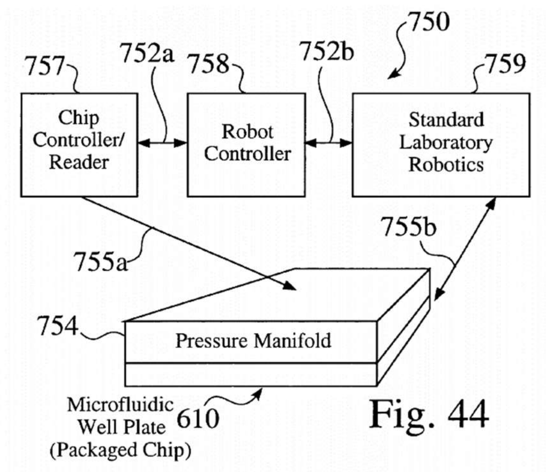
C. Ground 3: Claims 9 Is Rendered Obvious by Quake in View of Dale, Chien I and Chien II and Further in View of Modlin

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." Modlin, which was cited by the Examiner but applied only against other dependent claims (claims 3-4), renders claim 9 obvious in combination with Quake, Dale, and Chien I/II. (Ex. 1002 p. 257.)

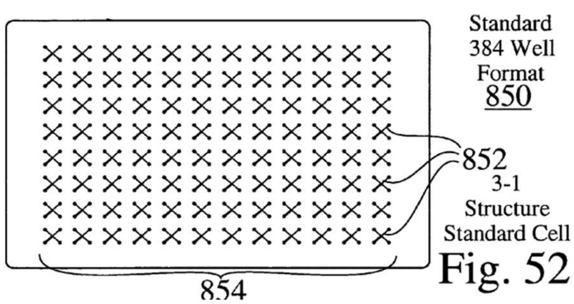
Modlin's microfluidic well plate 610 meets the recitation of claim 9. As shown in Fig. 34, reproduced below, microfluidic well plate assembly 610 includes "[s]ample wells 614 . . . preferably positioned over access ports 622, e.g., 104a, 112a . . . providing means for fluid connection and flow through channel 106f. . . ." (Ex. 1007 ¶178.) "Microfluidic well plate assembly 610 . . . [is] designed to be compatible with industry standard physical conventions provides an interface 755b to standard laboratory robotics 759," as shown in Fig. 44. (*Id*. ¶201, see also

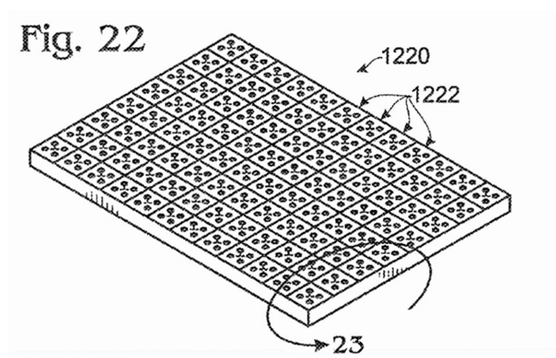
¶¶176-180, 186, 202.) "The well to well spacing or well pitch of the standard unit cells is designed to match industry standard microplate well pitches including but not limited to 96, 384, and 1536 well formats." (*Id.* ¶211.)





Indeed, the design of the "standard 384 well format" 850 of Modlin closely matches a preferred embodiment of the plate 1220 in the '392 patent – including the pattern of "X"-shaped emulsion production units:





Modlin **'392 patent**

One skilled in the art would have been strongly motivated to space the wells of the Combined System according to an industry standard pitch. (Ex. 1003 ¶172.) As Modlin teaches, using industry standard well-to-well spacing permits the devices "to be readily used in conjunction with industry standard fluid dispensing, detection, and other robotics and automated processing equipment." (Ex. 1007 ¶201.) A skilled artisan would thus have understood that configuring the plates of the Combined System so that the wells conformed to one of the industry-standard pitches would substantially promote industrial adoption, enable sharing of instrumentation, reduce consumption of laboratory space, and decrease the cost of the device and the ongoing cost of ownership. (Ex. 1003 ¶172.) An additional motivation to combine is provided by the fact that Dale's inputs are themselves spaced according to a standard microwell. (Ex. 1005 ¶¶34-36, Fig. 2; Ex. 1003 ¶173.)) That disclosure in Dale would have further encouraged a skilled artisan to use industry standard well spacing in the Combined System. (*Id*.)

In light of the level of skill of art, a skilled artisan would have found it routine to space the wells of the Combined System according to an industry standard pitch yielding the claimed limitation. (Ex. 1003 ¶¶22-37, 174.)

D. Ground 4: Claims 12-17 and 19-20 are Rendered Obvious by Quake in View of Dale, Chien I and Chien II 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 Dale, Chien I and Chien II 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

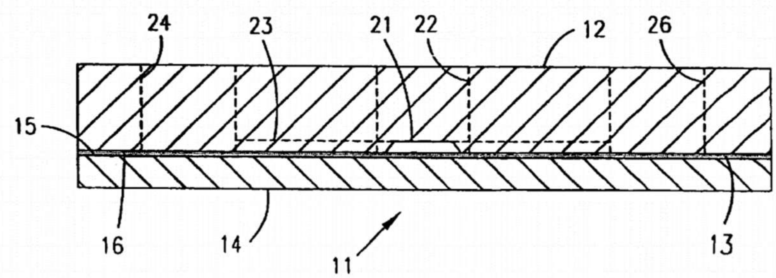


FIG. 6

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/Dale/Chien 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 pro cessed 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 ¶176.)

One skilled in the art would have had a reasonable expectation of success using the Soane method to fabricate Combined System of Quake, Dale, Chien I and Chien II. (Ex. 1003 ¶177.) Soane provides various working examples which could be directly applied to fabricate the Quake/Dale/Chien 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, 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*., see also ¶¶22-37.)

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

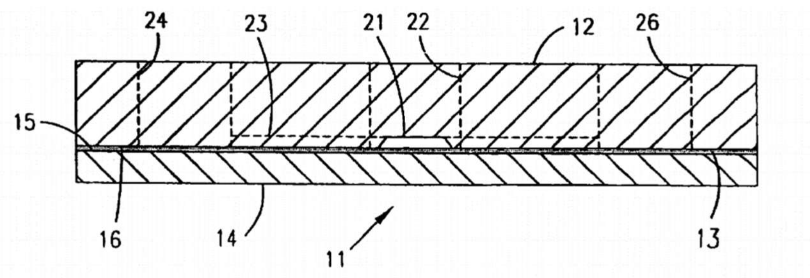


FIG. 6

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 ¶¶182-184.)

2. Dependent Claim 13

Claims 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 ¶186.) "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 ¶¶186, 188.)

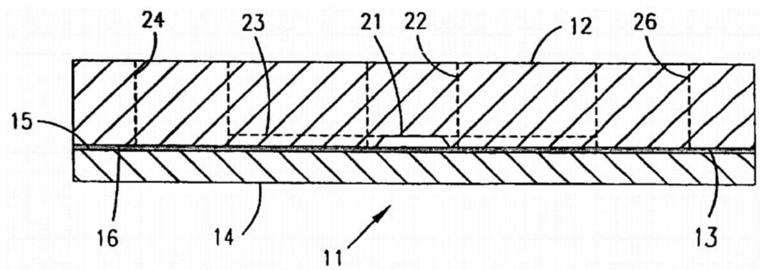


FIG. 6

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.) The channels and junctions are bounded on three sides by the top and middle layers and on a fourth side by the bottom layer. (*Id*. ¶¶277-282.) "Input wells for the different fluids, such as water and oil, were then be drilled through the device using a No. 73 drill bit." (*Id*. ¶284.) Thus, 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 ¶187.)

3. Dependent Claim 14

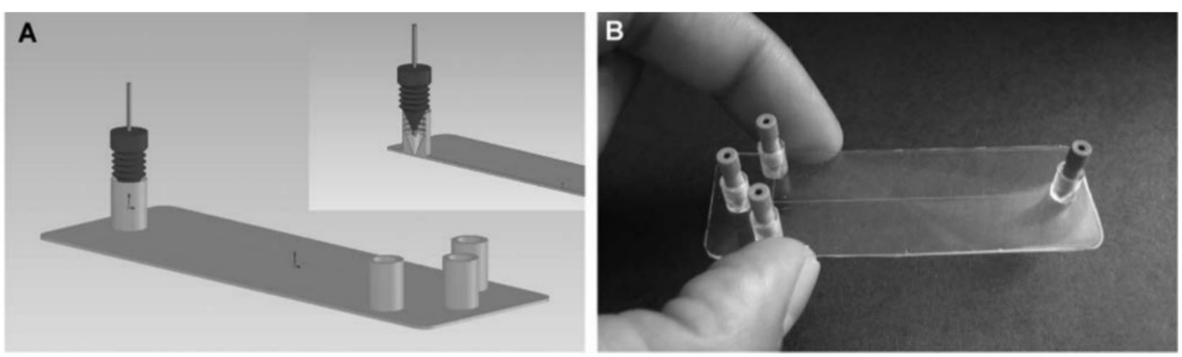
Claims 14 depends from claims 1 and 13 and recites that "the upper member is formed of an injection-molded polymer."

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 ¶¶189-190.)

A skilled artisan would have considered it routine to fabricate the middle layer and upper layers of Quake in a single piece by injection molding at the time

of filing. (Ex. 1003 ¶190.) 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 ¶190.) 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, 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.*; Ex. 1003 ¶¶22-37, 190.)

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 10:36-40, see also 11:27-31, 12:7-13:7; Ex. 1003 ¶191.) "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

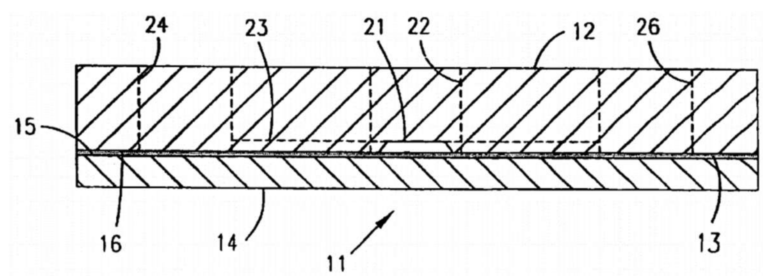


FIG. 6

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 ¶192.)

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 lower member (film 16) that forms a bottom wall below each through-hole and groove. (Ex. 1003

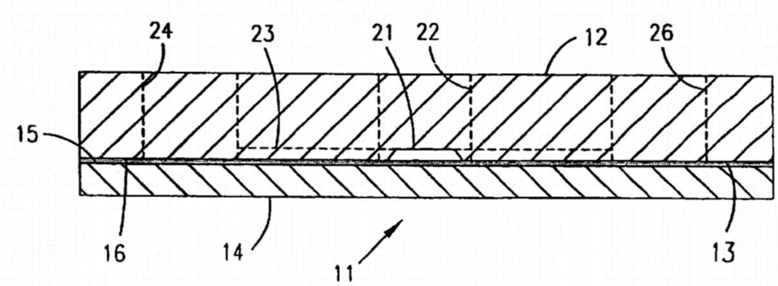


FIG. 6

¶195.) "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, 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. 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 ¶¶195-196.)

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 ¶198.)

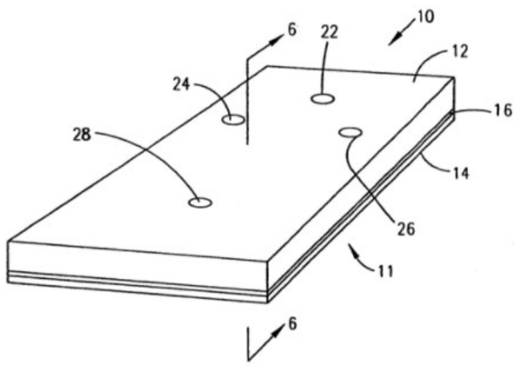


FIG. 5

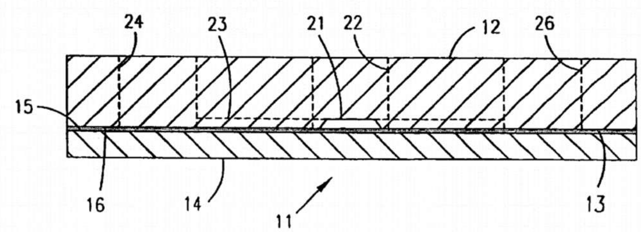


FIG. 6

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 1µm 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 um) 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 ¶¶200-203.) As discussed in connection with claim 1, Dale teaches an array of six parallel microfluidic circuits and one skilled in the art would have considered it obvious to parallelize droplet generator of Quake according to the teachings of Dale. (*Id.*) In the Combined System, each droplet generator has its own input and outputs, as taught in Figs. 1a and 3 of Dale, and thus produces a separate emulsion, thus meeting claim 19. (Ex. 1003 ¶¶203, 205.)

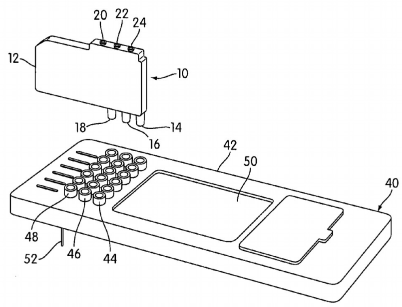


FIG. 1a

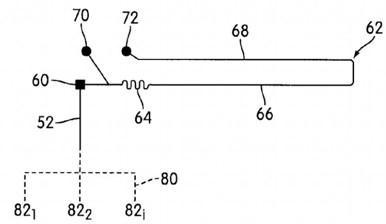


FIG. 3

8. <u>Dependent Claim 20</u>

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."

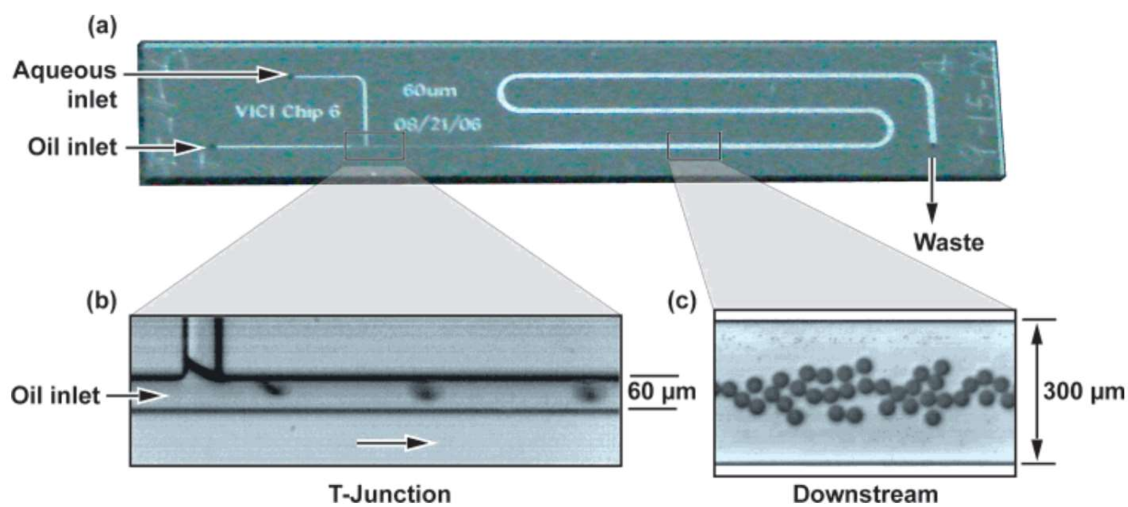
The discussion of claim 15 is incorporated herein by reference. As explained therein, it would have been obvious to fabricate the upper and lower members of a respective, continuous piece of material.

For the foregoing reasons claims 12-17 and 19-20 are thus rendered obvious when Quake in view of Dale, Chien I and Chien II are taken further in view of Soane. (Ex. 1003 ¶¶175-207.)

E. Ground 5: Claim 18 Is Rendered Obvious by Quake in View of Dale, Chien I and Chien II 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/Dale/Chien device meets claim 18. Beer teaches performing PCR in droplets formed with microfluidic emulstion 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 Quake/Dale/Chien system is used to perform PCR as taught by Beer the Combined System meets claim 18. (Ex. 1003 ¶210.)) 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/Dale/Chien 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 ¶210.) Making the proposed modification would, as taught by Beer, provide the high-throughput system of Quake/Dale/Chien system "a level of control over microdroplet compartmentalization not achievable by 'shake-and-bake' methods." (Ex. 1032 p. 2; Ex. 1003 ¶210.) 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 ¶210.) 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/Dale/Chien device) in the same way (providing improved control and detection). *KSR*, 550 U.S. at 415-421 (2007) *(Id.)*

In light of the level of skill of art, a skilled artisan would have found it routine to make the foregoing combination, yielding the claimed limitation. (*Id.* ¶¶22-37, 211.)

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 13,651 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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