

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NANOCELLECT BIOMEDICAL, INC.,
Petitioner,

v.

CYTONOME/ST, LLC,
Patent Owner.

Case No. IPR2020-00548
Patent No. 8,623,295

**PETITION FOR INTER PARTES REVIEW
OF U.S. PATENT NO. 8,623,295**

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I. INTRODUCTION

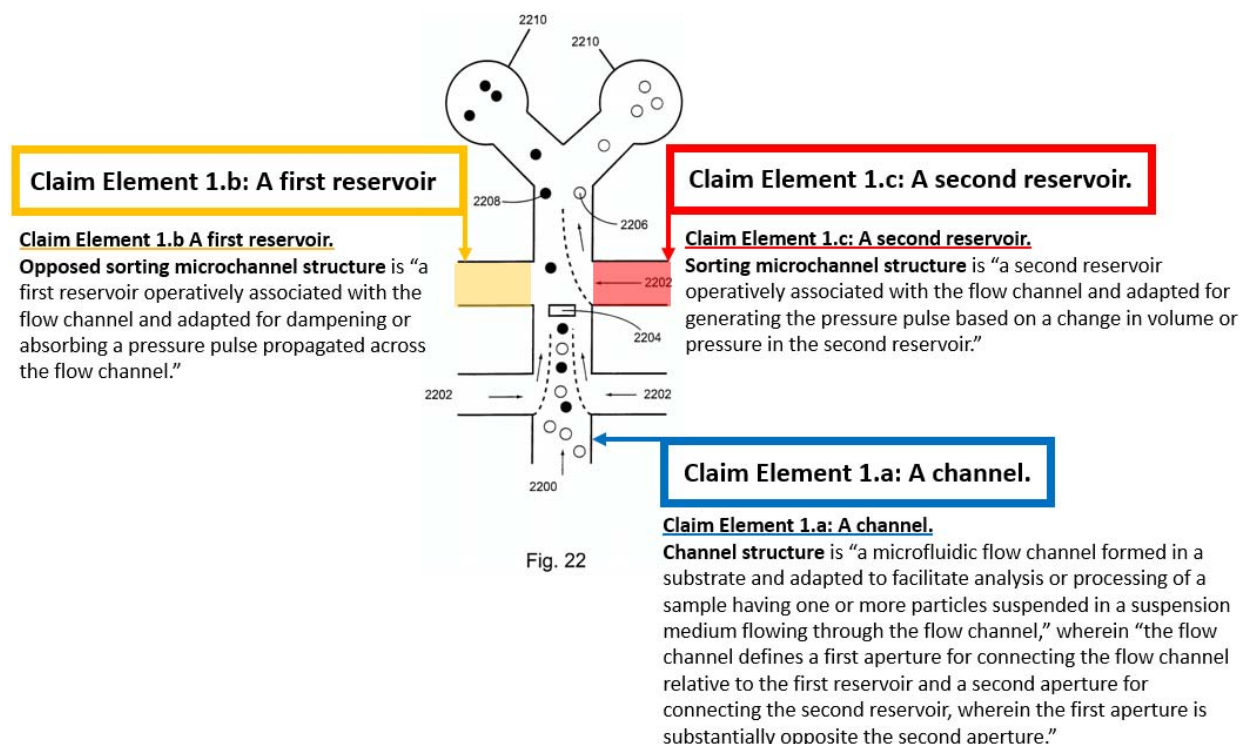
NanoCollect Biomedical, Inc. (“NanoCollect” or “Petitioner”) requests *inter partes* review of claims 1-3, 9, and 17-18 of U.S. Patent No. 8,623,295 to Gilbert, *et al.* (“the ’295 patent,” EX1001), which issued on January 7, 2014. This Petition demonstrates that there is a reasonable likelihood that each of claims 1-3, 9, and 17-18 is obvious under 35 U.S.C. §103. Petitioner thus requests that *inter partes* review be instituted and claims 1-3, 9, and 17-18 of the ’295 patent be cancelled.

At a high level, the challenged claims are directed to a microfluidic system comprising: (a) a microfluidic flow channel; (b) a first reservoir; and (c) a second reservoir. The microfluidic flow channel facilitates analysis of particles suspended in a medium. The first reservoir dampens a pressure pulse propagated from across the flow channel. Correspondingly, the second reservoir generates the pressure pulse based on a change in volume or pressure.

However, the claimed combination of elements was already disclosed in, for example, the Wada reference, as discussed in detail herein. For example, the annotations to Wada Figure 22 below illustrate how Wada renders claim 1 unpatentable. Further, each of the elements recited in the challenged dependent claims was also known in the prior art for use in microfluidic systems. In other words, the challenged claims are not patentable, but are, at most, merely the “combination of familiar elements according to known methods.” *KSR Int’l Co. v.*

Teleflex Inc., 550 U.S. 398, 416 (2007); *In re McDaniel*, 293 F.3d 1379, 1385

(Fed. Cir. 2002) (“anticipation is the epitome of obviousness”). Each of claims 1-3, 9, and 17-18 is thus unpatentable over the prior art.



See EX1006, FIG. 22; EX1002, ¶108.

II. MANDATORY NOTICES

A. Real Parties-In-Interest (37 C.F.R. §42.8(b)(1))

NanoCollect Biomedical, Inc. is the Petitioner and the real party-in-interest in this IPR. Out of an abundance of caution, Petitioner discloses that it was founded in late 2009 as a spinout from UCSD. Initial funding for R&D was graciously funded by multiple NIH SBIR grants and contracts. Petitioner’s business operations have been backed by Illumina Ventures, FusionX Ventures,

Anzu Partners, Agilent Technologies, Vertical Ventures (Highlander Fund and Triton Fund), and other private investors.

B. Related Matters (37 C.F.R. §42.8(b)(2))

The '295 patent was asserted in *Cytonome/ST, LLC v. NanoCollect Biomedical, Inc.*, Case No. 1:19-cv-00301-UNA (D. Del.), filed February 12, 2019 and served no earlier than February 13, 2019 (EX1044). NanoCollect is also filing IPRs challenging claims from U.S. Patent Nos. 6,875,528; 9,011,797; 9,339,850; 10,029,263; 10,029,283; and 10,065,188 (together with the '295 patent, collectively “the asserted patents”). Each of the asserted patents was asserted in Case No 1:19-cv-00301-UNA.

In an abundance of caution, Petitioner also identifies the four IPR petitions filed by a different petitioner against different patents owned by Cytonome/ST, LLC (“Cytonome”). These cases are *ABS Global, Inc. v. Cytonome/ST, LLC*, IPR2017-02097; *ABS Global, Inc. v. Cytonome/ST, LLC*, IPR2017-02161; *ABS Global, Inc. v. Cytonome/ST, LLC*, IPR2017-02162; *ABS Global, Inc. v. Cytonome/ST, LLC*, IPR2017-02163. The patents challenged in those IPRs are different than the patents challenged herein and are not in the same chain of continuity as any of the asserted patents.

C. Identification of Counsel (37 C.F.R. §42.8(b)(3)) and Service Information (37 C.F.R. §42.8(b)(4))

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Please direct all correspondence to lead counsel and back-up counsel at the contact information above. NanoCollect consents to electronic mail service at the email addresses above. A power of attorney accompanies this Petition.

III. CERTIFICATIONS (37 C.F.R. §42.104(A))

NanoCollect certifies that the '295 patent is available for IPR and that NanoCollect is not barred or estopped from requesting IPR on the identified grounds.

IV. IDENTIFICATION OF CHALLENGE AND STATEMENT OF THE PRECISE RELIEF REQUESTED

NanoCollect requests review of claims 1-3, 9, and 17-18 of the '295 patent under 35 U.S.C. §311 and AIA §6, as NanoCollect's detailed statement of the reasons for the relief requested sets forth, supported with exhibits, including the Declaration of Dr. Bernhard H. Weigl. *See, generally*, EX1002; *see also id.*, ¶¶1-2, 21-22.

Ground	Claims	Obvious under 35 U.S.C. §103 over
1	1-3, 9, 18	International PCT Publication No. WO 00/70080 ("Wada," EX1006)
2	1-3, 9, 17-18	Wada in view of International PCT Publication No. WO 97/002357 ("Anderson," EX1012)
3	1-3, 9, 17-18	U.S. Patent No. 5,101,978 ("Marcus," EX1005) in view of Anderson

V. STATEMENT OF NON-REDUNDANCY AND EFFICIENCY

Ground 1 addresses the obviousness of claims 1-3, 9, and 18 over Wada, and Ground 2 addresses the obviousness of claims 1-3, 9, and 17-18 over Wada in further view of Anderson. Anderson was cited in Wada itself as providing suitable teachings for implementing the actuators of Wada's microfluidic devices. Further reflecting the unpatentability of the challenged claims, Ground 3 demonstrates the obviousness of claims 1-3, 9, and 17-18 over Marcus in view of Anderson.

NanoCollect has presented the issues for resolution in this Petition in a manner that is efficient for both the parties and the Board. Indeed, NanoCollect has worked tirelessly to narrow the dispute between the parties before seeking IPR.

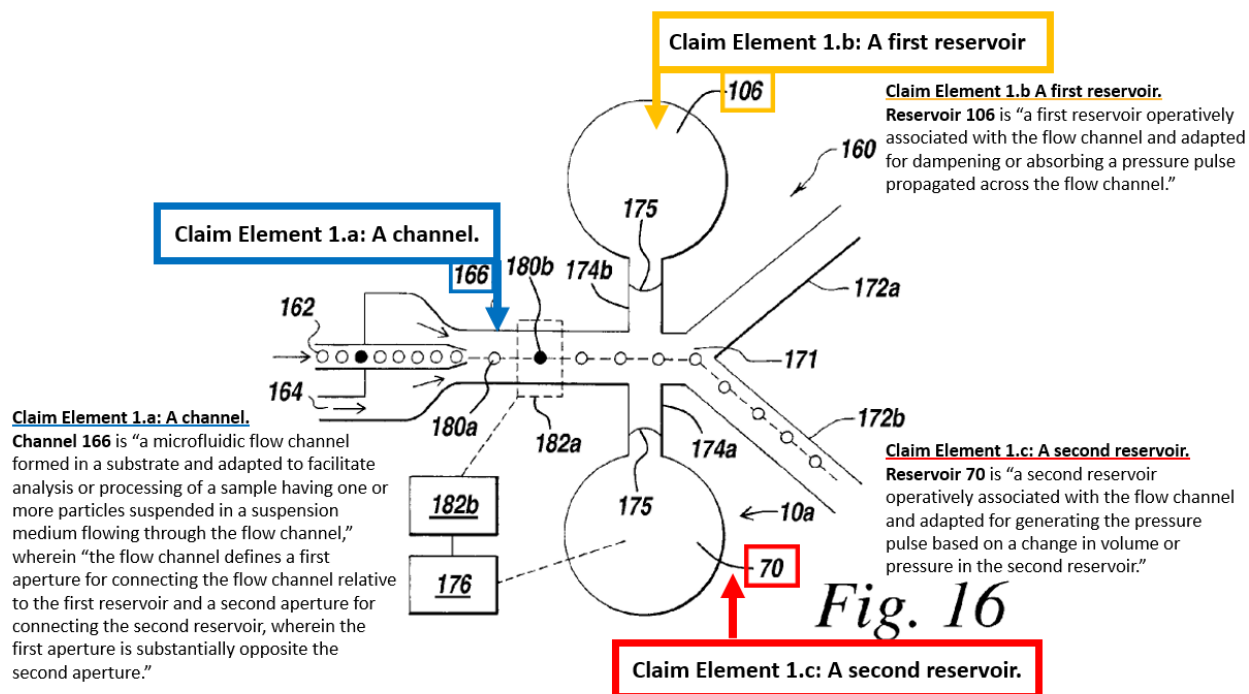
The asserted patents contain 130 claims. In the co-pending district court proceeding, NanoCollect repeatedly asked Cytonome to identify a reasonable number of asserted claims. Cytonome initially reduced the asserted claims to 104 in August 2019, but refused to further reduce the number until the week before Thanksgiving 2019. Even then, the number of asserted claims was only reduced to 42. NanoCollect asked the district court to order Cytonome to further reduce the number of asserted claims to a reasonable number. The district court denied that motion without prejudice on January 2, 2020, pending other developments in the case. In order to make efficient use of the finite resources of the Board and of the parties, NanoCollect's petitions focus almost exclusively on the remaining asserted claims.

NanoCollect also worked to eliminate the dispute between the parties before seeking IPR of these patents by engaging in lengthy settlement discussions with Cytonome, to no avail. Now that Cytonome has identified the claims in dispute and settlement discussions have reached an impasse, NanoCollect promptly submits the present Petition and other petitions challenging claims of the asserted patents. NanoCollect has filed only one petition against each patent and is not aware of any prior IPR petitions being filed by any other party against any of the Cytonome patents it is challenging.

VI. THE CHALLENGED PATENT

A. Background

The '295 patent describes a microfluidic system that uses a bubble valve and an actuator to “separate[e] particles having a predetermined characteristic from particles” that do not. EX1001, Abstract, 4:31-34; EX1002, ¶¶23-28. The '295 patent sets forth the use of an externally operated mechanical or pneumatic actuator bubble valve for regulating fluid flow through a channel without heating the fluid as the point of novelty. EX1001, 2:36-3:3. However, as the '295 patent itself notes, microfluidic systems that use bubble valves and actuators were well-known in the prior art. *Id.*, 2:27-55 (describing various prior art valves including bubble valves).



See EX1001, FIG. 16; EX1002, ¶26.

Figure 16 of the '295 patent illustrates an embodiment of the claimed subject matter. A version of Figure 16 (annotated by Dr. Weigl) is reproduced above identifying the elements of claim 18. EX1001, 4:54-57, 5:66-67, 8:32-33; EX1002, ¶26.

B. Claims

The '295 patent issued with 18 claims. In the interest of efficiency, this Petition challenges only claims 1-3, 9, and 17-18. Of the challenged claims, claim 1 is the only independent claim and recites:

1. A microfluidic system comprising:
 - a microfluidic flow channel formed in a substrate and adapted to facilitate analysis or processing of a sample having one or more particles suspended in a suspension medium flowing through the flow channel;
 - a first reservoir operatively associated with the flow channel and adapted for dampening or absorbing a pressure pulse propagated across the flow channel; and
 - a second reservoir operatively associated with the flow channel and adapted for generating the pressure pulse based on a change in volume or pressure in the second reservoir;wherein the flow channel defines a first aperture for connecting the flow channel relative to the first reservoir and a second aperture for connecting the flow relative to the second reservoir, wherein the first aperture is substantially opposite the second aperture.

EX1001 (the '295 patent), 13:42-14:3.

Claims 2-3, 9, and 17-18 each depend from independent claim 1. Claim 2 recites use of an actuator or pressurizer for generating a pressure pulse by varying the volume or pressure in the second reservoir. Claim 3 recites the flow channel further comprising a branched portion, and wherein the pressure pulse is used to sort the particles into a selected branch of the branched portion. Claim 9 further recites that the first reservoir includes a resilient wall for dampening or absorbing of the pressure pulse. Claim 17 adds a deflectable flexible membrane in the second reservoir. Lastly, claim 18 recites that the change in volume or pressure of the second reservoir is a transient change.

C. Prosecution History

The '295 patent issued from U.S. Patent Application No. 13/245,331 ("the '331 application"), which claims priority through a series of continuation, continuation-in-part, and divisional applications to U.S. Patent Application No. 10/179,488, filed on June 24, 2002, to U.S. Provisional Patent Application No. 60/411,058, filed on September 16, 2002, and to U.S. Provisional Patent Application No. 60/373,256, filed April 17, 2002. Claims 1-3, 9, and 17-18 thus have an earliest claimed filing date of April 17, 2002. EX1002, ¶29.

During prosecution of the '331 application, Applicant amended the claims to distinguish over some prior art cited by the examiner. For example, Applicant amended the independent claims to recite "a second reservoir operatively

associated with the flow channel and adapted for generating the pressure pulse based on a change in volume or pressure in the second reservoir” and “wherein the flow channel defines a first aperture for connecting the flow channel relative to the first reservoir and a second aperture for connecting the flow channel relative to the second reservoir, wherein the first aperture is substantially opposite the second aperture.” EX1004, 0027-29. However, as discussed in more detail below, these features were all well-known and well documented in the art. A Notice of Allowance was granted on August 28, 2013. *Id.*, 0009; EX1002, ¶¶30-33. None of the references relied upon herein were relied upon in prosecution of the ’295 patent.

VII. CLAIM CONSTRUCTION

Claim terms should be interpreted according to their ordinary and customary meaning to a person of ordinary skill in the art (POSA) at the relevant priority date, consistent with the specification. 37 C.F.R. §42.100(b); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (en banc). This Petition applies the prior art to the claims using this standard. EX1002, ¶¶34-45.

The Board need not expressly construe undisputed claim terms. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (“[W]e need only construe terms ‘that are in controversy, and only to

the extent necessary to resolve the controversy”) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

Even if the exact metes and bounds of a claim are indefinite, the Board nevertheless can determine whether embodiments plainly within the scope of the claim would have been obvious. *See Samsung Elecs. Am., Inc. v. Prisia Eng’g Corp.*, 2019-1169, 2019-1260, 2020 WL543427, at *8-9 & n.5 (Fed. Cir. Feb. 4, 2020) (remanding for PTAB to address petitioner’s argument that the Board could “apply the prior art” for purposes of anticipation and obviousness to an indisputably *IPXL*-type indefinite claim); *Ex parte Tanksley*, 26 U.S.P.Q.2d 1384, 1387 (B.P.A.I. 1991) (embodiment within scope despite indefiniteness); *Ex parte Sussman*, 8 U.S.P.Q.2d 1443, 1445 n.* (B.P.A.I. 1988) (affirming obviousness despite indefinite claim format); *see also Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901, 911 (2014) (rejecting “insolubly ambiguous” or “amenable to construction” standard and holding claims are indefinite if the scope of the claim cannot be ascertained with “reasonable certainty”); *cf. Enzo Biochem, Inv. v. Applera Corp.*, 599 F.3d 1325, 1332 (Fed. Cir. 2010) (stating in dicta that “a claim cannot be both indefinite and anticipated” because a claim is only indefinite if it is incapable of construction).

Petitioner does not believe any express claim constructions are required for the Board to conclude the asserted prior art renders the challenged claims

unpatentable. Further discussion of the challenged claims appears *infra* during the discussion of how the cited art renders each challenged claim unpatentable. The analysis of the challenged claims vis-à-vis the cited art is consistent with the claim construction positions that Cytonome has offered in district court.

No claim construction order has been issued by the district court in the co-pending district court proceeding. However, Cytonome made several admissions about the meanings of claim terms in the asserted patents. These admissions can be found in Cytonome's Reply Claim Construction Brief (EX1042), and its expert declaration regarding the meaning of certain claim terms in the asserted patents (EX1043).

Among other things, Cytonome's declarant opined that the terms "reservoir" and "chamber" as used in the challenged claims of the asserted patents each should be understood as *a physical structure that contains fluid*. EX1043, ¶¶25-26, 31, 34 (reservoir); *id.*, ¶¶44-48 (chamber); *see also* EX1042, 20 (even when a microfluidic chamber is "empty" it still contains a gas (air) and thus contains a fluid); EX1002, ¶43. As an example of a reservoir/chamber, Cytonome's declarant points to "well" 1602 in Figure 15 of U.S. Patent No. 6,592,821 to Wada *et al.* EX1043, ¶27 ("This is a typical example of a fluid reservoir formed as (often) a shallow cylindrical well in one or more layers of a substrate. Reservoirs are

typically formed in this way in microfluidic devices due to ease of fabrication, but the exact geometry may vary.”).

As another example, Cytonome’s declarant opined that the term “absorbing” as used in the challenged claims means *to receive, take up, or take in the pressure pulse*. EX1043, ¶¶50-52, *see also* EX1042, 1, 7-8, 18-19; EX1045, 8-10, 18-20; EX1002, ¶44. Cytonome’s declarant has also opined that the terms “dampen” or “dampening” as used in other claims of the asserted patents means *to meaningfully dissipate so as to prevent a pressure wave from affecting the flow of the remaining particles in the stream of particles*. EX1043, ¶¶56-57; *see also* EX1042, 13-14; EX1002, ¶45.

As set forth herein, the disclosures relied upon in the prior art discussed herein are plainly within the scope of the challenged claims, including as construed by Cytonome as discussed above.

VIII. LEVEL OF ORDINARY SKILL IN THE ART

The ’295 patent relates to microfluidic systems for sorting particles in a suspension. EX1001, 1:25-28. Dr. Bernhard H. Weigl is an Affiliate Professor in the Department of Bioengineering at the University of Washington and has more than thirty years of experience with methods and apparatuses for sorting particles in a suspension as an analytical chemist and was well-versed in microfluidic particle sorting devices at the relevant time. EX1002, ¶¶3-9; EX1003.

As Dr. Weigl explains, a POSA at the relevant time would have had a bachelor's or master's degree in the field of bioengineering, mechanical engineering, chemical engineering, or analytical chemistry; or a bachelor's or master's degree in a related field and at least three years of experience in designing or developing microfluidic systems. EX1002, ¶¶46-49. The prior art cited in this Petition, including the background art, demonstrates information with which a POSA would have been familiar at the relevant time. *Id.*, ¶¶46-106.

IX. SUMMARY OF THE PRIOR ART

A. Background

The relevant state of the art supports the unpatentability of the challenged claims. EX1002, ¶50. Flow cytometers have long been used to sort particles. *Id.*, ¶¶51-61 (discussing EX1014, EX1016, EX1005). In fact, microfluidic devices (with channels have inner diameters of approximately 100 microns or less) were available at least as early as the 1970's. *Id.*, ¶¶53-57 (discussing EX1016). By the earliest claimed priority date, particle sorting flow cytometers, including sorters using heater electrodes and piezoelectric actuators were widely available. *Id.*, ¶¶53, 58, 65-66, 73, 75-76. (discussing EX1007, EX1014, EX1016, EX1020).

Structures for making functioning microfluidic devices also were widely known. EX1002, ¶¶59-61 (discussing EX1005). Microfluidic devices, including the "lab-on-a-chip" or "μTAS" concept, became increasingly popular as

microfabrication techniques such as photolithography allowed for the manufacture of increasingly complex microfluidic devices with that could be run in “massively parallel” fashion. *Id.*, ¶¶62-66 (discussing EX1017-EX1018, EX1020). Computer-aided design (CAD) in the 1990’s enabled even better and more efficient μ TAS designs, resulting in mass-production of microfluidic chips capable of running analytical work serially or in parallel. *Id.*, ¶¶64-65 (discussing EX1018, EX1020). Microfluidic devices having actuators comprising a flexible wall or malleable material were also known in the art. *Id.*, ¶¶65-66 (discussing EX1020).

Precise control of flow within microfluidic channels was achieved due to the normally laminar flow in microfabricated devices. EX1002, ¶¶67-68 (discussing EX1017, EX1022, EX1033). Micropumps, including piezoelectric membrane-displacement pumps, were known to provide a pressure pulse by deflecting a microfabricated membrane, such as a flexible silicone diaphragm or the interface of a fluid/gas meniscus. EX1002, ¶¶69-73 (discussing EX1012, EX1014, EX1022-EX1023). Particle selection by increasing fluid flow perpendicular to the flow channel was known as the “simplest switching component,” which was taught to be accomplished by creating a gas bubble to generate a “momentary pressure increase” to deflect the particle of interest into the desired outlet. EX1002, ¶¶74-76 (discussing EX1007, EX1016, EX1018). As explained by Dr. Weigl, it was known that controlling “bleeding over of material” from the deflection pulse could be

achieved, for example, by using a vent, chamber, passageway or other compliance device to “isolate the effects of output loading from control flow characteristics,” including by using elastic elements or oppositely-facing buffer structures. EX1002, ¶¶77-89 (discussing EX1007, EX1016, EX1018, EX1032-EX1035).

B. Asserted References

As Dr. Weigl explains, and as addressed in further detail below, claims 1-3, 9, and 17-18 would have been obvious to a POSA at the relevant time. EX1002, ¶¶21-22. Numerous microfluidic systems were known well-before April 17, 2002, including many that used the same three-component structure broadly claimed in the '295 patent.

i. Wada

International PCT Publication No. WO 00/70080 to Wada, *et al.*, entitled “Focusing of Microparticles in Microfluidic Systems,” published on November 23, 2000. EX1002, ¶90. Wada is prior art to the '295 patent under pre-AIA §102(b).

Id.

Wada discloses microfluidic systems for focusing and sorting particles in microchannels. EX1006, 3:13-15, 7:5-8:8, FIGS. 1A, 22-24 (including the corresponding discussion in the Wada reference); EX1002, ¶¶91-92. Figures 22-24 are representative schematics.

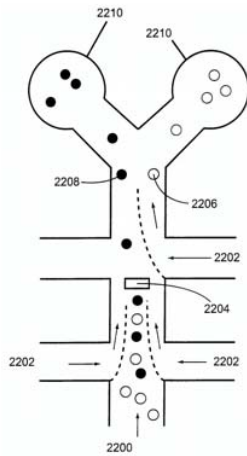


Fig. 22

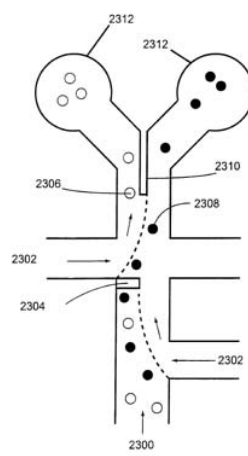


Fig. 23

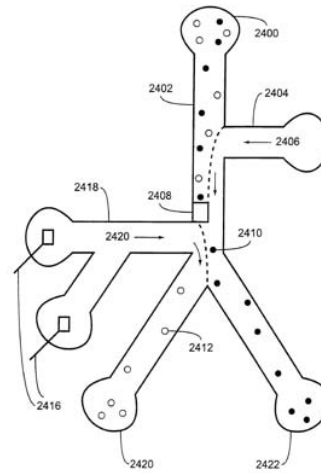


Fig. 24

EX1006, FIGS. 22-34; EX1002, ¶¶95.

Wada describes a flow control regulator is used to focus the particles prior to sorting. EX1006, 4:1-5 (listing known fluid direction components, including “a fluid pressure force modulator, an electrokinetic force modulator, a capillary force modulator, a fluid wicking element”). Once focused, a signal detector detects a “signal produced by a selected member of the particle population.” *Id.*, 7:13-24. Then, based on whether a particular characteristic was detected, cells are sorted into different microchannels or branches using hydrodynamic flow. *Id.*, 26:26-7:2; *see also id.*, 19:23-23:18, FIGS. 22-24; EX1002, ¶¶93-94.

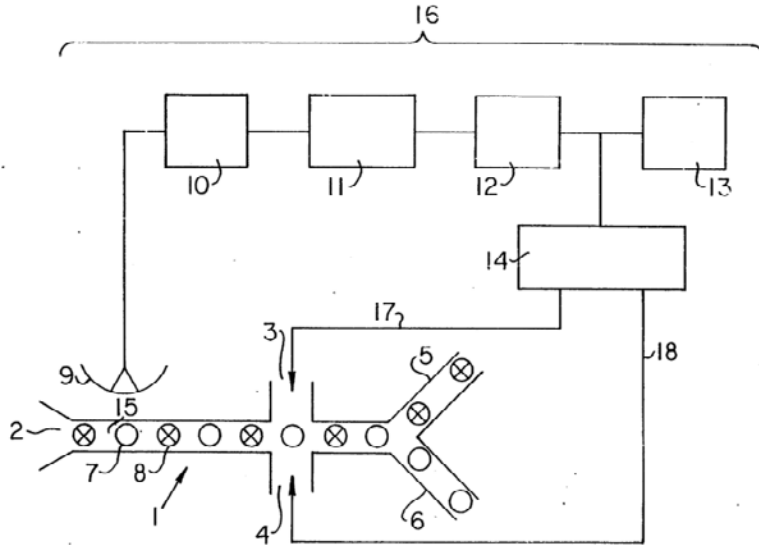
Wada describes various methods for controlling the flow of particles, including heating and “pressure, hydrostatic, wicking, capillary, and other forces.”

ii. *Marcus*

U.S. Patent No. 5,101,978 to Marcus issued April 7, 1992. Marcus is prior art to the '295 patent under pre-AIA §102(b). EX1002, ¶96.

Marcus describes microfluidic systems that separates particles, such as different blood cells. Marcus combines “two conventional components...a fluidic sorting device and a machine vision apparatus.” EX1005, 2:7-13 (“[n]o novelty lies in either one” of these components).

Marcus teaches that the fluidic logic element (labeled generally as “1,” in Figure 1, reproduced below) comprises an inlet (2), two control ports (3 and 4) for sorting particles (7 and 8) within a fluid carrier (15), and two outlets (5 and 6). EX1005, 2:14-18, 3:30-62; EX1002, ¶¶97-100. The fluidic logic unit is described as “conventional” and able to “be produced using conventional micromachining technology or any other conventional means.” EX1005, 2:14-18, 3:30-62. The machine vision apparatus (16) identifies particles with visually distinct features and subsequently conveys a “message to control ports in the fluidic logic element” to sort particles 7 and 8. *Id.*, 2:49-66, 4:30-39. Specifically, a signal from the decision control device (12) is sent to a fluidic controller device (14), which transmits the signal to actuate the fluidic element control ports (3 and 4). *Id.*; see also *id.*, 3:41-43, 4:58-64.



Id., FIG. 1.

iii. *Anderson*

International PCT Patent Publication No. WO 97/02357 to Anderson, *et al.*, entitled “Integrated Nucleic Acid Diagnostic Device,” published on January 23, 1997. Anderson is prior art to the ’283 patent under pre-AIA §102(b). EX1002, ¶101.

Wada specifically references Anderson as having applicable teachings regarding pumps for use in microfluidic devices. EX1006, 43:13-14. Anderson describes various advances in “the fabrication of micromechanical structures, e.g., micropumps, microvalves and the like, and microfluidic devices including miniature chambers and flow passages.” EX1012, 2:29-34; *see also id.*, 28:3-29 (noting that “[m]icrofabrication of microfluidic devices...has been discussed in detail in” the prior art), 34:5-21, 37:13-28; EX1002, ¶¶102-3.

As Anderson explains, fluid may be moved from a first channel or chamber into another by applying positive pressure to the first chamber. EX1012, 5:14-31. This “positive pressure forces said fluid sample from the [at] least first chamber into the common chamber or channel.” *Id.*; *see also id.*, 46:23-29 (describing “application of pressure differentials provided by either external or internal sources”), 46:30-48:16 (moving fluids using positive or negative pressure pulses), 62:18-63:13 (“pumps which hav[e] a bulging diaphragm” and those “powered by a piezoelectric” actuator “may be used to move the sample through the various operations of the device”); EX1002, ¶¶104-5.

For example, a chamber may act as a pumping chamber with “a diaphragm pump as one surface of the chamber” with “zero displacement when the diaphragm is not deflected.” EX1012, 44:28-46:23 (noting that the “diaphragm pump will generally be fabricated from any one of a variety of flexible materials, e.g., silicon, latex, teflon, mylar, and the like”); *id.*, 38:1-39:4 (chamber etched into substrate); EX1002, ¶¶105-06.

X. STATEMENT OF REASONS FOR THE RELIEF REQUESTED

A. Ground 1: Claims 1-3, 9, and 18 Are Obvious in View of Wada

Wada discloses each and every element of each of claims 1-3, 9, and 18. In fact, at least some embodiments of Wada (*e.g.*, Figures 22-23) reasonably would have been viewed by a POSA as anticipating the claimed subject matter. EX1002,

¶¶107-70. Given the well-known maxim that anticipation is the “epitome of obviousness,” Petitioner submits that claims 1-3, 9, and 18 are obvious in view of Wada. *McDaniel*, 293 F.3d at 1385.

To the extent the challenged claim elements are viewed as illustrated in multiple embodiments of Wada, as discussed in detail below, a POSA would have had good reason to use all the elements in a single embodiment and a reasonable expectation of success of thereby obtaining what is claimed. *E.g.*, EX1002, ¶¶107-111. Those in the art at the time typically would read the prior art reference as a whole for all that it discloses and would not mechanically limit its teachings to individual embodiments only as specifically illustrated. This is particularly true for the Wada reference, in which the embodiments and teachings are disclosed such that they are cooperative and integral. Indeed, Wada expressly teaches “all the techniques and apparatus described above may be used in various combinations.” EX1006, 49:13-20; *see also id.*, 23:19-28 (describing applying actuator wells illustrated in Figure 24 to opposed channel configuration of Figure 22); EX1002, ¶108. *See also: McDaniel*.

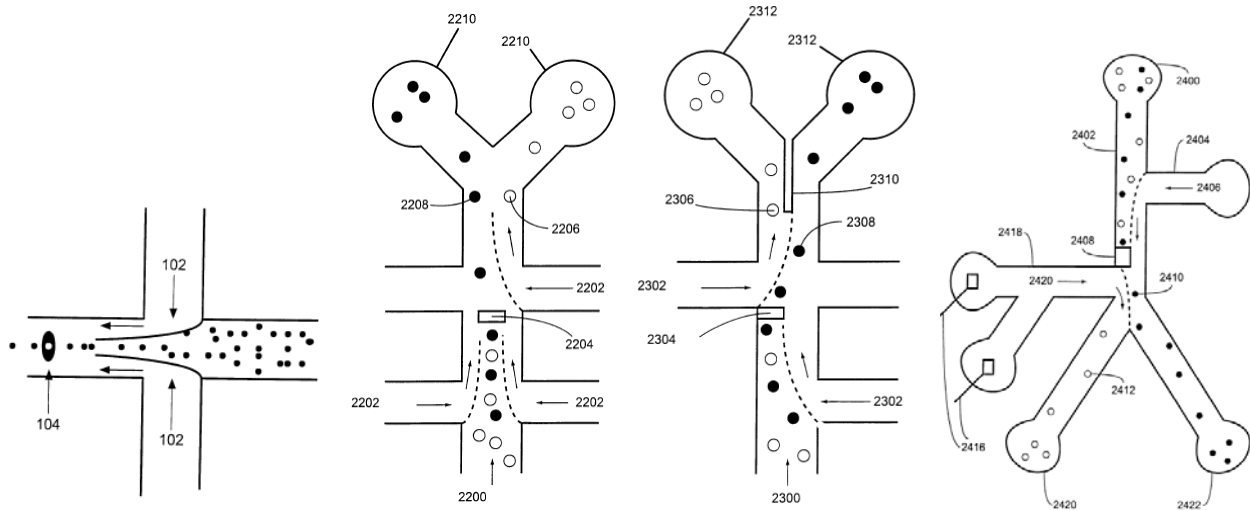
For example, Wada teaches the opposed sorting microchannel structures in Figures 22 and 23, like specifically illustrated for the sorting microchannel structure in Figure 24, have actuators (*e.g.*, Joule heating electrodes). *E.g.*, EX1006, 23:19-28; 8:6-23. Consistent with Figures 22 and 23, Wada discloses and

illustrates employing a reservoir opposite the sorting microchannel. EX1002, ¶¶133-51. Moreover, as Dr. Weigl explains, it was conventional and well-known to use an opposing vent, chamber, passageway, or other compliance device to isolate the effects of the control flow characteristics. *E.g. id.*, ¶¶80, 137-38; Section IX.A above. From the teachings of Wada, a POSA would have immediately appreciated that the opposing sorting microchannel structure is readily inclusive to other illustrated channel configurations of Wada (*e.g.*, Fig. 24). EX1002, ¶¶119-23, 139-40. As such, Wada discloses and renders obvious the claimed subject matter.

i. Claim 1

1.[preamble] A microfluidic system comprising:

At a high level, Wada's disclosure is directed to microfluidic systems. Entitled "Focusing of Microparticles in Microfluidic Systems," Wada discloses "systems for particle focusing to increase assay throughput in microscale systems." EX1006, Title, Abstract. Wada's microfluidic systems can sort "particle populations, such as cells and various subcellular components." *Id.*; *see also id.*, 3:13-33, 12:3-14, FIGS. 1A, 22-24 & corresponding discussion in the Wada reference. Example schematics of Wada's microfluidic systems can be seen in Figures 1A and 22-24, reproduced below. Thus, Wada discloses the preamble of claim 1. EX1002, ¶¶112-14; *see also* Section IX above.



EX1006, FIGS. 1A, 22-24.

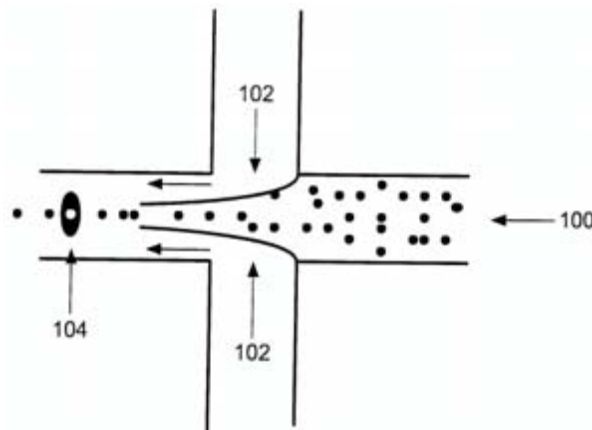
[1.a] a microfluidic flow channel formed in a substrate and adapted to facilitate analysis or processing of a sample having one or more particles suspended in a suspension medium flowing through the flow channel;

Wada discloses microfluidic flow channels in the form of “*channels* and/or chambers of the microfluidic devices” EX1006, 21:3-5; *see also* Section IX above. These microfluidic flow channels are formed in a substrate. As Wada explains, the channels are “integrated into the body structure of a microfluidic device.” EX1006, 37:23-32; *see also id.*, 38:1-31 (microfluidic channels formed in a substrate), 21:3-5 (forming microscale channels on a wide range of different substrate materials), 39:19-33 (channels fabricated into upper surface of the bottom substrate); EX1002, ¶¶115-16.

Wada’s flow channels are adapted to facilitate analysis and processing of a sample with particles suspended in a suspension medium flowing through the flow channel. As Wada explains, its systems for sorting particle populations “are carried

out *within fluidic channels, along which the cell suspensions and/or other particles are flowed.*” EX1006, 37:24-28; *see also id.*, 3:22-23 (“particles flowing in a first microchannel”), 2:30-32 (focusing particles of a particle stream flowing in a microchannel), 12:1-14 (focusing aligns cells “into a narrow region of a microchannel to facilitate single particle or narrow streamline detection”), 42:8-24 (describing mechanisms for flowing cells, including pressure-based flow); EX1002, ¶¶117-18.

Wada also makes clear that the sample analyzed has particles suspended in a suspension medium, as illustrated below. EX1006, 11:19-20, 34:14-16 (analyzing compounds “injected, free in solution”), 45:14-23 (preparing assays to be sorted by suspending particles).

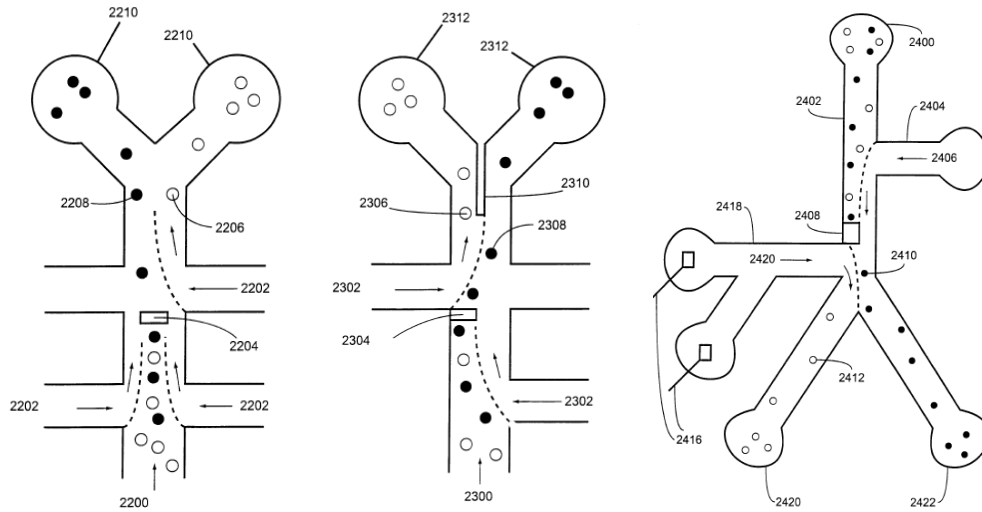


EX1006, FIG. 1A; EX1002, ¶119.

Various examples of the microfluidic flow channel recited in element **1.a** are depicted in the figures of Wada. *E.g.* EX1006, FIG. 21, 14:3-14. For example, Figure 1A of Wada depicts a microfluidic system in which “cells 100 (or other

particles) are typically flowed from one microchannels into a cross-junction.” *Id.*, 13:11-23-31. The stream of particles (*e.g.*, cells 100) are conveyed through a microfluidic flow channel suspended in a carrier fluid. *Id.*; *see also* EX1002, ¶119.

Each of Figures 22, 23, and 24 and their accompanying descriptions also teach the microfluidic flow channel formed in a substrate and adapted to facilitate analysis or processing of a sample having one or more particles suspended in a suspension medium flowing through the flow channel. As discussed below, the main vertical flow channel illustrated in Figures 22-24 is a microfluidic flow channel as claimed. Figure 22 depicts a vertical main microchannel, wherein a stream of particles (cells 2200) is flowed through the flow channel. EX1006, 18:26-20:20. Similarly, Figure 23 depicts conveying a stream of particles (cells 2300) suspended in a suspension medium flowing along a vertical main microchannel towards a detector (2304). *Id.*, 11:6-7, 20:3-14. Figure 24 also depicts flowing a sample of particles within a vertical microfluidic flow channel toward a detector (2408). *Id.*, 11:8-9, 22:23-23:18. More specifically, the microfluidic flow channel in Figure 24 comprises a vertical main microchannel 2402, with the main flow direction moving from the top of the figure to the bottom of the figure. *Id.*, 23:7-18; EX1002, ¶¶120-24.

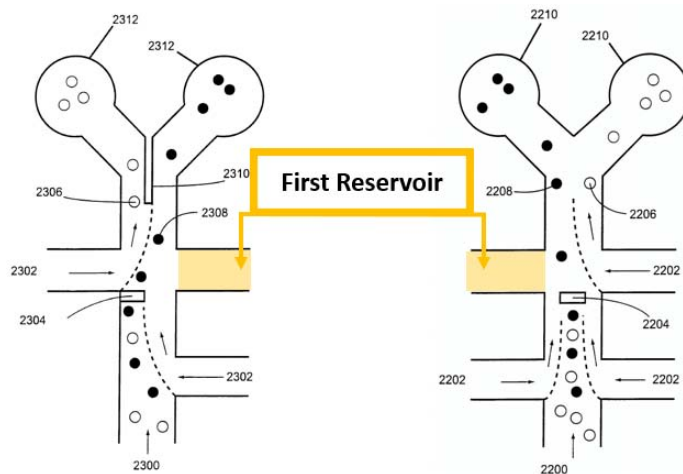


EX1006, FIG. 22-24.

Thus, Wada discloses claim element **1.a.** EX1002, ¶¶115-24.

[1.b] a first reservoir operatively associated with the flow channel and adapted for dampening or absorbing a pressure pulse propagated across the flow channel; and

Wada teaches a first reservoir operatively associated with the flow channel and adapted for dampening or absorbing a pressure pulse propagated across the flow channel. EX1002, ¶¶125-39; *see also* Section IX above.

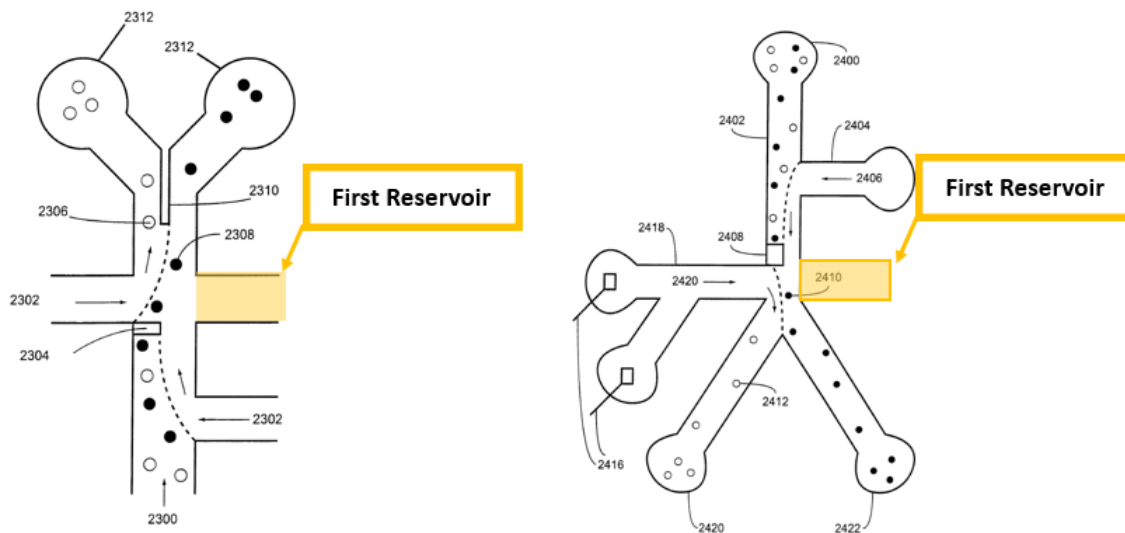


EX1006, FIGS. 22-23; EX1002, ¶125.

For example, Wada Figures 22-23, (annotated above by Dr. Weigl), depict a reservoir in the form of an opposing microchannel structure disposed opposite of the actuated sorting microchannel structure (through which the actuator mechanism selectively applies a pressure pulse represented by arrows 2202 and 2302) disposed downstream of the detectors 2204 and 2304. EX1006, 19:23-20:14. A POSA would have recognized that the opposing microchannel structure—in the context of Wada’s microfluidic devices and how Wada discloses they operate—is a physical structure that contains fluid, receives a pressure pulse, and is operatively associated with the flow channel via its fluid communication with the flow channel. EX1002, ¶125; *see also* Section IX above.

Further, each of Figures 22-23 discloses a pressure pulse propagated across the flow channel (flow 2202 or 2302) to deflect a selected particle from one side of the microchannel into a selected branch on the other side of the flow channel. A POSA would have recognized that the opposed microchannel structure in each of Figures 22-23, in the context of Wada’s microfluidic devices and how Wada discloses they operate, is configured to receive the pressure pulse and to dampen and absorb the pressure pulse because the structure opening is aligned with the direction of the pressure pulse (substantially perpendicular to the main microchannel). A POSA would have recognized the use of the opposed second reservoir was equally applicable to the microchannel structure of Wada’s Figure 24

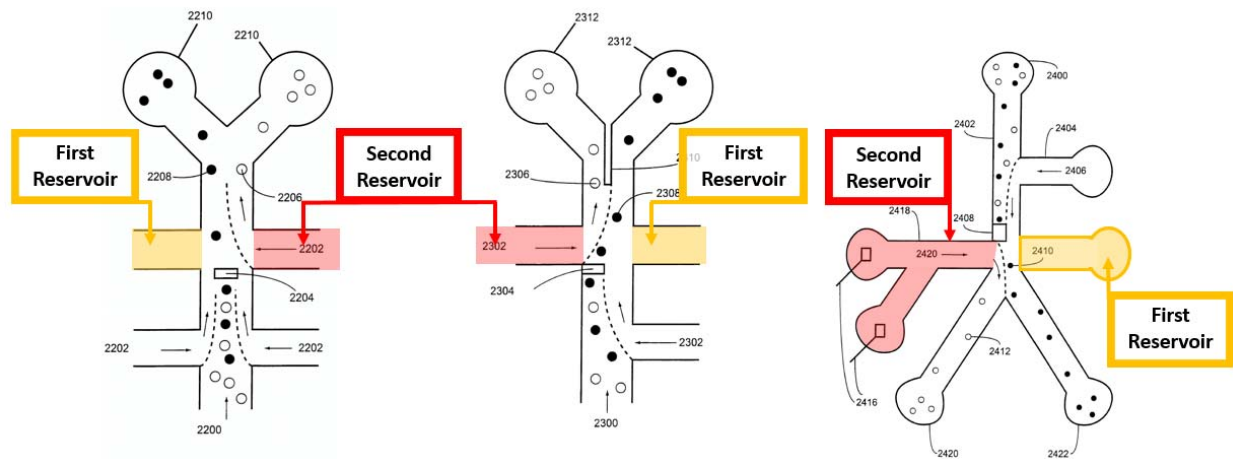
(Figures 23 and 24 annotated by Dr. Weigl, below). EX1002, ¶129. A POSA would thus have understood that the opposed microchannel structure in the context and operation of Wada is thus not only a reservoir, but it is also a structure that is adapted for dampening or absorbing a pressure pulse propagated across the flow channel as recited in [1.b]. EX1002, ¶¶126-30 (citing EX1005, FIG. 1; EX1007, FIG. 2; EX1016, 1:49-2:19, 5:44-54, FIG. 1; EX1018, 341-42; EX1032, 8:4-8; EX1033, 198; EX1034, 2:23-34, 39:25-34, 40:20-25; EX1035, 377, 382-83).



EX1006, FIGS. 23-24; *see also* EX1002, ¶129.

Wada’s teachings further make clear that a pressure pulse is propagated across the flow channel to be dampened by the first reservoir. Wada discloses its fluid direction components “‘nudge’ materials across the width of a first channel” in order to “direct sample flow towards or away from” a first flow channel, and “into, e.g., an additional intersecting channel or into a channel region.” EX1006, 18:26-19:13. Wada also explains that an actuator (including a Joule heating

electrode) may be disposed in a well on the distal end of each of the opposing sorting channels and being operatively associated with the flow channel. *E.g., id.*, 7:25-29; 8:12-23; 22:30-23: 24. When the actuator in only one of the two opposed sorting microchannel structures of Wada is activated at a given time, as illustrated in each of Dr. Weigl’s annotated Figures 22-24 below, the well at the distal end of the opposite (non-actuated) sorting microchannel dampens or absorbs the pressure pulse propagated across the flow channel. EX1002, ¶¶133-37.



EX1006, FIGS. 22-24; *see also* EX1002, ¶¶132-34.

Although Wada’s opposed microchannel structure is depicted in Figures 22-23, such feature is not limited to Figures 22-23 but applies equally to Figure 24. EX1006, 49:13-20. For instance, the use of a second reservoir is equally applicable to the embodiment represented in Figure 24, as shown above. EX1002, ¶¶129-34.

Further, Wada makes clear that the well of the opposed microchannel structure may be a chamber (*i.e.*, cavity). That is, “Joule heating is typically

produced by flowing current through an electrode or other conductive component positioned within a well, microscale channel, or other cavity within the device.” EX1006, 20:23-25; EX1002, ¶135. A POSA would have recognized the phrase “other cavity within the device” as teaching a chamber. *Id.*, 37:29-32, 38:11-29, 39:19-33; EX1002, ¶¶134-38. A POSA would thus have had good reason to place the Joule heating electrode (an exemplary actuating mechanism) on the substrate within a chamber at the distal end of each opposed sorting microchannel to generate a pressure pulse that will propagate across the flow channel downstream of the detector a deflect a selected particle into a selected branch of the flow channel. EX1002, ¶¶134-38; EX1006, 43:5-14; *see also* Sections IX, X.A.i above.

For the reasons discussed above, Wada teaches claim element **1.b** and it would have been obvious to provide, in a microfluidic system, a first reservoir operatively associated with the flow channel and adapted for dampening or absorbing a pressure pulse propagated across the flow channel.

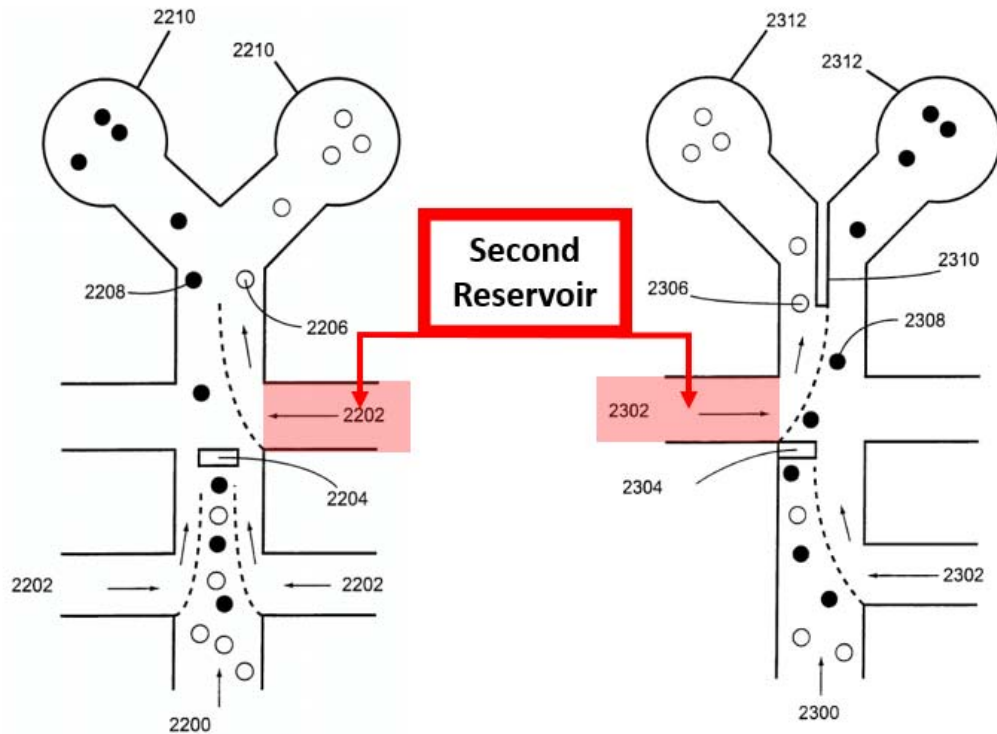
[1.c] a second reservoir operatively associated with the flow channel and adapted for generating the pressure pulse based on a change in volume or pressure in the second reservoir;

As discussed above, Wada teaches reservoirs as part of opposing sorting microchannel structures. When actuated, the opposed sorting microchannel structure of Wada, including its well or chamber from which the pressure pulse enters the flow channel, is a second reservoir operatively associated with the flow

channel and adapted for generating the pressure pulse based on a change in volume or pressure in the second reservoir. EX1002, ¶¶139-47.

For example, as illustrated below, Figures 22-23 of Wada depict second reservoirs as part of opposing microchannel structures. EX1006, 19:23-20:14; EX1002, ¶¶139 (citing EX1042, 9-10, 18-20; EX1045, 8-10, 18-20; EX1043, ¶¶25-27, 31, 33-34, 44, 48). Each of Figures 22-23 discloses a transient pressure pulse (*i.e.*, 2302 and 2202 located downstream of detectors 2304 and 2204, respectively) flowing from an actuated sorting microchannel structure into the opposing sorting microchannel structure. Each opposed sorting microchannel is a structure that contains fluid. A POSA would have understood the non-actuated, opposed sorting microchannel structure in Figures 22-23, in the context of Wada's microfluidic devices and how they operate, includes a reservoir adapted for dampening or absorbing the transient pressure pulse propagated across the microfluidic channel. EX1002, ¶¶140-46.

As Dr. Weigl explains, a POSA would have recognized that these second reservoirs are operatively associated with the microfluidic flow channel because they are in fluid communication with it and generate a transient fluid flow (*e.g.*, 2202, 2302) into the flow channel. EX1002, ¶139.



EX1006, FIGS. 22, 23; EX1002, ¶139. As discussed above, this feature is not limited to Figures 22-23 but applies equally to Figure 24. EX1006, 49:13-20; EX1002, ¶¶129-31; FIGS. 22-24 annotated by Dr. Weigl discussing claim element **1.b**, above.

Further, Wada teaches that these reservoirs can include an actuator to generate a pressure pulse based on a change in volume or pressure in the second reservoir. EX1006, 4:1-5, 19:9-13, 7:18-29, 42:8-30, 43:5-14, FIGS. 23-24 (describing various actuators and methods of directing fluid flow). Wada Figure 22 likewise includes an actuator to generate a pressure pulse based on a change in volume or pressure in a second reservoir. EX1006, 19:23-20:2, 23:18-24; *see also id.*, 8:6-23, FIGS. 22-24. Using such an actuator mechanism allows for deflecting or

redirecting of the flow of target particles. Specifically, the introduction of various fluids or particles into the microchannels of the microfluidic device can be controlled by “activating a heating element,” such as “a Joule heating electrode” located in one or both of the opposed sorting microchannels or in wells or chamber/cavity at the distal ends of the opposed sorting microchannels. *Id.*, 7:25-29; *see also id.*, 8:12-23, 20:23-25, 22:30-23:18, 37:29-32, 38:11-17, 39:19-33, FIG. 24; EX1002, ¶140.

As Dr. Weigl explains, the heating of the fluid in the sorting microchannel by the Joule heating electrode selectively generates and applies a pressure pulse based on a change in pressure in the second reservoir and propagates it across the flow channel to deflect a particle into a selected branch of the flow channel. EX1002, ¶141. Wada describes this pressure pulse in terms of a decrease in the viscosity of the heated fluid resulting in flow of the fluid, but this is, in fact, a pressure pulse. *See, e.g.*, EX1006, 20:30-31 (describing temperature oscillation period as short as 100 milliseconds), 21:27-32 (describing applying the power supply to generate the heat as a “pulse”), 21:32-22:2 (describing the change in temperature that generates the sorting fluid flow as “extremely rapid and easily controlled”). This pressure pulse is selectively generated and applied when the detector indicates the particle is selected for deflection from the stream of particles. Based on Wada’s disclosures, a POSA would have had good reason to employ an

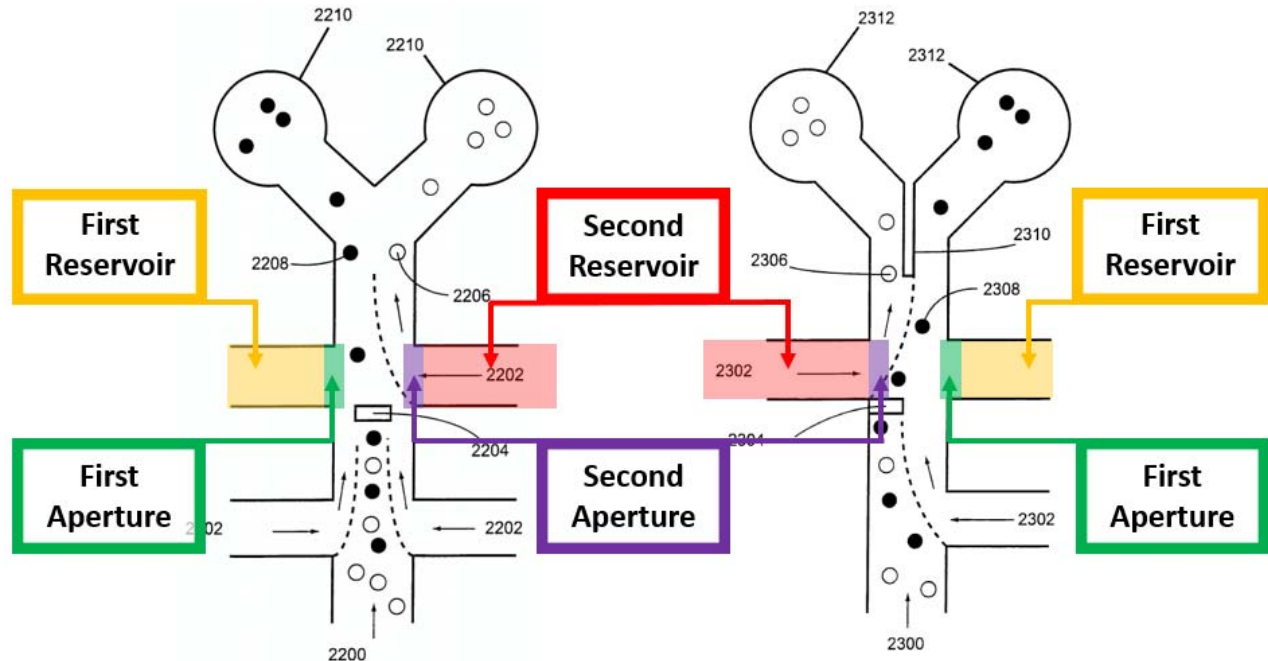
actuator comprising a reservoir and a pressurized gas (*i.e.*, a compressible fluid) at the distal end of each of the opposed sorting microchannels. EX1002, ¶¶142-46 (describing usages of such feature in the prior art and citing EX1020, 1:42-64, 2:31-3:17; EX1023, ¶¶0026, 0032; EX1014, 4; EX1016, FIG. 2; EX1022, 107).

More specifically, a POSA would have recognized that Wada teaches a pressurized reservoir at the distal end of the non-actuated, opposed second side microchannel. Further when actuated, the reservoir serves as a second reservoir operatively associated with the flow channels and adapted for generating a pressure pulse based on a change in volume in the second reservoir and propagating it across the flow channel. Accordingly, Wada teaches claim element 1.c of the '295 patent. EX1002, ¶¶139-47; *see also* Sections IX, X.A.i above.

[1.d] wherein the flow channel defines a first aperture for connecting the flow channel relative to the first reservoir and a second aperture for connecting the flow relative to the second reservoir, wherein the first aperture is substantially opposite the second aperture.

As discussed and as illustrated below, the first reservoir and second reservoir are operatively associated with the flow channel. Indeed, in describing Figure 22, Wada explains that the “opposing microchannels [are] located downstream from detector 2204 for introducing at least one hydrodynamic flow 2202 so as to direct selected cells 2208 (e.g., fluorescently-labeled cells) and non-selected cells 2206 into, in this case, one of two microchannels, each terminating in particular

collection wells 2210.” EX1006, 19:30-20:2; EX1002, ¶148. A similar arrangement is depicted and described relative to Figure 23. EX1006, 20:8-11.



EX1006, FIGS. 22-23; EX1002, ¶148.

Based on Wada’s disclosure, a POSA would have recognized that the first reservoir opens into the microfluidic flow channel and, similarly, the second reservoir opens into the microfluidic flow channel. That is, the flow channel defines a first aperture for connecting the flow channel relative to the first reservoir and a second aperture for connecting the flow relative to the second reservoir. The first and second aperture are depicted in the above versions of Figures 22-23 (annotated by Dr. Weigl). As explained by Dr. Weigl, Wada also teaches an embodiment of Figure 24 comprising a reservoir operatively associated with the flow channel. EX1002, ¶¶129, 148-49. An embodiment of Figure 24 would also

have the flow channel defining a first aperture for connecting the flow channel relative to the first reservoir and a second aperture for connecting the flow relative to the second reservoir, wherein the first aperture is substantially opposite the second aperture of claim element **1.d**. *Id.* As seen in these figures, the first aperture is substantially opposite to the second aperture. Wada thus discloses element **1.d**. EX1002, ¶¶148-50.

As set forth above, Wada teaches each and every element of claim 1. To the extent the challenged claim elements are viewed as illustrated in multiple embodiments of Wada, Wada teaches “all the techniques and apparatus described above may be used in various combinations.” EX1006, 49:13-20; EX1002, ¶108; *see also* Section X.A.i above. Accordingly, Wada discloses and renders obvious the subject matter of claim 1. EX1002, ¶¶112-50.

ii. Dependent Claims 2-3, 9, and 18

Dependent claim 2-3, 9, and 18 each depend from independent claim 1, the analysis for which in Ground 1 is included herein. EX1002, ¶151.

2. The system of claim 1 further comprising an actuator or pressurizer operatively associated with the second reservoir and adapted for generating the pressure pulse by varying the volume or pressure in the second reservoir.

As discussed above for element **1.c**, Wada teaches the use of an actuator in association with the second reservoir, wherein the actuator generates a pressure pulse and propagate the pressure pulse across the flow channel. *E.g.*, EX1006,

7:18-8:23; *see* Section X.A.ii above. For the same reasons discussed above, the actuator is operatively associated with the second reservoir and adapted for generating the pressure pulse by varying the pressure in the second reservoir.

As one example, Wada uses of an actuator in the form of Joule heating electrode, which selectively applies a pressure pulse to the stream by varying the pressure in the second reservoir. EX1006, 7:25-27; 8:19-22, FIG. 24; EX1002, ¶¶152-53. However, Wada's disclosures are not limited to embodiments where the actuator (e.g. 2416 of FIG. 24) is in the form of a heating element. For instance, particle sorting may be achieved via focusing, and particles may be focused "using one or more *fluid direction components* (e.g., a *fluid pressure force modulator*...)." EX1006, 4:1-5; *see also id.*, 7:18-29 (describing "*fluid direction components*" and a "*flow control regulator*"), 42:8-30 (describing mechanisms such as *pressure based-flow*), 43:5-14 (describing various pressurizers and pumps). Notably, Wada discloses that these actuators can be included in "one or both microchannels of the second set of opposing microchannels located downstream from detector." *Id.*, 23:21-22. That is, Wada discloses the use of an actuator operatively associated with the second reservoir.

A POSA would have had good reason to employ an actuator comprising a reservoir and a pressurized gas (*i.e.*, a compressible fluid) at the distal end of each of the opposed sorting microchannels. An actuator comprising a reservoir and

pressurized gas in the opposed microchannel structure, as suggested by Wada, is an actuator that is a pressurizer operatively associated with the second reservoir and adapted for generating the pressure pulse by varying the volume or pressure in the second reservoir, as recited in claim 2. EX1002, ¶¶155-56 (describing prior art use of such features and citing EX1016, FIG. 2; EX1022, 107; EX1014, 4; EX1020, 10:48-65, 12:16-19, 13:46-48).

Accordingly, claim 2 is obvious in view of Wada. EX1002, ¶¶152-57.

3. The system of claim 1, wherein the flow channel includes a branched portion, wherein the pressure pulse is used to sort one or more particles into a selected branch of the branched portion.

As discussed, Wada discloses sorting particles into one of two microchannels, each terminating in a collection well (*e.g.*, 2210, 2312, 2420, 2422). *E.g.*, EX1006, 19:23-23:26, FIGS. 22-24. The two microchannels that each terminate into a particular collection well as described by Wada together constitute a branched portion of the flow channel, wherein the pressure pulse is used to sort a particle into a selected branch of the branched portion. *Id.*

Wada uses a pressure pulse to sort a particle into a selected branch of the branched portion across the flow channel. For instance, in describing Figure 22, Wada explains that the fluid flow is induced by heating, which creates a pressure pulse (*see discussion re element [1.c] and claim 2*). As a result of the pressure pulse, “selected cells 220 (*e.g.*, fluorescently-labeled cells) and non-selected cells

2206” are directed into “one of two microchannels, each terminating in particular collection wells 2210.” EX1006, 19:29-20:2. That is, as illustrated below, the pressure pulse applied across the flow channel in Figure 22 is used to sort one or more particles into a selected branch of the branched portion. Similar disclosures are provided in Wada relative to Figures 23-24, illustrated below (annotated by Dr. Weigl). *Id.*, 20:10-14; 22:23-23:18.

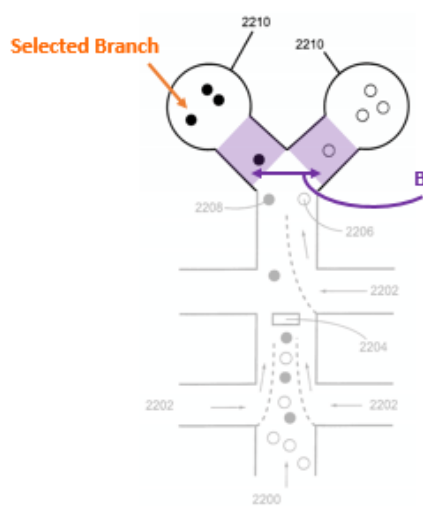


Fig. 22

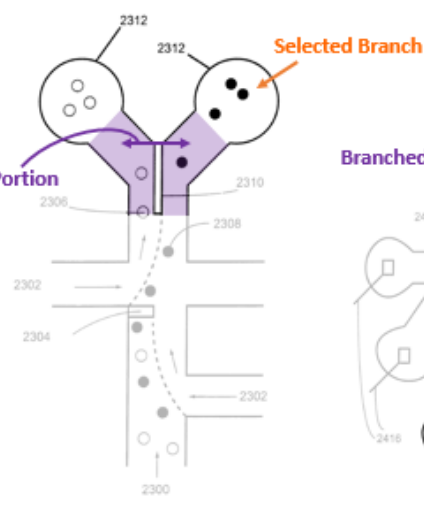


Fig. 23

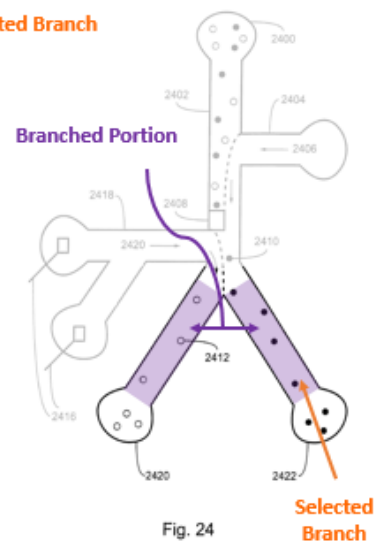


Fig. 24

EX1006, FIGS. 22-24; EX1002, ¶158.

Accordingly, Wada teaches that the flow channel includes a branched portion, and wherein the pressure pulse is used to sort one or more particles into a selected branch of the branched portion. EX1002, ¶¶158-62.

9. The system of claim 1, wherein first reservoir includes a resilient wall for facilitating dampening or absorbing of the pressure pulse.

As discussed, Wada discloses a first reservoir that dampens or absorbs a pressure pulse propagated across the flow channel. *See* Section X.A.ii above. As also discussed, Wada discloses the use of various actuators, including “a pressurized gas, or alternatively...a positive displacement mechanism, i.e., a plunger fitted into a cell suspension reservoir” that would pump the contents of the reservoir into the adjacent channel when actuated. EX1006, 43:5-9; EX1002, ¶¶164-68 (citing EX1042, 9-14, 18-20; EX1045, 8-10, 18-20; EX1043, ¶¶25-27, 31, 33-34, 37-38, 40-44, 48, 50-52, 56-57). Wada further discloses that actuator pressure sources may be “*internal to the device*, e.g., microfabricated pumps integrated into the device and operably linked to a channel.” EX1006, 43:9-14; EX1002, ¶165. Thus, a POSA would have had good reason to employ an actuator comprising a reservoir and a pressurized gas (*i.e.*, a compressible fluid) at the distal end of each of the opposed sorting microchannels. Further, a POSA would have had good reason to employ a resilient wall for facilitating dampening or absorbing of the pressure pulse by the first reservoir. For example, a POSA would have recognized that a resilient wall in the reservoir would further facilitate dampening and absorbing of the pressure pulse.

Indeed, Wada itself suggests including a resilient wall in the reservoirs. For example, Wada explains that the substrate for the microfluidic system, in which the first reservoir is formed, may be made from a resilient material. Specifically, the substrate materials are “generally selected for their compatibility with the full range of conditions to which the microfluidic devices are typically exposed, including extremes of pH, temperature, salt concentration, and application of electric fields.” EX1006, 38:24-27. Accordingly, Wada discloses making the substrate out of flexible and resilient materials. *Id.*, 39:3-8; EX1002, ¶168 (describing use of such features as known in the art and citing EX1033, 198; EX1034, 39:25-34, 40:20-25). Thus, Wada teaches or suggests the microfluidic device of claim 1 further comprising a first reservoir having a resilient wall for facilitating dampening or absorbing of the pressure pulse. EX1002, ¶¶163-69.

18. The system of claim 1, wherein the change in volume or pressure in the second reservoir is a transient change in volume or pressure.

Wada discloses that the change in pressure in the second reservoir is a transient change in pressure. For instance, when using Joule heating in the second reservoir to facilitate sorting, Wada notes that “transitions between temperatures are typically extremely short.” EX1006, 20:28-31; *see also id.*, 18:26-19:13 (describing that the pressure pulse as a “nudge”); 20:30-31 (describing temperature oscillation period as short as 100 milliseconds), 21:27-32 (describing applying the

power supply to generate the heat as a “pulse”), 21:32-22:2 (describing the change in temperature that generates the sorting fluid flow as “extremely rapid and easily controlled”). Based on these disclosure in Wada, a POSA would have understood that, because the duration of the temperature change is extremely short, the corresponding change in pressure is also short-lived, meaning transient. EX1002, ¶170 (citing EX1042, 9-10, 18-20; EX1045, 8-10, 18-20; EX1043, ¶¶25-27, 31, 33-34, 44, 48). Thus, claim 18 is obvious in view of Wada. EX1002, ¶¶170-71.

B. Ground 2: Claims 1-3, 9, and 17-18 Are Obvious in View of Wada and Anderson

As discussed in Ground 1, Wada discloses and renders obvious the microfluidic system of claims 1-3, 9, and 18. The disclosures of Anderson further demonstrate the obviousness of these claims as well as claim 17. Anderson provides additional disclosures regarding specific actuators, including the use of a reservoir or chamber that comprises a flexible membrane suitable for generating or absorbing a pressure pulse. The analysis above with respect to Ground 1 in Section X.A is included herein.

i. Rationale to Combine

A POSA would have had good reason to combine the teachings of Anderson about how to move particles in a fluid in a microfluidic device to the microfluidic systems of Wada for several reasons. As discussed above in Section IX.B, Wada even directs a POSA to Anderson to provide additional details on actuators useful

to provide fluid flow in Wada's microfluidic channels. EX1006, 43:13-14; EX1002, ¶¶173-77. This rationale to combine Wada and Anderson is discussed now in greater detail.

As discussed above in Ground 1, which is included herein in Ground 2, Wada discloses using fluid pressure force modulators to move particles through the main flow channel as well as to focus and sort the particles. *See* Section X.A. For example, Wada teaches particles are “flowed in the microchannel, e.g., using ***pressure-based flow***” and optionally are focused horizontally and/or vertically in first microchannel to provide substantially uniform flow velocity. EX1006, 3:23-25, 23:29-4:1 (emphasis added). Wada also discloses that particles may be “focused using one or more fluid direction components (e.g., ***a fluid pressure force modulator***...or the like). Additional options include sorting, detecting or otherwise manipulating the focused particles.” *Id.*, 4:1-5.

Wada further discloses that its fluid direction components “(e.g., ***a fluid pressure force modulator***...or the like)” are used to perform the sorting operations. For example, Wada explains that sorting is accomplished by using a “signal detector” to inform a computer when a detectable signal is produced by a particle. EX1006, 6:30-7:4. The computer then causes a “flow control regulator” to activate a “fluid direction component” and direct “fluid from the third microchannel into the first microchannel such that the selected member [particle] is

directed into the fourth microchannel in response to the detectable signal[.]” *Id.*, 7:5-24. Wada gives a specific example of particle sorting where the computer gives an instruction set that “activat[es] a heating element...disposed within the third microchannel or a well that fluidly communicates with the third microchannel.” *Id.*, 7:18-29. Wada thus discloses using pressure-based flow from a fluid direction component to sort the particles in addition to using pressure-based flow to flow the particles through the main channel.

As explained by Dr. Weigl, a POSA would have had good reason to look to Anderson regarding microfabricated pumps capable of generating pressure-based fluid flow in microfluidic channels for actuating Wada’s fluid direction components for sorting the particles. EX1002, ¶¶175-77. When describing the use of pressure for flowing the particle through the main channel, Wada discloses the pressure source may be “pneumatic, e.g., a pressurized gas, or alternatively a positive displacement mechanism, i.e., a plunger fitted into a cell suspension reservoir, for forcing the cell suspension through the analysis channel.” EX1006, 42:31-43:8. Wada states that pressure may be applied to the microchannel by integrating “microfabricated pumps” into the device “and operably linked to a channel.” *Id.*, 43:9-13. Wada then states: “Examples of microfabricated pumps have been widely described in the art. See, e.g., published international Application No. WO 97/02357.” *Id.*, 43:13-14. WO 97/02357 is the Anderson

reference. Anderson teaches micropumps and how to make and use them to move particles in fluid in microfluidic devices. EX1012, 2:29-34, 5:14-30, 28:1-29, 34:5-21, 37:13-28, 46:23-48:16, 62:25-63:13. A POSA would have naturally combined the teachings of Wada and Anderson with a reasonable expectation of success because a POSA would have recognized that Anderson's pumps were useful as fluid pressure force modulator for actuating Wada's fluid direction components for sorting the particles, as specifically taught by Wada, and were capable of generating pressure-based fluid flow in microfluidic channels. EX1002, ¶¶173-77.

ii. Independent Claim 1 and Dependent Claims 2-3

As discussed, Wada discloses many "techniques for inducing the flow of focusing fluids to sort particles." EX1006, 19:9-13 (using pressure as a suitable sorting mechanism); *see also* Sections X.A.i, X.B.i above. or further teachings on actuators that generate pressure pulses, Wada points to and incorporates the disclosures of Anderson. EX1006, 43:1-14. A POSA would therefore have naturally looked to Anderson for further discussion regarding these features. EX1002, ¶¶172-77.

Anderson discloses suitable pumping devices, including those with "***a bulging diaphragm.***" EX1012, 63:1-13. For example, a microfluidic device can include a chamber with "***a diaphragm pump as one surface of the chamber.***" *Id.*, 45:3-12 (noting that this "diaphragm pump will generally be fabricated from any

one of a variety of flexible materials, e.g., silicone, latex, Teflon, mylar and the like”); *see also id.*, 38:17-27, 45:3-12 (noting that the flexible diaphragm pump is “similar to the valve structure” comprising a flexible diaphragm).

A POSA would have found it natural to include such features of Anderson in the microfluidic device of Wada. EX1002, ¶¶172-77. Indeed, since Wada expressly points to Anderson for teaching applicable pumps for incorporation into its microfluidic systems, a POSA would have had good reason to employ, in the microfluidic systems taught by Wada, a micropump comprising a flexible membrane, as taught by Anderson, in each of the opposing sorting microchannel structures (*i.e.*, first and second reservoirs), including at the distal end of the structures. When one of the opposed sorting microchannels is actuated and the other is not, as disclosed at least in Wada Figures 22 and 23, the actuated opposed sorting microchannel structure will generate a pressure pulse to sort a particle in the microfluidic flow channel and the non-actuated microchannel will act as the recited second reservoir. In contrast, the non-actuated opposed sorting microchannel structure will dampen or absorb the pressure pulse and act as the recited first reservoir. It would also have been obvious for each of the reservoirs to include a resilient wall, including a deflectable membrane, for facilitating dampening or absorbing of the pressure pulse (in the non-actuated reservoir) and for increasing pressure (in the actuated reservoir).

Based on these disclosures, a POSA would have recognized that Anderson further renders obvious elements [1.b] and [1.c], directed to the dampening or absorbing a pressure pulse propagated across the flow channel, and the generating of a pressure pulse based on a change in volume or pressure in the second reservoir. Thus, the combination of Wada and Anderson further demonstrates the obviousness of claims 1-3. EX1002, ¶¶172-77.

iii. Dependent Claims 9 and 17-18

9. The system of claim 1, wherein the first reservoir includes a resilient wall for facilitating dampening or absorbing of the pressure pulse.

Anderson discloses using a diaphragm pump “as one surface of the chamber” in microfluidic device. EX1012, 45:3-12; EX1002, ¶¶178-80 (citing EX1042, 9-10, 18-20; EX1043, ¶¶25-27, 31, 33-34, 44, 48; EX1042, 13-14, 18-20; EX1043, ¶¶37-38, 40-43, 50-52, 56-57). A POSA would have understood that a diaphragm pump has a resilient wall (*e.g.*, the diaphragm) that can dampen or absorb a pressure pulse. EX1002, ¶¶178-80. Specifically, a POSA would have appreciated that the diaphragm pump of Anderson has a resilient wall (*e.g.*, the diaphragm) that absorbs pressure. In view of Wada’s express invitation to turn to the teachings of Anderson, as well as Anderson’s teachings regarding resilient surfaces, a POSA would have had good reason to use a diaphragm pump in the first reservoir of the microfluidic system for dampening or absorbing a pressure

pulse propagated across the flow channel. *Id.* (describing use of a resilient wall in the prior art and citing EX1033, 198; EX1034, 39:25-34, 40:20-25); *see also* Section IX above. Accordingly, claim 9 is obvious in view of Wada and Anderson. EX1002, ¶181.

17. The system of claim 1, wherein the second reservoir includes a deflectable flexible membrane wherein deflection of the membrane increases the pressure in the second reservoir.

As discussed above, Wada points to Anderson's disclosures regarding actuators and diaphragm pumps. EX1012, 63:1-13. One example provided by Anderson is a chamber that "incorporate[s] a *diaphragm pump as one surface of the chamber.*" *Id.*, 45:3-12; *see also id.*, 38:17-27, 45:3-12. Based on these disclosures, a POSA would have understood that Anderson discloses the use of diaphragm pump for increasing the pressure in the microfluidic system. Furthermore, a POSA would appreciate that a diaphragm pump comprises a deflectable flexible membrane (*e.g.*, the diaphragm) wherein deflection of the membrane increases the pressure in the second reservoir. EX1002, ¶¶182-83.

Given Wada's express guidance to reference Anderson, a POSA would have had good reason to employ, and a reasonable expectation of success in using, a diaphragm pump in the microfluidic system taught by Wada. EX1006, 43:1-14; EX1002, ¶184 (describing the use of pressure-based actuation mechanism in the prior art and citing EX1022, 107; EX1014, 4; EX1020, 10:48-65, 12:16-19, 13:46-

48); *see also* Section IX above. Incorporating the features of Anderson as instructed by Wada would provide the second reservoir with a deflectable flexible membrane (*e.g.*, the diaphragm) wherein deflection of the membrane increases the pressure in the second reservoir when the flexible membrane flexes into the chamber volume. Thus, claim 17 is obvious in view of Wada and Anderson.

EX1002, ¶¶182-85.

18. The system of claim 1, wherein the change in volume or pressure in the second reservoir is a transient change in volume or pressure.

A POSA would have appreciated that deflection of a diaphragm pump as described in Anderson provides a corresponding change in volume or pressure. Such change is not permanent, however, and therefore the change in volume or pressure is a transient change in volume and pressure. Accordingly, claim 18 is obvious in view of Wada and Anderson. EX1002, ¶186; *see also* EX1006, 18:26-19:13 (describing that the pressure pulse as a “nudge”); 20:30-31 (describing temperature oscillation period as short as 100 milliseconds), 21:27-32 (describing applying the power supply to generate the heat as a “pulse”), 21:32-22:2 (describing the change in temperature that generates the sorting fluid flow as “extremely rapid and easily controlled”).

C. Ground 3: Claims 1-3, 9, and 17-18 Are Obvious in View of Marcus and Anderson

As discussed in detail below, Marcus in view of Anderson discloses each and every element of each of claims 1-3, 9, and 17-18 and a POSA would have had good reason to use the claimed elements in the claimed combination with a reasonable expectation of success. *E.g.* EX1002, ¶¶187-91.

i. Rationale to Combine

Marcus teaches combining conventional sensors for detecting a predetermined characteristic of a particle with conventional fluidic sorting devices and fluidic logic elements produced using conventional micromachining technology. *E.g.*, EX1005, 2:7-8 3:8-12. As explained by Dr. Weigl, a POSA would have recognized how to implement conventional fluidic sorting components to achieve the functionality described in Marcus. EX1002, ¶¶187-91. For instance, a POSA would have recognized the utility of using known actuator mechanisms (*e.g.*, thermopneumatic or piezoelectric micropumps) to generate a pressure pulse to sort individual particles in a stream of particles flowing through a duct of a microfluidic device. *Id.* Indeed, such conventional actuators were known well before the earliest priority date of the challenged claims. *E.g. Id.*, ¶209 (discussing EX1014, 4; EX1016, FIG. 2; EX1018, 341-42; EX1020, 1:42-64, 2:31-3:17; EX1022, 107; EX1023, ¶¶0026, 0032; EX1032, 8:4-8).

To the extent that additional guidance on such conventional components was needed, a POSA would have reasonably looked to references teaching conventional fluidic sorting components, such as thermopneumatic or piezoelectric micropumps. EX1002, ¶¶69, 190, 206-9.

Anderson describes conventional microfabricated fluidic sorting components, including thermopneumatic and piezoelectric micropumps, useful to implementing that microfabricated fluidic sorting device of Marcus. As discussed above in Grounds 1 and 2, it was expressly taught in the art to look to Anderson for microfabricated pumps to induce fluid flow to move particles in microfluidic particle sorting devices. Based on the express suggestion of Marcus to look to conventional fluidic sorting components, a POSA would have had good reason to implement the conventional actuators disclosed by Anderson in the microfluidic device of Marcus to perform the fluidic sorting functions described by Marcus. A POSA would have had sufficient reason to combine with a reasonable expectation of success. EX1002, ¶191.

ii. Independent Claim 1

1.[preamble] A microfluidic system comprising:

Marcus's disclosure is directed to microfluidic systems. For instance, Marcus discloses "a fluidic sorting device for the separation of two or more visually different materials." EX1005, Abstract. Marcus' microfluidic systems

allow for sorting of “a particle or material” via “value judgements” made by a machine vision apparatus that “decides as to whether the particle is to be separated out.” *Id.*; *see also id.*, 1:62-68, 2:15-66, 3:65-4:3, FIG. 1. Thus, Marcus discloses the preamble of claim 1. EX1002, ¶¶192-94.

[1.a] a microfluidic flow channel formed in a substrate and adapted to facilitate analysis or processing of a sample having one or more particles suspended in a suspension medium flowing through the flow channel;

Marcus discloses microfluidic flow channels that are “produced using conventional micromachining technology or any other conventional means...so as to accommodate the sizes of the particles to be sorted.” EX1005, 2:14-30. For example, a POSA would have understood the microchannel configurations depicted in Figure 1 of Marcus, shown below (annotated by Dr. Weigl), to provide a microfluidic flow channel formed in a substrate. In fact, Marcus explains that the substrate “may be composed of semi-conductor materials, such as silicon and gallium arsenide.” *Id.* (explaining that, in “order for the machine vision apparatus to capture an image of the particles flowing therethrough, the top surface cover over the fluidic logic device is composed of a transparent material”). EX1002, ¶¶195-96 (describing forming channels in substrate as known in the art and citing EX1017, 330-31).

detector (e.g., machine vision camera lens 9) and flowing towards the sorting control ports (3 and 4). *Id*; EX1002, ¶¶197-200.

Accordingly, Marcus and Anderson disclose claim element **1.a.** EX1002, ¶¶195-201.

[1.b] a first reservoir operatively associated with the flow channel and adapted for dampening or absorbing a pressure pulse propagated across the flow channel; and

Marcus in view of Anderson discloses teaches a first reservoir operatively associated with the flow channel and adapted for dampening or absorbing a pressure pulse propagated across the flow channel. EX1002, ¶¶202-03.

As to be discussed below in claim element **[1.c]**, Marcus in view of Anderson teaches propagating a pressure pulse across the flow channel. Marcus teaches “*fluidic controller device 14* which transmits using leads 17 and 18 the input signal from the control decision device 12 to the fluidic element control ports 3 and 4. The input signal *instructs the control ports 3 and 4 as to how the particulate materials 7 and 8 should be sorted.*” EX1005, 3:37-48; *see also id.*, 3:43-62; FIG. 1 (annotated below by Dr. Weigl). A POSA would have recognized the fluidic controller device of Marcus as an actuator that facilitates analysis or processing of a particle sample. EX1002, ¶¶202-5.

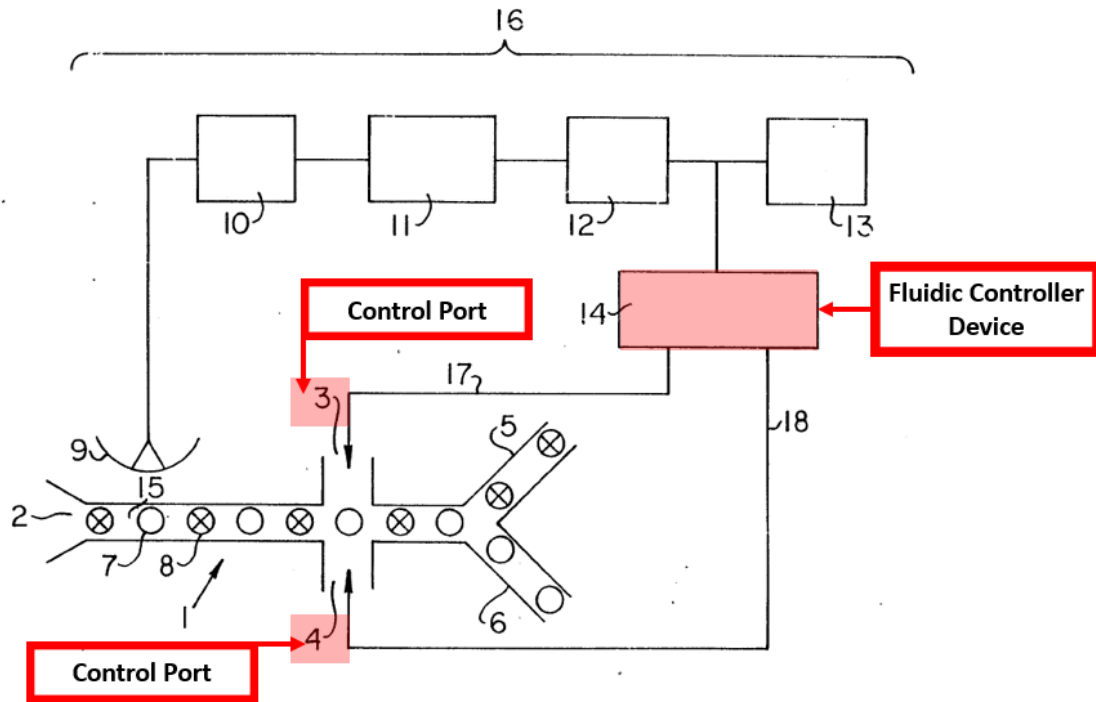


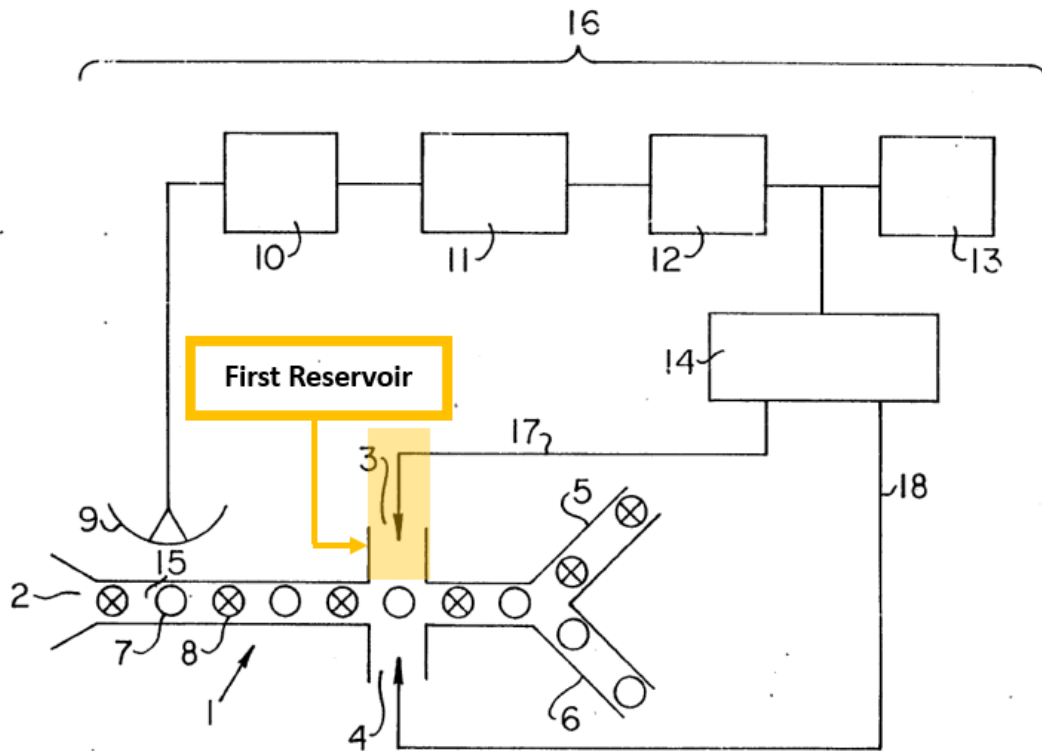
FIG. 1

See EX1005, FIG. 1; EX1002, ¶204.

To the extent that Marcus does not expressly state that the actuator propagates a pressure pulse, such implementation was conventional. Marcus teaches its microfluidic device is comprised of conventional components. *E.g.* EX1005, 3:8-12. As discussed above, Anderson provides disclosures regarding conventional actuators and pumps that were adopted by microfluidic devices during the relevant time. EX1012, 2:29-34; 28:1-29, 34:5-21, 37:13-28; *see also* EX1006, 43:14 (directing POSA to reference Anderson's teachings regarding pumps for use in microfluidic devices). As Dr. Weigl explains, a POSA would have recognized that Anderson's pumps were conventional and were suitable for

implementing Marcus's microsorter. EX1002, ¶¶206-07; EX1012, 2:29-34, 20:9-17, 38:17-27, 44:28-46:44, 52:1-15, 63:1-13, 65:6-11. Thus, in view of Marcus and Anderson, a POSA would have recognized that fluidic controller device 14 direct fluid control ports 3 and 4 to propagate a pressure pulse across the flow channel to facilitate analysis or processing of a particle sample. EX1002, ¶¶206-9 (describing such features as conventional and citing EX1020, 1:42-64, 2:31-3:17; EX1023, ¶¶0026, 0032; EX1014, 4; EX1016, FIG. 2; EX1022, 107).

Marcus in view of Anderson also teach a first reservoir operatively associated with the flow channel for dampening or absorbing the pressure pulse that is propagated across the flow channel. Marcus Figure 1, shown below, depicts a reservoir in the form of an opposing microchannel structure disposed opposite the actuated sorting microchannel structure (through which the actuator selectively applies a pressure pulse represented by the arrow associated with fluidic control port 4) disposed downstream of the detector, machine camera lens 9. EX1005, 3:28-62; EX1002, ¶¶210-16 (citing EX1042, 9-10, 13-14, 18-20; EX1043, ¶¶25-27, 31, 33-34, 37-38, 40-43, 44-48, 50-52, 56-57). Figure 1 (annotated below by Dr. Weigl) discloses to a POSA that the opposing microchannel structure is, in each case, a physical structure that contains fluid, receives a pressure pulse, and is operatively associated with the flow channel via its fluid communication with the flow channel.



EX1005, FIG. 1; E1002, ¶211.

Based on the teachings of Marcus and Anderson, a POSA would have understood the opposed microchannel structure (3) is configured to receive the pressure pulse (flow from fluidic control port 4) and to dampen or absorb the pressure pulse because the structure opening is aligned with the direction of the pressure pulse (substantially perpendicular to the main microchannel). The opposed microchannel structure is thus not only a reservoir, but it is also a structure associated with the flow channel and adapted for dampening or absorbing a pressure pulse propagated across the flow channel, as illustrated below (annotated by Dr. Weigl).

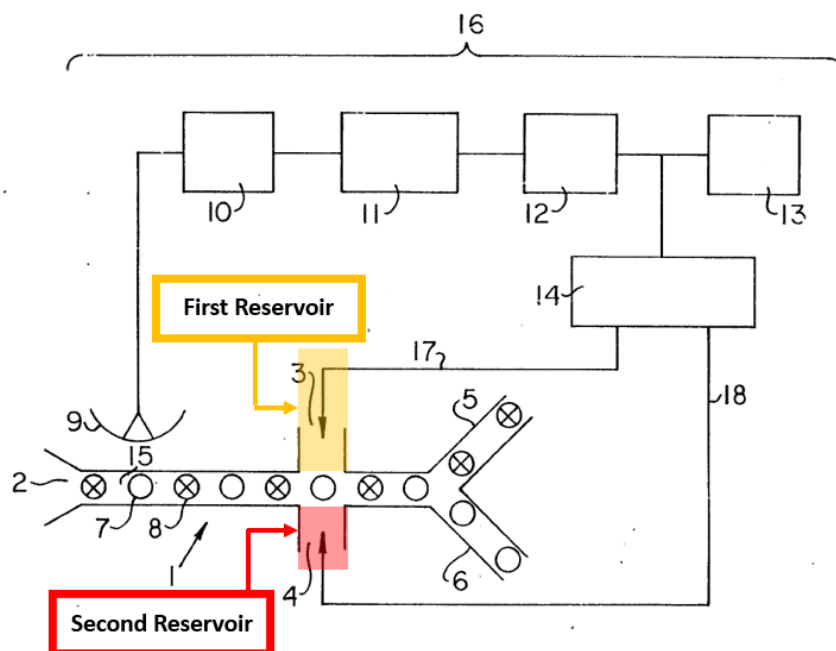


FIG. 1

EX1005, FIG. 1; EX1002, ¶213.

When the actuator (“fluidic controller device 14”) actuates only one of the two opposed sorting microchannel structures of Wada at a given time (*e.g.*, control port A, 4), as illustrated in Figure 1, the opposite (non-actuated) sorting microchannel (3) dampens or absorbs the pressure pulse propagated across the flow channel. EX1002, ¶¶212-13.

This symmetrical geometry, wherein opposing ends of a cross channel are adapted to individually actuate and individually dampen or absorb the resulting transient pressure pulse, was well-reported and well known in the art as allowing for more precise flow manipulations during particle sorting. EX1002, ¶¶210-16 (citing EX1016, 1:49-2:19, 5:44-54, FIG. 1; EX1018, 341-42; EX1032, 8:4-8; EX1033, 198; EX1034, 2:23-34, 39:25-34, 40:20-25; EX1035, 377, 382-83).

Accordingly, a POSA would have recognized that Marcus's first reservoir is configured for absorbing or dampening the pressure pulse, as recited in claim element **1.b**. Claim element **1.b** is therefore obvious in view of Marcus and Anderson. EX1002, ¶¶202-17.

[1.c] a second reservoir operatively associated with the flow channel and adapted for generating the pressure pulse based on a change in volume or pressure in the second reservoir;

As discussed above in claim element **[1.b]**, Marcus in view of Anderson teaches reservoirs as part of opposing sorting microchannel structures. When actuated, the opposed sorting microchannel structure of Wada, including its well or chamber from which the pressure pulse enters the flow channel, is a second reservoir operatively associated with the flow channel and adapted for generating the pressure pulse based on a change in volume or pressure in the second reservoir.

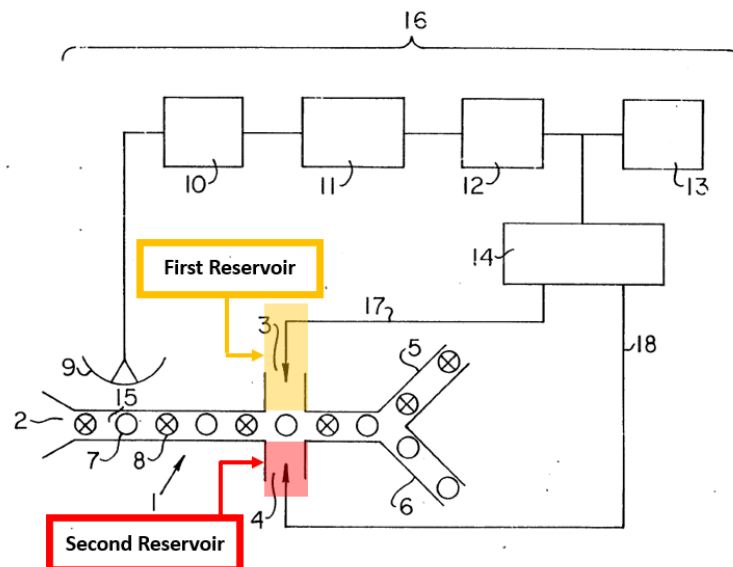


FIG. 1

EX1005, Fig. 1; EX1002, ¶¶218-25.

For example, Figure 1 of Marcus (annotated by Dr. Weigl), above, depicts a second reservoir as part of opposing microchannel structures. EX1005, FIG. 1; EX1002, ¶¶218-19 (citing EX1042, 9-10, 18-20; EX1043, ¶¶25-27, 31, 33-34, 44, 48). A POSA would have recognized that these second reservoirs are operatively associated with the microfluidic flow channel because they are in fluid communication with it and generate a transient fluid flow (*e.g.*, flow from fluidic controller port 4) into the flow channel. Further, the second reservoir (*e.g.*, 4) can be actuated using an actuator (fluidic controller device 14) to generate a pressure pulse based on a change in volume or pressure in the second reservoir. EX1005, 3:43-48.

Marcus explains that using such an actuator facilitates analysis or processing of a particle sample. Specifically, the introduction of various fluids or particles into the microchannels of the microfluidic device can be controlled by the “control ports in the fluidic logic element.” EX1005, 2:49-66. In use, detection of a selected particle (*e.g.*, particle A, labelled number 8 in Figure 1) triggers the actuator to redirect the selected particle from the stream of particles into a selected outlet channel (5). In contrast, a non-selected particle (*e.g.*, particle B, labelled number 7) flows into the outlet for the non-selected particles (6). *Id.*, Abstract, 2:49-66, 3:49-62, 5:13-6:2 (claim 1); EX1002, ¶¶220-23

A POSA would have recognized that the fluidic controller device (14) associated with the opposed sorting microchannels (fluidic control ports 3 and 4) generates and applies a pressure pulse based on a change in pressure in the second reservoir and propagates it across the flow channel to deflect a particle into a selected branch of the flow channel. Marcus describes this pressure pulse in terms of “fluidic control” actuated through “leads 17 and 18” “instruct[ing] the control ports 3 and 4 as to how the particulate materials 7 and 8 should be sorted,” but a POSA would have recognized this as a pressure pulse. EX1005, 3:28-62. Indeed, generating a pressure pulse based on a change in volume or pressure in a reservoir was well-known in the art. EX1002, ¶¶222-24 (describing EX1020, 1:42-64, 2:31-3:17; EX1023, ¶¶0026, 0032; EX1014, 4; EX1016, FIG. 2; EX1022, 107).

Thus, a POSA would have recognized that Marcus and Anderson teach a second reservoir operatively associated with the flow channel and adapted for generating the pressure pulse based on a change in volume or pressure in the second reservoir. Accordingly, claim element **1.c** is taught or suggested by Marcus and Anderson. EX1002, ¶¶218-25.

[1.d] wherein the flow channel defines a first aperture for connecting the flow channel relative to the first reservoir and a second aperture for connecting the flow relative to the second reservoir, wherein the first aperture is substantially opposite the second aperture.

Marcus explains that the machine vision apparatus “signals a fluidic controller device 14 to instruct control ports A and B, 4 and 3 respectively, to separate out said particles 7 and 8. These particles 7 and 8 are then sorted through output port A and output port B, 5 and 6.” EX1005, 3:43-48; EX1002, ¶¶226-27. As discussed, using opposing sorting microchannels in a microfluidic system would have been readily apparent to a POSA in view of Marcus and Anderson. *See* Sections X.C.i-ii, above.

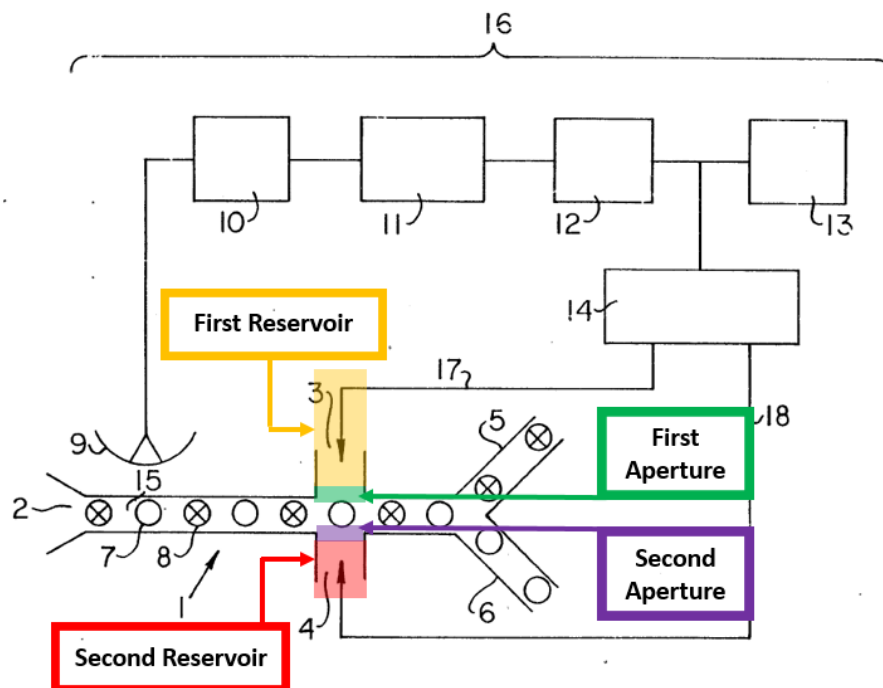


FIG. 1

EX1005, FIG. 1; EX1002, ¶227.

Based on Marcus's disclosure, a POSA would have recognized that the first reservoir opens into the microfluidic flow channel and, similarly, the second reservoir opens into the microfluidic flow channel. That is, the flow channel defines a first aperture for connecting the flow channel relative to the first reservoir and a second aperture for connecting the flow relative to the second reservoir. The first and second aperture are depicted in the version of Figure 1, shown above, annotated by Dr. Weigl. EX1002, ¶227. As seen in these figures, the first aperture is substantially opposite to the second aperture. Marcus and Anderson thus disclose claim element **1.d.**

As discussed above, Marcus and Anderson disclose each element of claim 1 in the claimed configuration and provide a POSA with good reason to employ the claimed combination of elements with a reasonable expectation of success. Marcus and Anderson thus render claim 1 obvious as a whole. EX1002, ¶¶226-29.

iii. Dependent Claims 2-3, 9, and 17-18

Dependent claims 2-3, 9, and 17-18 each depend from independent claim 1. As discussed above, Marcus renders obvious the microfluidic system of claim 1. The analysis above with respect to claim 1 is included herein for each of the dependent claims. *See* Section X.A; *see also* EX1002, ¶230.

2. The system of claim 1 further comprising an actuator or pressurizer operatively associated with the second reservoir and adapted for generating the pressure pulse by varying the volume or pressure in the second reservoir.

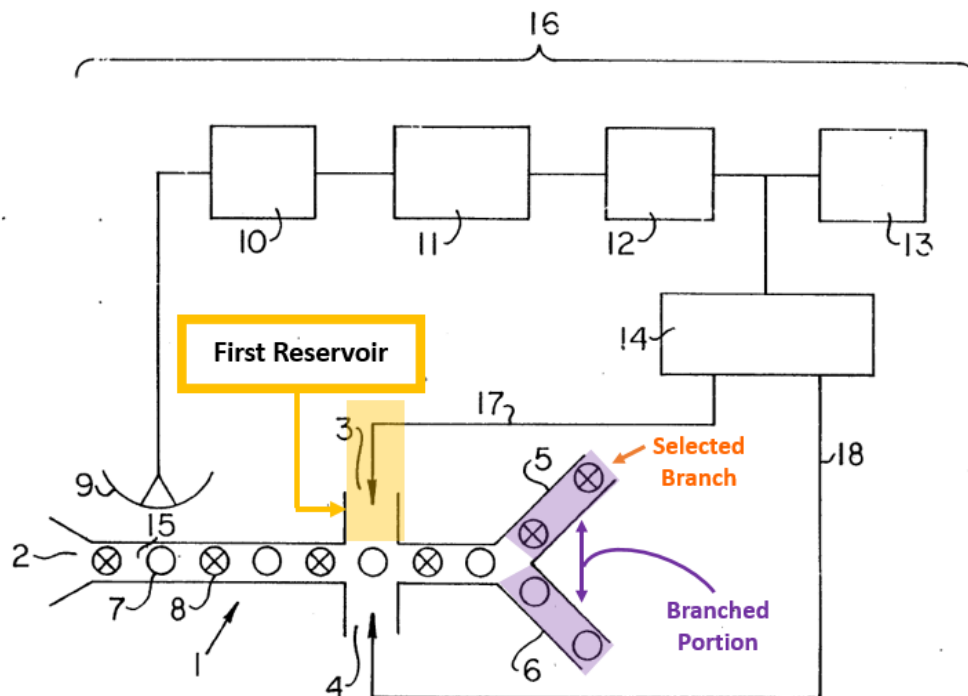
As discussed above for element 1.c, Marcus and Anderson teach the use of an actuator in association with the second reservoir. For instance, Marcus and Anderson teach using an actuator to generate a pressure pulse and propagate the pressure pulse across the flow channel based on a change in pressure in the second reservoir to deflect a particle and direct the selected particle into a selected outlet channel. *See, e.g.*, EX1005, 3:28-62. For the same reasons discussed above, the actuator is operatively associated with the second reservoir and adapted for generating the pressure pulse by varying the pressure in the second reservoir.

As one example, Marcus uses of an actuator in the form of “fluidic controller device 14 which transmits using leads 17 and 18 the input signal from the control decision device 12 to the fluidic element control ports 3 and 4. The input signal instructs the control ports 3 and 4 as to how the particulate materials 7 and 8 should be sorted.” EX1005, 3:37-48, FIG. 1. As discussed above, a POSA would have recognized that fluidic controller device generates a pressure pulse that is selectively applied when the detector indicates the particle is selected for deflection from the stream of particles. *Id.*, 3:28-62; EX1002, ¶¶233-34 (explaining that the recited actuation mechanism was well-known and citing EX1016, FIG. 2;

EX1022, 107; EX1014, 4; EX1020, 10:48-65, 12:16-19, 13:46-48). Accordingly, claim 2 is obvious in view of Marcus and Anderson. EX1002, ¶¶231-35.

3. The system of claim 1, wherein the flow channel includes a branched portion, wherein the pressure pulse is used to sort one or more particles into a selected branch of the branched portion.

As discussed for claim 1, Marcus sorts particles into one of two microchannels output port A (5) and output port B (6). *E.g.*, EX1005, 3:49-62, FIG. 1 (below). The two microchannels defining output ports A and B (5 and 6) provide a branched portion of the flow channel, wherein the pressure pulse is used to sort a particle into a selected branch of the branched portion. Further, Marcus makes clear that the pressure pulse is used to sort a particle into a selected branch of the branched portion across the flow channel.



EX1005, FIG. 1.; EX1002, ¶236.

For instance, in Figure 1 (annotated above by Dr. Weigl), the fluid flow is induced by fluidic controller device 14, which creates a pressure pulse at controller port 4. “[P]articles 7 and 8 are then sorted through output port A and output port B, 5 and 6.” EX1005, 3:43-48. That is, the pressure pulse is used to sort one or more particles into a selected branch of the branched portion. Accordingly, claim 3 is obvious in view of Marcus and Anderson. EX1002, ¶¶236-38.

9. The system of claim 1, wherein the first reservoir includes a resilient wall for facilitating dampening or absorbing of the pressure pulse.

As discussed above, Marcus discloses a first reservoir formed in the substrate that is adapted for dampening or absorbing a pressure pulse propagated across the flow channel. EX1002, ¶¶202-25; *see also* Section X.C.ii above. Marcus also suggests including a resilient wall in the reservoirs. For example, Marcus explains that the substrate for the microfluidic system, in which the first reservoir is formed, may be made from a resilient material. Specifically, the substrate materials are “produced using conventional micromachining technology or any other conventional means” and may be “composed of semi-conductor materials, such as silicon and gallium arsenide.” EX1005, 2:20-30 (noting that the substrate may also be comprised of “metallic laminates,” and additionally noting that a “top surface cover” is provided “over the fluidic logic device” that is “composed of a

transparent material,” the composition of which “is not critical”). Marcus thus teaches making the substrate out of flexible and resilient materials.

A POSA would have recognized that making the substrate, including the first reservoir formed thereon, out of flexible and resilient materials was known in the art. EX1002, ¶¶239-45 (citing EX1022, 107; EX1023, ¶0007; EX1033, 193-199, 201; EX1034, 8:18-25, 13:17-27, 39:25-34, 40:20-25); *see also* Section IX above. Indeed, it would have been conventional for at least one wall of the reservoir to be formed by a substrate comprised of silicon, as taught by Marcus, which is resilient and flexible. Marcus thus provides good reason for the first reservoir to include a resilient wall for facilitating dampening or absorbing of the pressure pulse.

Accordingly, claim 9 is obvious in view of Marcus and Anderson. EX1002, ¶¶239-46.

17. The system of claim 1, wherein the second reservoir includes a deflectable flexible membrane wherein deflection of the membrane increases the pressure in the second reservoir.

As discussed, Anderson teaches “[p]umping devices that are particularly useful in a variety of *micromachined pumps*,” including those with “*a bulging diaphragm*.” EX1012, 63:1-13; *see also* Section X.B above. One specific example includes a chamber with “*a diaphragm pump as one surface of the chamber*.” EX1012, 45:3-12 (noting that this “diaphragm pump will generally be fabricated

from any one of a variety of flexible materials, e.g., silicone, latex, Teflon, mylar and the like”); *see also id.*, 38:17-27, 45:3-12 (describing “[d]eflection of [a] diaphragm valve”). Based on these disclosures, a POSA would have understood Anderson to teach using a flexible membrane. EX1002, ¶¶247-48. Further, it would be apparent to a POSA that deflection of said membrane increases the pressure in the microfluidic system. *Id.*, ¶¶28-29. Indeed, a POSA would have been familiar with the incorporation and use of such conventional components. *Id.*, ¶¶247-50 (discussing EX1014, 4; EX1016, FIG. 2; EX1018, 341-42; EX1020, 1:42-64, 2:31-3:17; EX1022, 107; EX1023, ¶¶0026, 0032; EX1032, 8:4-8); *see also* Sections X.B.i, X.C.i above. Since Marcus makes clear that its microfluidic devices comprise conventional and known components, it would have been natural for a POSA to utilize, in the second reservoir of the microfluidic device of Marcus, a deflectable flexible membrane wherein deflection of the membrane increases the pressure in the second reservoir. *E.g.* EX1005, 3:8-12.

Accordingly, claim 17 is obvious in view of Marcus and Anderson. EX1002, ¶¶247-51.

18. The system of claim 1, wherein the change in volume or pressure in the second reservoir is a transient change in volume or pressure.

When the second reservoir of Marcus is actuated to facilitate sorting, the “timing and flow rate control of the suspensions should be such as to allow the

suspended materials to be properly diverted to the desired port.” EX1005, 4:4-7; EX1002, ¶¶252-53. Marcus’s fluidic sorting device identifies “a particle,” “decides as to whether the particle is to be separated out,” and then provides a pressure pulse to sort said selected particle (*e.g.*, particle A, 8) into a selected output (*e.g.*, output port A), while non-selected particle (*e.g.*, particle B, 7) flows into a second output (*e.g.*, output port B). EX1005, Abstract, FIG. 1. A POSA would have recognized that the individual sorting of particle indicates that the pressure pulse of Marcus is short-lived, *i.e.*, transient. Accordingly, claim 18 is obvious in view of Marcus and Anderson. EX1002, ¶¶252-53.

XI. CONCLUSION

For the reasons set forth above, claims 1-3, 9, and 17-18 of the ’295 patent are unpatentable over the asserted prior art. Petitioners therefore request that an *inter partes* review of these claims be instituted and that they be found unpatentable and canceled.

Respectfully submitted,

Dated: February 12, 2020

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Reg. No. 52,182
WILSON SONSINI GOODRICH &
ROSATI

XII. CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. §42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 12,908 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

Respectfully submitted,

Dated: February 12, 2020

/ Michael T. Rosato /
Michael T. Rosato, Lead Counsel
Reg. No. 52,182

XIII. PAYMENT OF FEES UNDER 37 C.F.R. §§ 42.15(A) AND 42.103

The required fees are submitted herewith. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 23-2415.

XIV. APPENDIX – LIST OF EXHIBITS

Exhibit No	Description
1001	U.S. Patent No. 8,623,295 to Gilbert, <i>et al.</i>
1002	Declaration of Bernhard H. Weigl, Ph.D.
1003	<i>Curriculum Vitae</i> of Bernhard H. Weigl, Ph.D.
1004	Prosecution History of U.S. Patent No. 8,623,295 to Gilbert, <i>et al.</i>
1005	U.S. Patent No. 5,101,978 to Marcus (issued April 7, 1992)
1006	International PCT Publication No. WO 00/70080 to Wada, <i>et al.</i> (published November 23, 2000)
1007	U.S. Patent No. 4,936,465 to Zöld (issued June 26, 1990)
1008-11	<i>Intentionally left blank</i>
1012	International PCT Patent Publication No. WO 97/02357 to Anderson, <i>et al.</i> (published January 23, 1997)
1013	<i>Intentionally left blank</i>
1014	Chapman, <i>Instrumentation for flow Cytometry</i> , J. IMMUNOL. METHODS 243 (2000) 3-12
1015	<i>Intentionally left blank</i>
1016	U.S. Patent No. 3,508,654 to Glaettli (issued April 28, 1970)
1017	Figeys, <i>et al.</i> , <i>Lab-on-a-Chip: A Revolution in Biological and Medicinal Sciences</i> , ANAL. CHEM. (2000) 330-35
1018	Deshpande, <i>et al.</i> , <i>Novel Designs for Electrokinetic Injection in μTAS</i> , MICRO TOTAL ANAL. SYS. (2000) 339-42

Exhibit No	Description
1019	<i>Intentionally left blank</i>
1020	U.S. Patent No. 6,068,751 to Neukermans (issued May 30, 2000)
1021	<i>Intentionally left blank</i>
1022	Zeng, <i>Fabrication and characterization of electroosmotic micropumps</i> , SENS ACTUAT. B, 79 (2001) 107-14
1023	U.S. Patent Publication No. 2001/0054702 to Williams (published December 27, 2001)
1024-31	<i>Intentionally left blank</i>
1032	International PCT Publication No. WO 99/43432 to Dubrow, <i>et al.</i> (published September 2, 1999)
1033	Zengerle, <i>et al.</i> , <i>Simulation of Microfluid Systems</i> , J. MICROMECH. MICROENG. 4 (1994) 192-204
1034	International Patent Publication No. WO 02/29106 to Chou, <i>et al.</i> (filed October 2, 2001, published April 11, 2002)
1035	Veenstra, <i>et al.</i> , <i>The Design of an In-Plane Compliance Structure for Microfluidical Systems</i> , SENS. ACTUATORS B, 81 (2002) 377-83
1036-41	<i>Intentionally left blank</i>
1042	Plaintiff's Reply Claim Construction Brief, <i>Cytonome/ST, LLC v. NanoCollect Biomedical, Inc.</i> , C.A. No. 19-301 (RGA) (D. Del. filed Jan. 31, 2020)
1043	Exhibit A: Declaration of Giacomo Vacca, Plaintiff's Reply Claim Construction Brief, <i>Cytonome/ST, LLC v. NanoCollect Biomedical, Inc.</i> , C.A. No. 19-301 (RGA) (D. Del. filed Jan. 31, 2020)
1044	Complaint, <i>Cytonome/St, LLC v. NanoCollect Biomedical, Inc.</i> , C.A. No. 1:19-00301 (UNA) (D. Del., filed Feb. 12, 2019)

Exhibit No	Description
1045	Plaintiff's Opening Claim Construction Brief, <i>Cytonome/St, LLC v. NanoCollect Biomedical, Inc.</i> , C.A. No. 1:19-00301 (RGA) (D.Del.)

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), this is to certify that I caused to be served a true and correct copy of the foregoing Petition for *inter partes* review of U.S. Patent No. 8,623,295 (and accompanying Exhibits 1001-1045) by overnight courier (Federal Express or UPS), on this 12th day of February, 2020, on the Patent Owner at the correspondence address of the Patent Owner as follows:

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