

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. IPR2019-00550
Patent No. 9,011,797

**PETITION FOR INTER PARTES REVIEW
OF U.S. PATENT NO. 9,011,797**

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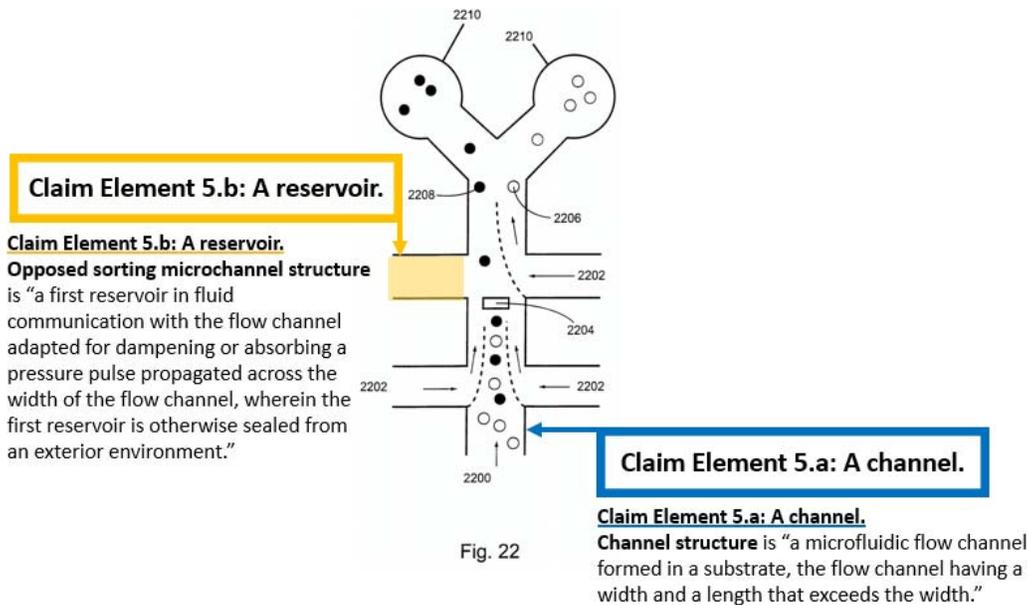
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I. INTRODUCTION

NanoCollect Biomedical, Inc. (“NanoCollect” or “Petitioner”) requests *inter partes* review of claims 1-2, 5, 13, 16, and 18-19 of U.S. Patent No. 9,011,797 to Gilbert, *et al.* (“the ’797 patent,” EX1001), which issued on April 21, 2015. This Petition demonstrates that there is a reasonable likelihood that each of claims 1-2, 5, 13, 16, and 18-19 is obvious under 35 U.S.C. §103. Petitioner thus requests that *inter partes* review be instituted and claims 1-2, 5, 13, 16, and 18-19 of the ’797 patent be cancelled.

At a high level, the challenged claims are directed to a microfluidic device comprising: (a) a channel and (b) a reservoir or a method of using the reservoir to dampen or absorb a pressure pulse propagated across the channel. The channel, formed on a substrate, has a length that exceeds a width. The reservoir is adapted to dampen or absorb a pressure pulse propagated across the width of the flow channel.



EX1005, FIG. 22 (annotated by Dr. Weigl); EX1002, ¶¶109, 134-35.

However, the claimed combination of elements was already disclosed in, for example, the Wada reference, as discussed in detail herein. The annotations to Wada Figure 22 above illustrate, for example, how Wada renders claim 5 unpatentable. Further, each of the elements recited in the remaining challenged claims was also known in the prior art. In other words, the challenged claims 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 1-2, 5, 13, 16, and 18-19 is thus unpatentable over the prior art.

II. MANDATORY NOTICES

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

NanoCollect 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 '797 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. 6,877,528; 8,623,295; 9,339,850; 10,029,263; 10,029,283; and 10,065,188 (together with the '797 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 '797 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 1-2, 5, 13, 16, and 18-19 of the '797 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	1-2, 5, 13, 16, 18-19	International PCT Publication No. WO 00/70080 ("Wada," EX1006)
2	1-2, 5, 13, 16, 18-19	Wada in view of International PCT Publication No. WO 97/002357 ("Anderson," EX1012)
3	1-2, 5, 13, 16, 18-19	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 1-2, 5, 13, 16, and 18-19 over Wada, and Ground 2 addresses the obviousness of these claims 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 and

methods. Further reflecting the unpatentability of the challenged claims, Ground 3 demonstrates the obviousness of these claims 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.

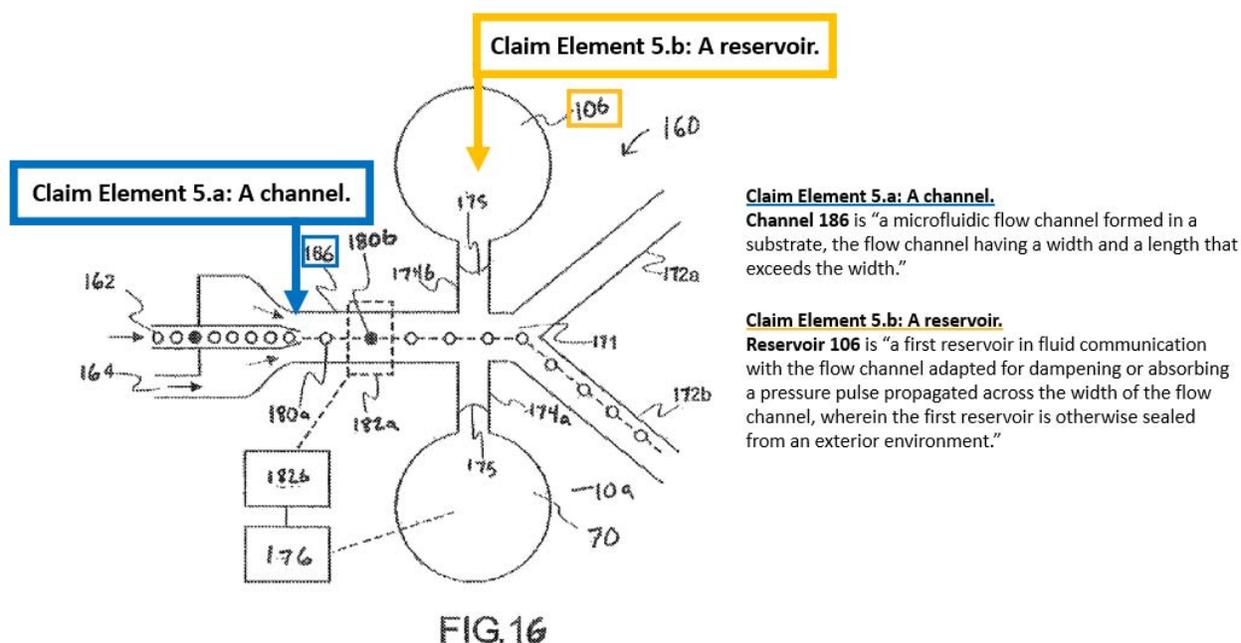
NanoCollect also worked to eliminate the dispute between the parties before seeking IPR of these patents by engaging in settlement discussions with Cytonome, to no avail. Now that Cytonome has identified the claims in dispute and settlement discussions have reached an impasse, NanoCollect promptly submits 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 '797 patent relates to microfluidic methods and devices that use a bubble valve and an actuator to “separat[e] particles having a predetermined characteristic from particles” that do not. EX1001, Abstract, 4:31-34; EX1002, ¶¶23-24. The specification of the '797 patent describes 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, 2:16-67. Figure 16 of the '797 patent exemplifies the claimed subject matter. Figure 16 is annotated below by Dr. Weigl to identify the elements of claim 5. *Id.*, 4:54-57, 5:66-67, 8:32-33.



EX1001, FIG. 16; *see also* EX1002, ¶¶23-31.

B. Claims

The '797 patent issued with 19 claims. Of the challenged claims, the only independent claims are claims 1 and 5, which recite similar subject matter. By way of example, claim 5 recites:

5. A microfluidic device adapted to facilitate analysis or processing of a sample, the microfluidic device comprising:
 - a microfluidic flow channel formed in a substrate, the flow channel having a width and a length that exceeds the width; and
 - a first reservoir in fluid communication with the flow channel adapted for dampening or absorbing a pressure pulse propagated across the width of the flow channel, wherein the first reservoir is otherwise sealed from an exterior environment.

EX1001, claim 5.

Claim 1 recites similar subject matter, though is directed towards a method for facilitating analysis or processing of a sample. Claim 18 depends from claim 5 and recites a method similar to that of claim 1. Claims 2, 13, 16, and 18-19 each depend from either claim 18 or 22.

C. Prosecution History

The '797 patent issued from U.S. Patent Application No. 13/527,331 (“the '331 application”), which claims priority to U.S. Provisional Application No. 60/373,256, filed on April 17, 2002. EX1002, ¶32.

During prosecution, the '331 application was rejected in view of some prior art. EX1004; EX1002, ¶¶33-35, 51-90. None of the references relied upon herein were relied upon for rejection.

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, ¶¶36-37.

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’”).

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); *Ex parte Sussman*, 8 U.S.P.Q.2d 1443, 1445 n.* (B.P.A.I. 1988).

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. 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 (EX1043).

For example, Cytonome’s declarant opined that the term “reservoir” as used in the challenged claims of the asserted patents 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). 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.

Cytonome’s declarant has opined that the term “absorbing” as used in the challenged claims of the asserted patents means *to receive, take up, or take in the pressure pulse*. EX1043, ¶¶50-52, *see also* EX1042, 13-14, 18-19. Cytonome’s declarant has also opined that the terms “dampen” or “dampening” as used in the challenged 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; EX1042, 13-14, 18-19.

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. EX1002, ¶¶36-46.

VIII. LEVEL OF ORDINARY SKILL IN THE ART

The '797 patent relates to microscale fluid handling devices and methods for separation or sorting particle samples in a microchannel. *E.g.* EX1001, 1:23-27.

Dr. Bernhard H. Weigl is an Affiliate Professor in the Department of Bioengineering at the University of Washington who has more than thirty years of experience with methods and apparatus 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 times 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, ¶¶47-50. 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. EX1002, ¶¶47-107.

IX. SUMMARY OF THE PRIOR ART

A. Background

The relevant state of the art supports the unpatentability of the challenged claims. EX1002, ¶51. Flow cytometers have long been used to sort particles. *Id.*, ¶¶52-62 (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.*, ¶¶54-58 (discussing EX1016). By the earliest claimed priority date, particle sorting flow cytometers, including sorters using heater electrodes and piezoelectric actuators were widely available. *Id.*, ¶¶54, 59, 66-67, 74, 76-77 (discussing EX1007, EX1014, EX1016, EX1020).

Structures for making functioning microfluidic devices also were widely known. EX1002, ¶¶60-62 (discussing EX1005). Microfluidic devices, including the “lab-on-a-chip” or “ μ TAS” 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.*, ¶¶63-67 (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.*, ¶¶65-66 (discussing EX1018, EX1020). Microfluidic devices having actuators comprising a flexible wall or malleable material were also known in the art. *Id.*, ¶¶66-67 (discussing EX1020).

Precise control of flow within microfluidic channels was achieved due to the normally laminar flow in microfabricated devices. EX1002, ¶¶68-69 (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. *Id.*, ¶¶70-74 (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. *Id.*, ¶¶75-77 (discussing EX1007, EX1016, EX1018). 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. *Id.*, ¶¶78-90 (discussing EX1007, EX1016, EX1018, EX1032-EX1035).

B. Asserted References

As Dr. Weigl explains, and as addressed in further detail below, claims 1-2, 5, 13, 16, and 18-19 would have been obvious to a POSA at the relevant time. EX1002, ¶¶21-22. Numerous microfluidic methods and devices were known before April 17, 2002, including many that used the same features broadly claimed in the '797 patent.

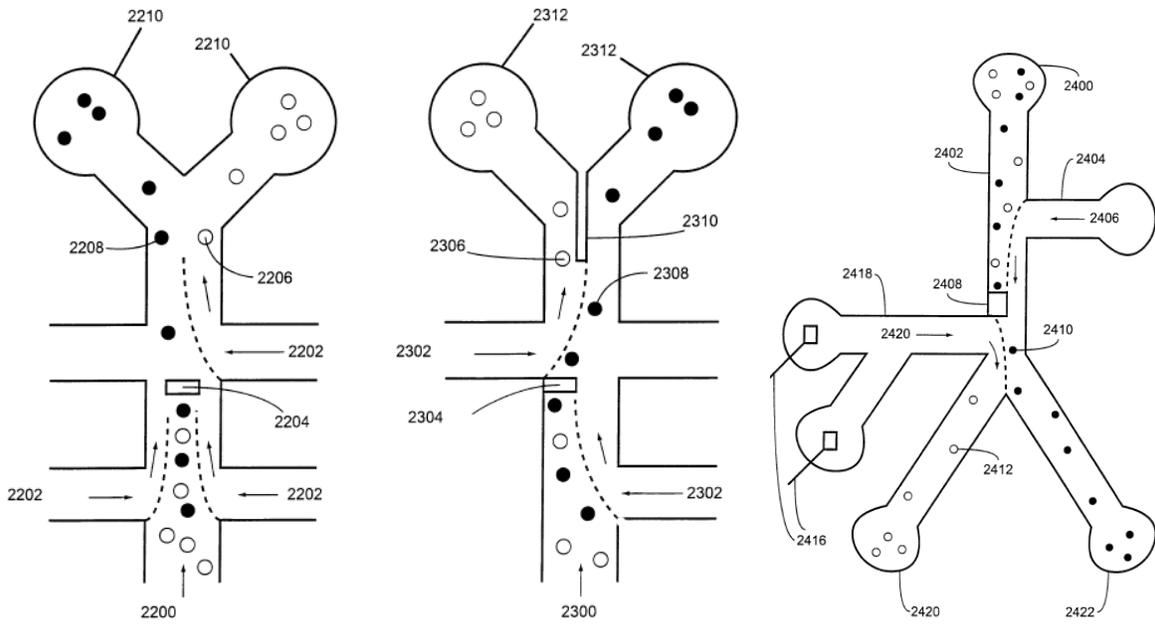
i. Wada

International PCT Publication No. WO 00/70080 to Wada, *et al.*, entitled “Focusing of Microparticles in Microfluidic Systems,” published on November 23,

2000. EX1002, ¶¶91. Wada is prior art to the '797 patent under pre-AIA §102(b).

Id.

Wada discloses methods of focusing particles in microchannels for subsequent sorting. EX1006, 3:13-15, 7:5-8:8, FIGS. 1A, 22-24 & corresponding discussion in the Wada reference; EX1002, ¶¶92-93. 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; *id.* FIGS. 22-24. 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, ¶¶94-95. Wada describes various methods for controlling the flow of particles, including heating and “pressure, hydrostatic, wicking, capillary, and other forces.” EX1006, 18:26-19:13, 24:9-12. Figures 22-24 of Wada, reproduced below, illustrate exemplary schematics of microfluidic devices.



EX1006, FIGS. 22-24; EX1002, ¶¶96.

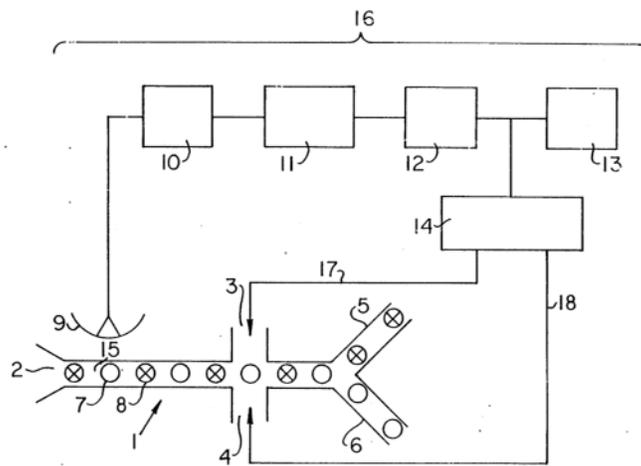
ii. Marcus

U.S. Patent No. 5,101,978 to Marcus issued April 7, 1992. Marcus is prior art to the '797 patent under pre-AIA §102(b). EX1002, ¶¶97.

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.

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, ¶¶98-101. 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 ’797 patent under pre-AIA §102(b). EX1002, ¶102.

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, ¶¶103-4.

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, ¶¶105-6.

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, 18eflon, mylar, and the like”); *id.*, 38:1-39:4 (chamber etched into substrate); EX1002, ¶¶106-7.

X. STATEMENT OF REASONS FOR THE RELIEF REQUESTED

A. **Ground 1: Claims 1-2, 5, 13, 16, and 18-19 Are Obvious in view of Wada**

Wada discloses each and every element of each of claims 1-2, 5, 13, 16, and 18-19, and, at least some of the embodiments (*e.g.*, Figures 22-23) reasonably would have been viewed by a POSA as anticipating the claimed subject matter. EX1002, ¶¶108-12. As anticipation is the “epitome of obviousness,” Petitioner submits that claims 1-2, 5, 13, 16, and 18-19 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, and as discussed in detail below, a POSA logically would have arrived at the claimed subject matter with a reasonable expectation of success in view of Wada. *E.g.* EX1002, ¶¶112, 123-51. As illustrated in further detail below, all aspects of the claimed subject matter are found in Wada. *Id.*, ¶206. As Dr. Weigl explains, a POSA typically would have viewed a given prior art disclosure such as the Wada reference as a whole for all it teaches, and as cooperative and integral. *Id.*, ¶112. 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, ¶¶112, 128. *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 actuator mechanisms (*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.*, ¶¶81, 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.*, Figure 24). EX1002, ¶140. As such, Wada discloses and renders obvious the claimed subject matter.

i. Independent Claim 1

1. A method for facilitating analysis or processing of a sample, the method comprising:

Wada discloses methods of analyzing and processing samples. Entitled “Focusing of Microparticles in Microfluidic Systems,” Wada provides “methods and systems for particle focusing to increase assay throughput in microscale systems....Methods of sorting members of particle populations, such as cells and

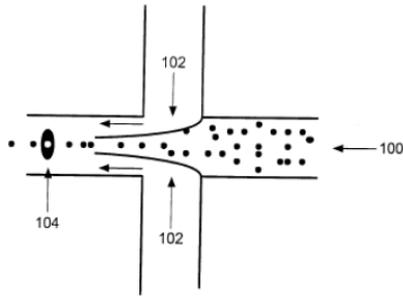
various subcellular components are also provided.” EX1006, Abstract; *see also id.*, 3:13-33. That is, Wada’s methods facilitate the analysis or processing of a sample, as recited in the preamble of claim 1. *E.g. id.*, 12:3-14, Figs. 1A, 22-24 & corresponding discussion in the Wada reference; EX1002, ¶113. *See also* Section IX above.

[1.a] flowing a sample through a microfluidic flow channel formed in a substrate;

Wada discloses a microfluidic flow channel formed in a substrate. Wada’s methods make use of microfluidic flow channels that are “integrated into the body structure of a microfluidic device.” EX1006, 37:23-32; *see also id.*, 21:3-5 (forming channels “on almost any type of substrate material”); 38:1-31 (microscale channels formed on substrates using photolithography and other techniques), 39:19-33 (channels fabricated into a surface of the substrate); EX1002, ¶¶114-15 (describing the fabrication of microfluidic flow channels in a substrate as routine and citing EX1017, 330-31).

Further, Wada’s methods involve flowing a sample through the aforementioned microfluidic flow channel formed in a substrate. *E.g.*, EX1006, 3:22-23. As Wada explains, its methods for sorting particle samples “are carried out within fluidic channels, along which the cell suspensions and/or other particles are flowed.” EX1006, 37:24-28. In use, Wada’s methods achieve “uniform flow

velocity to particles flowing in a first microchannel.” *Id.*, 3:22-23; *see also id.*, 12:1-14 (focusing cells “into a narrow region of a microchannel”); 12:30-32 (“position the stream within a desired region of a microchannel”); 42:8-24 (flowing a sample through a channel).



EX1006, FIG. 1A; EX1002, ¶¶116-18.

Various examples of flowing a sample through a microfluidic flow channel are depicted in the figures of Wada. EX1006, FIG. 21, 14:3-14. For example, Figure 1A of Wada depicts a microfluidic device in which particles are “flowed from one microchannels into a cross-junction.” *Id.*, 13:11-23-31; EX1002, ¶¶117-18.

Each of Figures 22, 23, and 24 and their accompanying descriptions also describe flowing a sample through a microfluidic flow channel. EX1002, ¶¶119-21. 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 conveyed in a carrier fluid from a focusing cross-junction towards a detector (2204). EX1006, 11:3-5, 19:23-20:2. Similarly, Figure 23 depicts conveying a stream of particles (cells

2300) in a carrier fluid along a vertical main microchannel towards a detector (2304). *Id.*, 11:6-7, 20:3-14. Figure 24 also depicts conveying a stream of particles in a carrier fluid within a vertical microchannel toward a detector (2408). *Id.*, 11:8-9, 22:23-23:18. The 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.

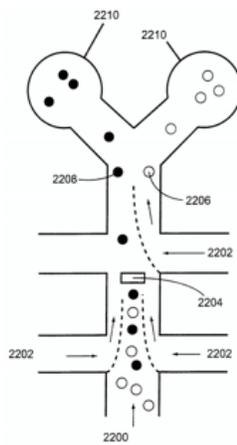


Fig. 22

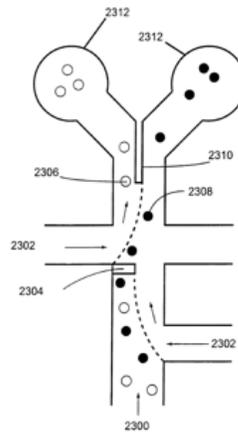


Fig. 23

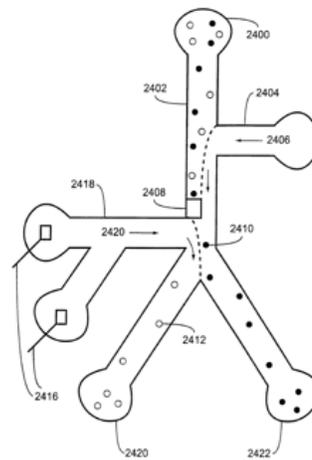


Fig. 24

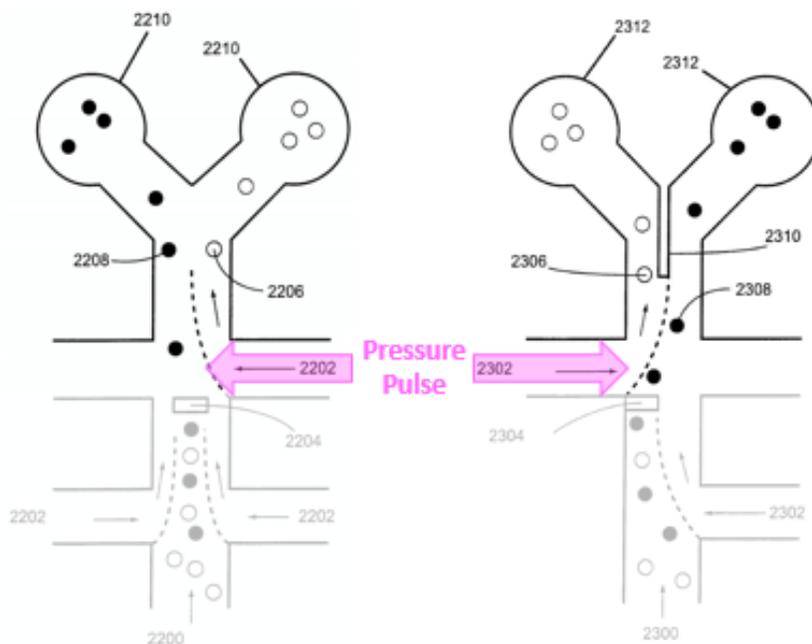
EX1006, FIGS. 22, 23, 24; EX1002, ¶¶119-21.

Accordingly, Wada discloses flowing a sample through a microfluidic flow channel formed in a substrate. EX1002, ¶¶114-22.

[1.b] propagating a pressure pulse across the microfluidic flow channel in a crosswise direction; and

Wada uses fluid direction components to propagate a pressure pulse across the microfluidic flow channel in a crosswise direction. For example, particles may

be “focused using one or more fluid direction components (e.g., a fluid pressure force modulator...or the like).” EX1006, 4:1-5. Wada sorts particle samples “such that selected individual members are directed into” a separate microchannel. *Id.*, 18:5-9.



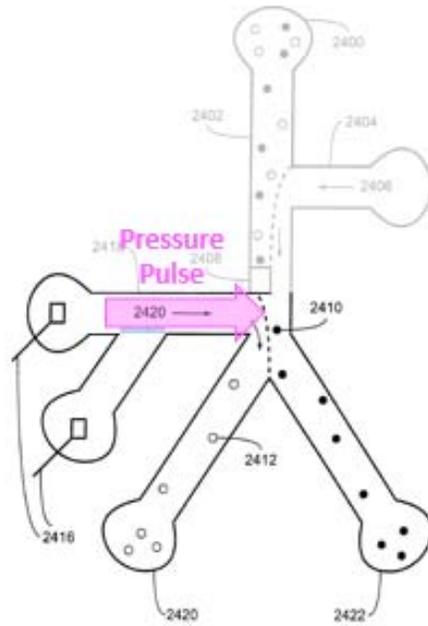
See EX1006, FIGS. 22-24 (annotated by Dr. Weigl); EX1002, ¶¶123-24.

Directing the flow of individual particles in a sample can be achieved with various methods, including pressure-based flow. EX1006, 18:18-25, claim 3. As Wada explains, pressure-based flow can be provided via a pressure pulse across the microfluidic flow channel in a crosswise direction. EX1006, 19:23-20:14, FIGS. 22-24. 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; EX1002, ¶¶123-24.

For example, in Figure 22, a pressure pulse is propagated across the microfluidic flow channel in a crosswise direction, moving from right to left. EX1006, 19:23-20:2. Figure 23 also depicts a similar usage of opposing microchannel structures, with a pressure pulse propagated across the microfluidic flow channel in a crosswise direction, moving from left to right. *Id.*, 20:3-14.

As another example, Figure 24 depicts an embodiment where Joule heating electrodes (an exemplary actuating mechanism) are provided in a microchannel structure disposed crosswise to the main microfluidic flow channel. EX1006, 22:23-24:12. “The heat produced by current flowing from Joule heating electrodes 2416 raises the temperature of, e.g., a buffer or gel disposed within branched particle sorting microchannel 2418, thus reducing hydrodynamic resistance in the buffer or 10 gel.” *Id.*, 23:7-10. Wada describes the Joule heating electrodes as decreasing the viscosity of the heated fluid, resulting in flow of the fluid. EX1006, 23:10-18. However, a POSA would have recognized that this this results in a pressure pulse being propagated across the microfluidic flow channel in a crosswise direction. EX1002, ¶¶127-28.



EX1006, FIG. 24 (annotated by Dr. Weigl); EX1002, ¶¶125-27.

A POSA also would have recognized that Wada’s disclosure of propagating a pressure pulse using an actuator is not limited to the embodiment of Figure 24. Wada Figure 22 likewise includes a set of opposing sorting microchannels downstream of the detector to direct selected cells into a selected outlet. EX1006, 19:23-20:2; *see also id.*, 8:6-23, 23:20-24, FIGS. 22-23. The use of a heating element to propagate a pressure pulse is broadly applicable throughout Wada’s embodiments, including those of Figures 22 and 23. *Id.*, 7:25-29; 8:12-23, 20:23-25, 22:30-23:3, 37:29-32, 38:11-17, 39:19-33; EX1002, ¶¶128-29, 140.

Similarly, Wada’s methods of propagating a pressure pulse are not limited to the use of heating elements such as the Joule heating electrodes. Wada discloses numerous “techniques for inducing the flow of focusing fluids to sort particles” using various fluid direction components and flow control regulators. EX1006,

19:9-13. These techniques include using “a fluid pressure force modulator, an electrokinetic force modulator, a capillary force modulator, a fluid wicking element, or the like”. *Id.*, 4:1-5; *see also id.*, 7:18-29, 42:8-43:14. Indeed, a POSA would have recognized that propagating a pressure pulse across a microfluidic flow channel was well-known in the art, and that there were ample teachings at the time for such feature. EX1002, ¶¶129-32 (discussing numerous prior art references disclosing such feature, including EX1014, 4; EX1016, FIG. 2; EX1020, 1:42-64, 2:31-3:17; EX1022, 107; EX1023, ¶¶0026, 0032).

Accordingly, Wada discloses propagating a pressure pulse across the microfluidic flow channel in a crosswise direction, as recited in claim element **1.b**. EX1002, ¶¶123-32.

[1.c] dampening or absorbing the pressure pulse using a first reservoir in fluid communication with the microfluidic flow channel,

Wada also discloses using a first reservoir to dampen or absorb the pressure pulse. *See* EX1002, ¶¶133-42; analysis of claim element **1.b** above.

For example, Wada Figures 22 and 23 depict a first reservoir in the form of a non-actuated, opposing microchannel structure disposed opposite the actuated sorting microchannel structure (from which an actuator mechanism applies the pressure pulse represented by arrows 2202 and 2302). EX1006, 19:23-20:14.

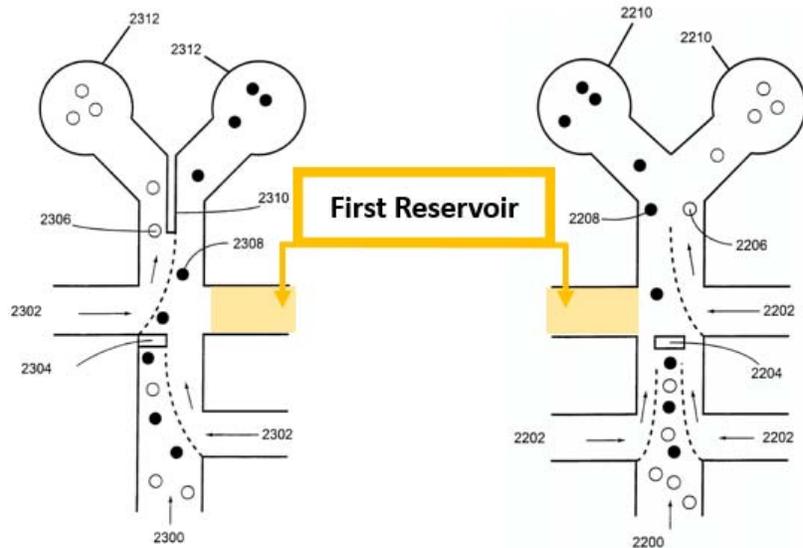


Fig. 23

Fig. 22

EX1006, FIGS. 22-23 (annotated by Dr. Weigl); EX1002, ¶¶133-34.

Wada discloses that the opposed sorting microchannel structures may each comprise a reservoir or other cavity. *See, e.g.*, EX1006, 20:23-25 (actuator positioned within a well, microscale channel, or other cavity), 23:19-26 (both opposing microchannels downstream of detector may include actuator); EX1002, ¶¶134-37, 146; *see also* EX1006, 37:29-32 (“microfluidic fluid passages, chambers or conduits”), 38:11-17 (“substantially defines the channels and chambers of the device”), 39:19-33 (“channels and/or chambers of the microfluidic devices are typically fabricated into the...bottom substrate” and covered or sealed).

Further, a POSA would understand that Wada’s teaching of opposing microchannel structures is not limited to Figures 22-23, but applies equally to Figure 24. EX1006, 49:13-20, 23:19-28; EX1002, ¶¶135-40.

Each of Figures 22 and 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. EX1002, ¶¶ 134, 238. A POSA would have understood the non-actuated, opposed sorting microchannel structure in each of Figures 22 and 23, in the context of Wada’s microfluidic devices and how Wada discloses they operate, includes a reservoir adapted for dampening or absorbing the transient pressure pulse propagated across the microfluidic channel. EX1002, ¶135.

As Dr. Weigl explains, Wada further suggests an embodiment of the microfluidic device of Figure 24 similarly comprising an opposed sorting microchannel structure, as illustrated in the annotated figure below:

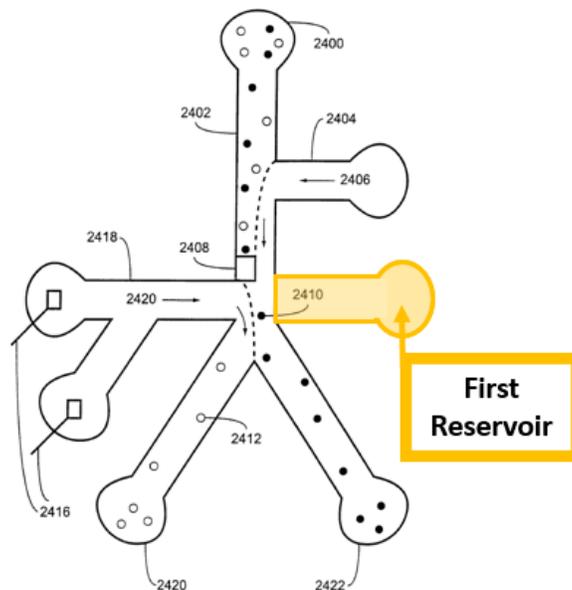
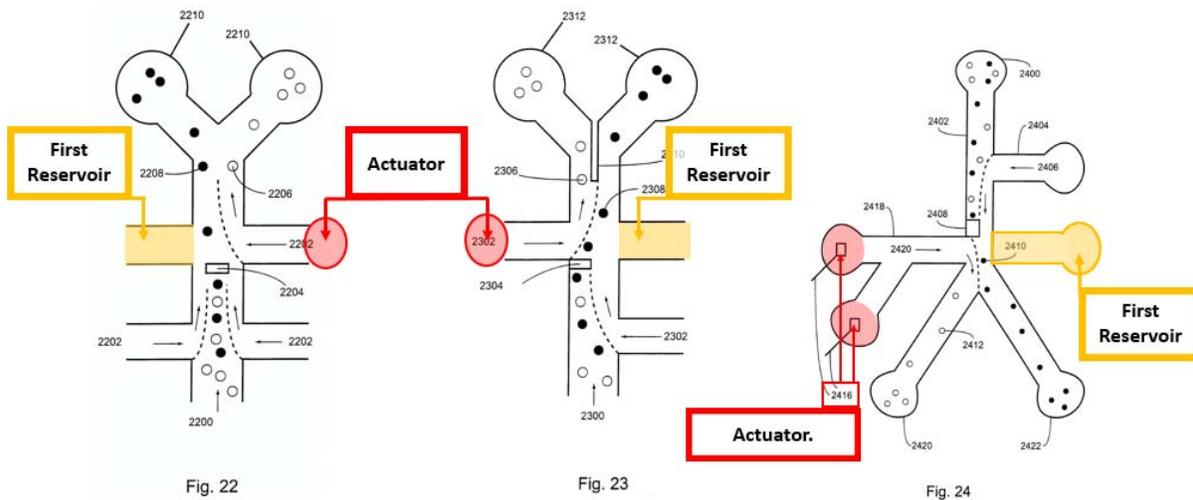


Fig. 24

EX1002, ¶140; EX1006, FIG. 24 (annotated by Dr. Weigl); *see also* EX1006, 49:13-20.

In Wada's microfluidic devices, the opening in the first microfluidic flow channel leading to the reservoir is aligned with the direction of the pressure pulse (substantially perpendicular to the main microchannel) so that fluid is allowed to flow into the opening and flow towards the reservoir. The non-actuated, opposed sorting microchannel structure of Wada thus is adapted for dampening or absorbing the pressure pulse as it receives displaced fluid and allows the fluid to enter the opposing channel and flow toward the reservoir. EX1002, ¶¶135-39.

As Dr. Weigl explains, when the microfluidic device is operated as described in Wada, the opening in the main flow channel leading to the buffer is aligned with the direction of the pressure pulse (substantially perpendicular to the main microchannel) so that the pressure pulse is allowed to flow into the opening and be absorbed by the buffer. EX1002, ¶¶135, 138-39, 143. The non-actuated, opposed sorting microchannel structure of Wada receiving the displaced fluid from the pressure pulse thus provides a first reservoir that dampens or absorbs the pressure pulse (*i.e.*, meaningfully dissipates the pressure pulse). Furthermore, since fluid from the main microfluidic channel can flow into the reservoir, a POSA would recognize that the reservoir is in fluid communication with the microfluidic flow channel. EX1002, ¶¶142-48.



EX1002, ¶145; *see also* EX1006, FIGS. 22-24 (annotated by Dr. Weigl).

As Dr. Weigl explains, using a reservoir opposite to the source of the pressure pulse for absorbing said pressure pulse was well-known in the art.

EX1002, ¶¶140-42 (discussing EX1005, FIG. 1; EX1007, FIG. 2; EX1016, 1:49-2:19, 5:44-54, FIG. 1; EX1018, 341-42; EX 1032, 8:4-8; EX1033, 196; EX1034, 2:23-34, 39:25-34, 40:20-25; EX1035, 377, 383). Further, the '528 patent itself admits that a non-actuated, opposed sorting microchannel structure absorbs the pressure pulse. EX1001, 12:27-30 (the “second side passage 174*b* and the second bubble valve 10*b* absorb the transient pressure variations”). EX1002, ¶¶137-41.

Accordingly, Wada discloses dampening or absorbing the pressure pulse using a first reservoir in fluid communication with the microfluidic flow channel, as recited in claim element 1.c EX1002, ¶¶133-50.

[1.d] wherein the pressure pulse is used to sort one or more particles suspended within the sample.

As discussed for claim elements **1.a**, **1.b**, and **1.c**, Wada uses a pressure pulse to sort different particles in a sample. *E.g.* EX1006, 18:18-25; EX1002, ¶¶114-51.

Wada's sorting process is "such that selected individual members are directed into" a separate microchannel. EX1006, 18:18-25. For example, in Figure 22 the pressure pulse propagated across the opposing microchannel structure "introduce[es] 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." *Id.*, 19:31-20:2, FIG. 22. A similar sorting process occurs in Figure 23 where a pressure pulse "direct[s] selected cells 2308 (e.g., fluorescently-labeled cells) and non-selected cells 2306 to either side of separation element 2310 and into, in this case, one of two microchannels, each terminating in particular collection wells." *Id.*, 20:10-13, FIG. 23.

Likewise, in Figure 24, a pressure pulse propagated by Joule heating electrodes (an exemplary actuating mechanism) "deflects or redirects the flow of selected particle 2410 into selected particle collection well 2422." EX1006, 23:15-16, FIG. 24. In contrast, a particle that is not impacted by the pressure pulse "flows

unimpeded into non-selected particle collection well 2420.” *Id.*, 23:18. Thus, Wada teaches methods wherein the pressure pulse is used to sort one or more particles.

EX1002, ¶¶151-54.

Wada makes clear that the particles being sorted are suspended within the sample. As Wada explains, its methods 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, 11:19-20 (sample includes “solubilized or suspended molecule”), 12:1-32, 34:14-16, 45:14-23. Thus, Wada discloses that the pressure pulse is used to sort one or more particles suspended within the sample, as recited in claim element **1.d**. EX1002, ¶¶152-57.

As discussed above, Wada discloses each element of claim 1 in the claimed configuration and provides a POSA with good reason to employ the claimed combination of elements with a reasonable expectation of success. Indeed, as Dr. Weigl explains, those in the art at the time would read Wada as a whole for all that it discloses and would not mechanically limit its teachings to individual embodiments only as specifically illustrated. Wada thus discloses and renders claim 1 obvious as a whole. EX1002, ¶¶152-57; *see* Section X.A.i above.

ii. *Independent Claim 5*

5. *A microfluidic device adapted to facilitate analysis or processing of a sample, the microfluidic device comprising:*

Wada disclose “providing substantially uniform flow velocity to flowing particles in microfluidic devices.” EX1006, Abstract. The microfluidic devices sort “particle populations, such as cells and various subcellular components.” *Id.*; *see also id.*, 3:13-33, 12:3-14, FIGS. 1A, 22-24. That is, Wada’s microfluidic devices facilitate analysis or processing of particle samples. Thus, Wada teaches the preamble of claim 5. EX1002, ¶¶158-60; *see also* Section X.A.i above.

[5.a] a microfluidic flow channel formed in a substrate, the flow channel having a width and a length that exceeds the width; and

Wada discloses a microfluidic flow channel formed in a substrate, the flow channel having a width and a length that exceeds the width. *See* analysis of claim element **1.a** above; EX1002, ¶161.

Wada’s microfluidic devices sort samples “within fluidic channels, along which the cell suspensions and/or other particles are flowed.” EX1006, 37:24-28; *id.*, 3:22-23 (“particles flowing in a first microchannel”), 12:1-32 (“position the stream within a desired region of a microchannel”); EX1002, ¶162.

Wada’s microfluidic flow channels are formed in a substrate. *E.g.*, EX1006, 37:23-32 (microchannels are “integrated into the body structure of a microfluidic

device”); 21:3-5 (forming microscale channels “on almost any type of substrate material”), 38:1-31 (forming microscale channels on substrates using photolithography and other techniques), 39:19-33 (forming channels on a surface of a substrate); EX1002, ¶¶161-62 (discussing EX1006; EX1017, 330-31).

Further, Wada’s microfluidic flow channels have a width and a length, with the length exceeding the width. For instance, each of Figures 22, 23, and 24 and their accompanying descriptions disclose such microfluidic flow channels.

EX1002, ¶¶119-21. Figure 22 depicts a vertical main microchannel, wherein a stream of particles (cells 2200) is conveyed in a carrier fluid from a focusing cross-junction towards a detector (2204). EX1006, 11:3-5, 19:23-20:2. Similarly, Figure 23 depicts conveying a stream of particles (cells 2300) in a carrier fluid along a vertical main microchannel towards a detector (2304). *Id.*, 11:6-7, 20:3-14. Figure 24 also depicts conveying a stream of particles in a carrier fluid within a vertical microchannel toward a detector (2408). *Id.*, 11:8-9, 22:23-23:18. The 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. In each case, the microfluidic flow channel has a length and a width, with the length of the microfluidic flow channel exceeding the width of the microfluidic flow channel.

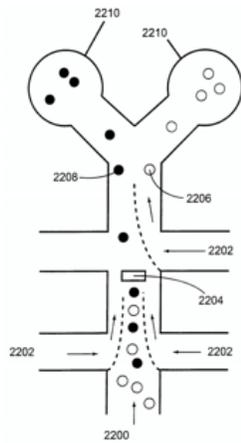


Fig. 22

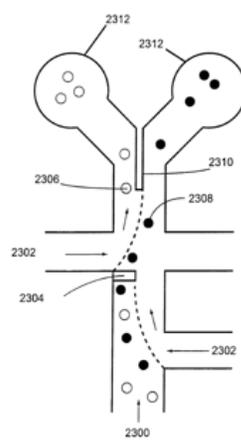


Fig. 23

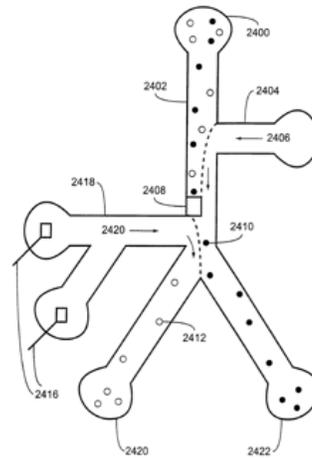


Fig. 24

EX1006, FIG. 22-24.

Thus, Wada discloses a microfluidic flow channel formed in a substrate, the flow channel having a width and a length that exceeds the width, as recited in claim 5. EX1002, ¶¶161-68.

[5.b] a first reservoir in fluid communication with the flow channel adapted for dampening or absorbing a pressure pulse propagated across the width of the flow channel,

As discussed above for claim 1, Wada discloses a first reservoir in fluid communication with the flow channel adapted for dampening or absorbing a pressure pulse propagated crosswise across the microfluidic flow channel. See analysis of claim elements **1.b**, **1.c** above; EX1002, ¶¶123-50.

As detailed above, Wada discloses opposed sorting microchannel structures wherein one sorting microchannel structure comprises an actuator for propagating

a pressure pulse across the width of the flow channel. EX1006, 20:23-25, 23:19-26, 37:29-32, 38:11-17, 39:19-33; *see also* Section X.A.i above. A POSA would have understood the non-actuated, opposed sorting microchannel structure of wada contains a fluid and receives and absorbs the pressure pulse. EX1002, ¶135, 186. As Dr. Weigl explains, the opening in the main flow channel leading to the buffer is aligned with the direction of the pressure pulse (substantially perpendicular to the main microchannel) so that the pressure pulse flows into the opening when actuated and is then absorbed by the buffer. The reservoir of the non-actuated, opposed sorting microchannel structure of Wada receives the displaced fluid and thus dampens or absorbs the pressure pulse as it is propagated across the width of the flow channel. EX1002, ¶¶169-72.

Accordingly, Wada teaches a first reservoir in fluid communication with the flow channel adapted for dampening or absorbing a pressure pulse propagated across the width of the flow channel, as recited in claim 5. EX1002, ¶¶169-72.

[5.c] wherein the first reservoir is otherwise sealed from an exterior environment.

Wada discloses that the first reservoir is otherwise sealed from an exterior environment. EX1006, 22:23-23:18, FIG. 24; EX1002, ¶173 (citing EX1042, 9-10, 18, 20; EX1043, ¶¶25-27, 31, 33-34, 44, 48); EX1045, 13-14; EX1042, 14-16.

As discussed above, Wada teaches sorting microchannels with an actuator, such as a Joule heating electrode. EX1006, 20:15-23:18, FIG. 24; *See* analysis of claim elements **1.b**, **1.c** above; EX1002, ¶¶123-50. For instance, Wada explains that the “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. The term “other cavity within the device” suggests a chamber, as Wada specifically teaches creating chambers in the substrate. *Id.*, 37:29-32, 38:11-17, 39:19-33; EX1002, ¶¶146, 176. Based on the disclosures of Wada, a POSA would have had good reason to place an actuator such as a Joule heating electrode on the substrate within a reservoir formed in the substrate of the microfluidic device.

Further, it would have been apparent to a POSA that the reservoir be otherwise sealed from an external environment to perform its stated function as a fluid direction component. Indeed, it was conventional at the time for an actuator to be disposed within a reservoir that has an opening in the direction of intended actuation flow but is otherwise sealed. *See, e.g.*, EX1012, 52:1-15 (describing thermopneumatic pump in a pressure chamber). As Dr. Weigl explains, a POSA, when using a Joule heating electrode as an actuator for sorting a particle of interest as disclosed in Wada, would have had good reason to dispose the electrode in an otherwise sealed chamber in order to better focus the increase in pressure in the

direction of the intended actuation flow to more efficiently discharge an amount of fluid in the direction of the intended actuation flow instead of dissipating it through competing fluidic connections. EX1002, ¶180. Accordingly, a POSA would have had good reason to employ a first reservoir that is in fluid communication with the flow channel and otherwise sealed from an exterior environment. EX1002, ¶¶173-82.

Wada Figure 24, for instance, does not depict the fluid direction component being in fluid communication with anything other than the duct. Wada also explains that the reservoir can be formed in the substrate and sealed by placing a covering on top of the chip substrate over the chamber. EX1006, 21:3-5, 38:11-39:33, FIG. 24; EX1002, ¶¶174-77.

Though Figures 22 and 23 do not graphically depict the actuator that generates the sorting flow 2202, 2302, Wada teaches that the microfluidic devices represented by these figures also comprise such an actuator within a reservoir formed in the substrate. *E.g.*, EX1006, 23:20-28. Wada thus discloses an embodiment of the schematics in Figures 22 and 23 wherein a chamber or reservoir formed in the substrate is positioned at the end of the active sorting channel. A POSA would have had good reason to employ a reservoir formed in the substrate, the reservoir in fluid communication with the flow channel via a side opening and otherwise sealed, consistent with the schematics disclosed in Wada Figures 22 and

23 (annotated below by Dr. Weigl). *See id.*, FIGS. 22-23, 20:3-22:30; *see also id.*, 37:29-32, 38:11-17, 39:19-33 (discussing creating chambers in the substrate); EX1002, ¶¶183-86.

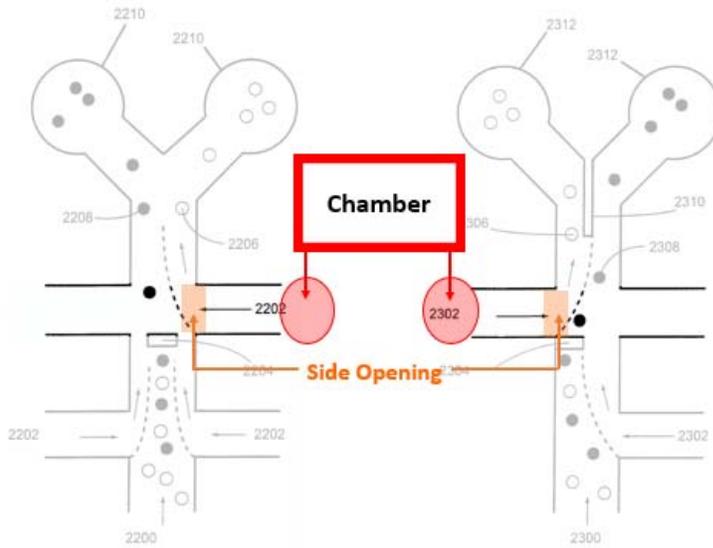


Fig. 22

Fig. 23

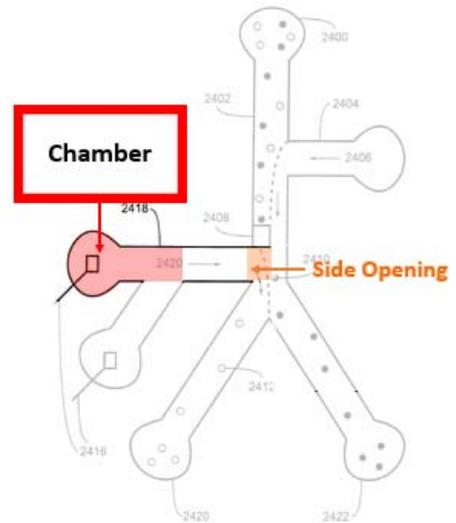


Fig. 24

See EX1006, FIG. 22-24; EX1002, ¶¶183-86.

Accordingly, Wada teaches a first reservoir in fluid communication with the flow channel and otherwise sealed from an external environment. EX1002, ¶¶173-86.

As discussed above, Wada discloses each element of claim 5 in the claimed configuration and provides a POSA with good reason to employ the claimed combination of elements with a reasonable expectation of success. Wada thus discloses and renders claim 5 obvious as a whole. EX1002, ¶187.

iii. Dependent Claims 2, 13, 16, and 18-19

Claims 2, 13, 16, and 18-19 each depend from either claims 1 or 5. The analysis above with respect to claims 1 or 5 is included herein for each dependent claim as discussed above. Wada also renders obvious the subject matter of claims 2, 13, 16, and 18-19, as discussed in detail below.

2. The method of claim 1, wherein the pressure pulse is used to selectively control or otherwise affect the flow of the sample through the flow channel.

As discussed above in claim element 1, Wada teaches using a pressure pulse to sort one or more particles suspended within a sample. EX1006, 19:14-20:14; EX1002, ¶¶113-87; *see* Section X.A.i above. Wada also makes clear that the pressure pulse is used to selectively control or otherwise affect the flow of the sample through the flow channel. For instance, Wada teaches generating a pressure pulse using a Joule heating electrode (an exemplary actuating mechanism). EX1006, 7:25-29; *see also id.*, 8:12-23, 20:23-25, 22:30-23:3, 37:29-32, 38:11-17, 39:19-33, FIG. 24. A POSA would have recognized that the heating of the fluid in the sorting microchannel by Joule heating electrode selectively generates and applies a pressure pulse that propagates across the microfluidic flow channel to deflect a particle into a selected branch of the flow channel. That is, the pressure pulse selectively controls or otherwise affects the flow of particles in a sample through the microfluidic flow channel.

Wada also specifically 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[.]” EX1006, 7:5-24. In view of the above, Wada teaches every element of claim 2. Accordingly, claim 2 is obvious in view of Wada. EX1002, ¶¶188-90.

13. The device of claim 5, further comprising an actuator or pressurizer operatively associated with flow channel and adapted for generating the pressure pulse across the width of the flow channel.

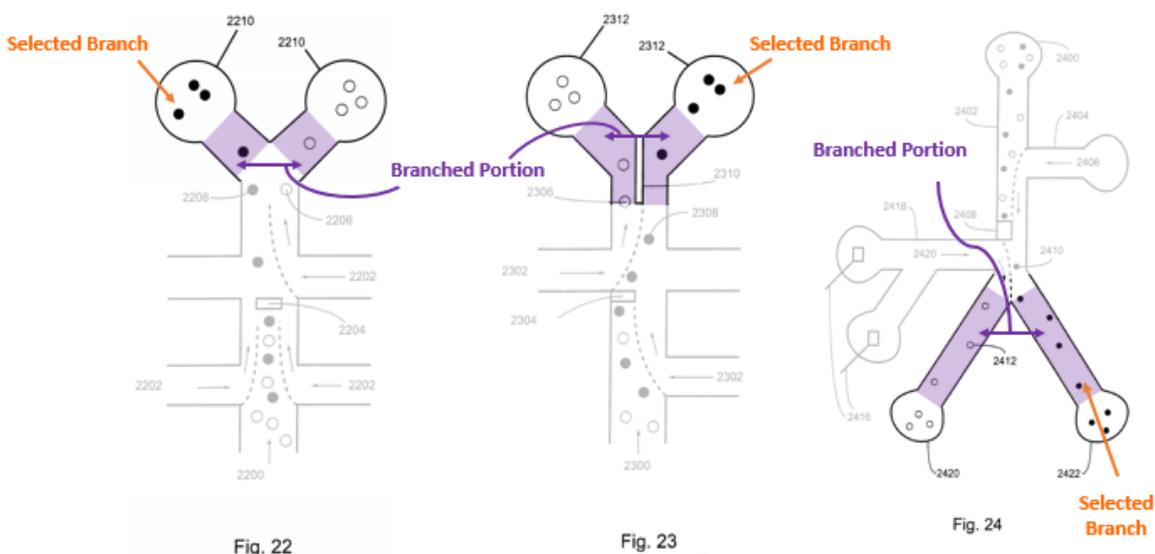
As discussed above in claims 1 and 5, Wada discloses generating a pressure pulse using an actuator such as a Joule heating electrode. EX1006, 7:25-29; 8:12-23, 20:23-25, 22:30-23:3, 37:29-32, 38:11-17, 39:19-33, FIG. 24; *see* Section X.A.i above. In addition to the Joule heating electrode, other actuators, including pressurizers, are also taught by Wada. For example, particle sorting may be achieved using “*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*,” noting that the “flow control regulator...further regulates flow” in the microchannels associated with sorting), 42:8-30 (teaching that the “flowing of the suspension of cells or other particles along one or more channels of the devices described herein is optionally carried out by a number of mechanisms, including *pressure based-flow*”).

Since the actuator or pressurizer provides a pressure pulse in a crosswise direction relative to the flow channel, the actuator or pressurizer is therefore operatively associated with microfluidic flow channel. Indeed, the association as well as the direction of the pressure pulse are depicted in Figure 24. EX1006, 23:18-24 (explaining that the features and positioning of actuators are not limited to Figure 24 and are broadly applicable to other embodiments, including that of Figure 22), FIG. 24. A POSA would understand that Wada teaches a microfluidic device further comprising an actuator or pressurizer operatively associated with flow channel and adapted for generating the pressure pulse across the width of the flow channel. For example, Figures 23 and 24 show Thus, claim 13 is obvious in view of Wada. EX1002, ¶¶191-93.

16. The device of claim 5, wherein the flow channel includes a branched portion, wherein the pressure pulse is used to sort one or more particles suspended within the sample into a selected branch of the branched portion.

Wada discloses sorting particles into one of two microchannels (*e.g.* outlet branches), each terminating in a collection well (*e.g.*, 2210 (left side), 2312 (right side), 2422). *See, e.g.*, EX1006, 19:23-23:26, FIGS. 22-24. A POSA would have recognized that the two outlets that each terminate into a particular collection well as described by Wada together constitute a branched portion of the flow channel, and that the pressure pulse is used to sort a particle into a selected branch of the branched portion. Indeed, such branched portions are depicted in each of Figures 22, 23, and 24 of Wada (annotated below by Dr. Weigl).



See EX1006, FIGS. 22-24; EX1002, ¶¶194.

Further, Wada makes clear that the pressure pulse is used 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. EX1002, ¶¶194-95. 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, 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 sorting processes are described in Wada relative to Figures 23 and 24. EX1006, 20:10-14; 22:23-23:18, 49:13-20. Accordingly, claim 16 is obvious in view of Wada. EX1002, ¶¶194-98.

[18.a] A method comprising: providing the microfluidic device of claim 5;

As discussed above, Wada disclose every element of the microfluidic device of claim 5 and that microfluidic device would have been obvious in view of Wada. It thus would have been obvious to provide that device in order to use it in the manner described. EX1002, ¶199; *see* Section X.A.i above.

[18.b] flowing a sample through the microfluidic flow channel;

Claim element **18.b** largely mirrors claim element **1.a**, the analysis for which is included here. For at least the same reasons discussed relative to claim element **1.a**, claim element **18.b** is also obvious in view of Wada. EX1002, ¶200; *see* Section X.A.i above.

[18.c] propagating the pressure pulse across the width of the flow channel; and

Claim element **18.c** largely mirrors claim element **1.b**, the analysis for which is included here. For at least the same reasons discussed relative to claim element **1.b**, claim element **18.c** is also obvious in view of Wada. EX1002, ¶201; *see* Section X.A.i above.

[18.d] dampening or absorbing the pressure pulse using the first reservoir in fluid communication with the flow channel.

Claim element **18.d** largely mirrors claim element **1.c**, the analysis for which is included here. For at least the same reasons discussed relative to claim element **1.c**, claim element **18.d** is also obvious in view of Wada. In view of the above, Wada teaches every element of claim 18. To the extent the challenged claim elements are viewed as illustrated in multiple embodiments of Wada, a POSA logically would have arrived at the claimed subject matter with a reasonable expectation of success in view of Wada. As Dr. Weigl explains, a POSA typically would have viewed a given prior art disclosure such as the Wada reference as a whole for all it teaches. *Id.*, ¶112. Indeed, Wada expressly teaches that “all the techniques and apparatus described above may be used in various combinations.” EX1006, 49:13-20.

Accordingly, claim 18 as a whole would have been obvious in view of Wada. EX1002, ¶202; *see* Section X.A.i above.

19. The method of claim 18, wherein the pressure pulse is used to sort one or more particles suspended within the sample.

As discussed, the method of claim 18 would have been obvious over Wada. Further, as discussed in claim element **1.d** and claim 2, Wada teaches using a pressure pulse to sort one or more particles suspended within a sample. EX1006, 19:14-20:14; *see* Section X.A.i above. Wada makes clear that the pressure pulse selectively controls or otherwise affect the flow of the sample through the flow channel. For instance, Wada teaches generating a pressure pulse using a Joule heating electrode. *Id.*, 7:25-29; 8:12-23, 20:23-25, 22:30-23:3, 37:29-32, 38:11-17, 39:19-33, FIG. 24. A POSA would have recognized that the heating of the fluid in the sorting microchannel by Joule heating electrode selectively generates and applies a pressure pulse that propagates across the microfluidic flow channel to deflect a particle into a selected branch of the flow channel. EX1002, ¶¶127, 204. That is, the pressure pulse sorts particles suspended in a sample through the microfluidic flow channel.

Accordingly, claim 19 as a whole would have been obvious in view of Wada. EX1002, ¶¶204-5.

B. Ground 2: Claims 1-2, 5, 13, 16, and 18-19 Are Obvious in view of Wada in view of Anderson

As discussed in Ground 1, the analysis for which is included herein, Wada renders obvious the microfluidic system of claims 1-2, 5, 13, 16, and 18-19. The disclosures of Anderson further demonstrate the obviousness of these claims. Specifically, Anderson provides additional disclosures regarding specific actuators, including the use of a reservoir or chamber suitable for generating or absorbing a pressure pulse. *E.g.* EX1002, ¶¶209-11.

i. Rationale to Combine

As discussed above in Section IX.B, Wada directs the ordinarily skilled artisan to Anderson to provide additional details on actuators to provide fluid flow in Wada's ducts. EX1006, 43:13-14. A POSA thus would have had good reason to combine the teachings of Anderson about how to move particles in a fluid in a microfluidic system to the microfluidic systems of Wada with a reasonable expectation of success. EX1002, ¶¶208-11.

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 duct as well as to focus and sort the particles. *See, e.g.*, EX1006, 3:23-4:5. 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. EX1006, 6:30-7:29, 26:26-27:2. 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.” EX1006, 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 duct.

As Dr. Weigl explains, a POSA would have had good reason to look to Anderson for microfabricated pumps capable of generating pressure-based fluid flow in ducts to actuate Wada’s fluid direction components for sorting the particles. EX1002, ¶¶207-08. When describing the use of pressure for flowing the particle through the duct, 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 duct 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 [Anderson].” *Id.*, 43:13-14.

Anderson teaches micropumps and how to make and use them to move particles in fluid in microfluidic systems. EX1012, 2:29-34, 5:14-31, 28:3-29, 34:5-21, 37:13-28, 46:23-48:16, 62:18-63:13. A POSA would have been motivated

to look to the combined teachings of Wada and Anderson with a reasonable expectation of success because she would have recognized that Anderson's microfabricated pumps were useful as fluid pressure force modulator for actuating Wada's fluid direction components for sorting the particles and were capable of generating pressure-based fluid flow in ducts. EX1002, ¶¶208-11.

As discussed in detail below, this combination renders obvious each of claims 1-2, 5, 13, 16, and 18-19.

ii. Independent Claims 1 and 5

Independent claims 1 and 5 each recite elements directed to a pressure pulse and a first reservoir for dampening or absorbing said pressure pulse. For instance, claim 1 recites "dampening or absorbing the pressure pulse using a first reservoir in fluid communication with the microfluidic flow channel." Similarly, claim 5 recites "a first reservoir in fluid communication with the flow channel adapted for dampening or absorbing a pressure pulse propagated across the width of the flow channel." EX1002, ¶207.

Wada teaches that many "techniques for inducing the flow of focusing fluids to sort particles" may be used. EX1006, 19:9-13. Suitable sorting forces include "pressure, hydrostatic, wicking, capillary, and other forces." *Id.* As discussed above, a POSA would have recognized that Wada teaches the use of an actuator mechanism for generating a pressure pulse and a first reservoir used for dampening

or absorbing said pressure pulse. For more specifics regarding actuator mechanisms, Wada points to and incorporates by reference Anderson's teachings in this regard. EX1006, 43:1-14. Thus, a POSA would have had good reason to look to Anderson for further discussion regarding actuators for generating pressure pulses. EX1002, ¶¶208-11. Anderson teaches specific embodiments utilizing such features that further demonstrates the obviousness of independent claims 1 and 5.

For example, 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. One example provided by Anderson includes a chamber that “incorporate[s] 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. Based on these disclosures, a POSA would have recognized that Anderson further renders obvious elements **1.b**, **1.c**, and **5.b**, directed to the propagating of a pressure pulse across the microfluidic flow channel in a crosswise direction, and the dampening or absorbing of the pressure pulse using a first reservoir. EX1002, ¶¶209-11.

In view of the teachings of Wada and Anderson, a POSA would have had good reason and a reasonable expectation of success to use the specific diaphragm pump, as taught by Anderson, in the method and microfluidic device of

independent claims 1 and 5, as disclosed by Wada. Accordingly, the combination of Wada and Anderson further demonstrates the obviousness of independent claims 1 and 5. EX1002, ¶¶208-11.

iii. Dependent Claims 2, 13, 16, and 18-19

Dependent claims 2, 13, 16, and 18-19 each depend from either independent claim 1 or 5. As discussed above, the disclosure of Anderson further demonstrates the obviousness of the method and microfluidic device of claims 1 and 5. The same reasoning applies to each of dependent claims 2, 13, 16, and 18-19, with their obviousness further bolstered when considering the teachings of Wada in further view of Anderson.

Indeed, each of dependent claims 2, 13, 16, and 18-19 recite further elements regarding the pressure pulse propagated in the microfluidic flow channel. Anderson provides specific teachings regarding the use of a diaphragm pump for propagating a pressure pulse. EX1012, 38:17-27, 45:3-12. As discussed above, Wada provides an express invitation to turn to the teachings of Anderson for suitable actuator mechanisms. Thus, a POSA would have had good reason to and a reasonable expectation of success in using a diaphragm pump to propagate a pressure pulse. Doing so would provide at least one of the opposing microchannel structures of Wada with a deflectable flexible membrane (*e.g.*, the diaphragm) wherein deflection of the membrane increases the pressure in a crosswise direction

along the width of the microfluidic channel when the flexible membrane flexes. Anderson's teachings thus further demonstrate the obviousness of the pressure pulse recited in dependent claims 2, 13, 16, and 18-19. EX1002, ¶¶212-13; *see* Sections IX, X.B.i-ii above.

C. Ground 3: Claims 1-2, 5, 13, 16, and 18-19 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 1-2, 5, 13, 16, and 18-19 and a POSA would have had good reason to use the claimed elements in the claimed combination with a reasonable expectation of success. EX1002, ¶¶214-18.

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, ¶¶214-18. For instance, a POSA would have recognized the utility of using known actuators (*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. EX1002, ¶131 (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, ¶¶211-13.

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. EX1002, ¶217-18; *see* Section X.B.i above. 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 actuator mechanisms disclosed by Anderson in the microfluidic device of Marcus to perform the fluidic sorting functions described by Marcus. The ordinarily skilled artisan would have had sufficient reason with a reasonable expectation of successfully obtaining thereby the subject matter of each of claims 18-24. EX1002, ¶¶214-18.

ii. Independent Claim 1

1. A method for facilitating analysis or processing of a sample, the method comprising:

Marcus in view of Anderson discloses a method for facilitating analysis or processing of a sample. Entitled “Fluidic Sorting Device for Two or More Materials Suspended in a Fluid,” Marcus teaches “a fluidic sorting device for the separation of two or more visually different materials.” EX1005, Abstract. Marcus’s microfluidic device allows 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, 3:28-62. Thus, Marcus in view of Anderson discloses the preamble of claim 1. EX1002, ¶¶219-20.

[1.a] flowing a sample through a microfluidic flow channel formed in a substrate;

Marcus’s method involves flowing a sample through a microfluidic flow channel formed in a substrate. Marcus’s microfluidic device comprises a channel for conveying a particle sample. EX1002, ¶¶221-22. Marcus’s method “utilizes a continuous flow of suspended materials or particles in a liquid.” EX1005, 1:37-53; *see also id.*, 2:49-66 (sorting particles by using an apparatus “programmed to identify and interpret different images suspended in a fluid medium”). Marcus

Figure 1 (annotated below by Dr. Weigl) specifically discloses the microfluidic device (1) comprises a channel for conveying a stream of particles (7, 8) in a carrier fluid (15).

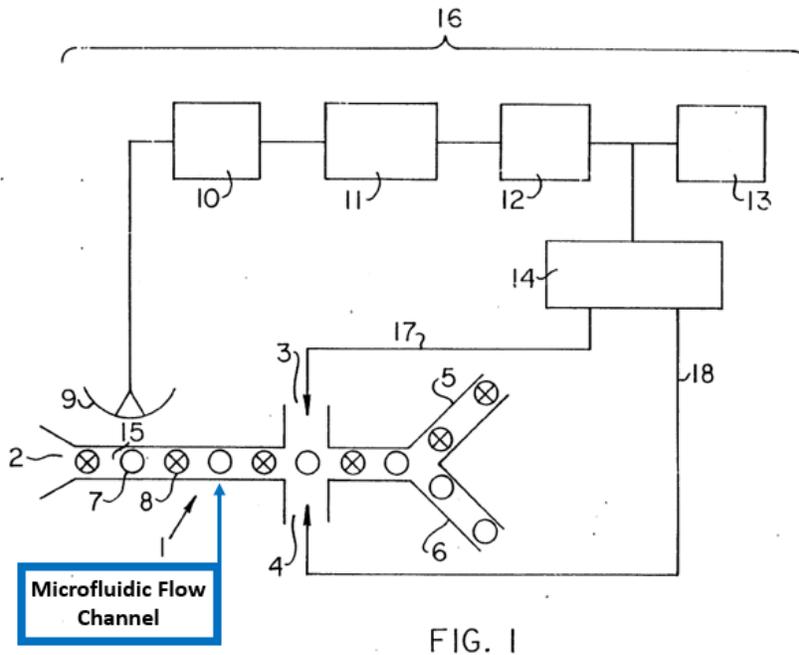


FIG. 1

See EX1005, FIG. 1; EX1002, ¶221.

Regarding Figure 1, Marcus explains that a particle sample (particles 7 and 8) flows through a microfluidic channel (e.g., the horizontal microchannel) suspended in a fluid carrier (15). EX1005, 3:30-62; EX1002, ¶¶222-24.

Further, Marcus’s microfluidic flow channel is formed in a substrate. For example, Marcus teaches microfluidic flow channels that are within the fluidic logic element that is “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. Marcus further explains that the substrate of the

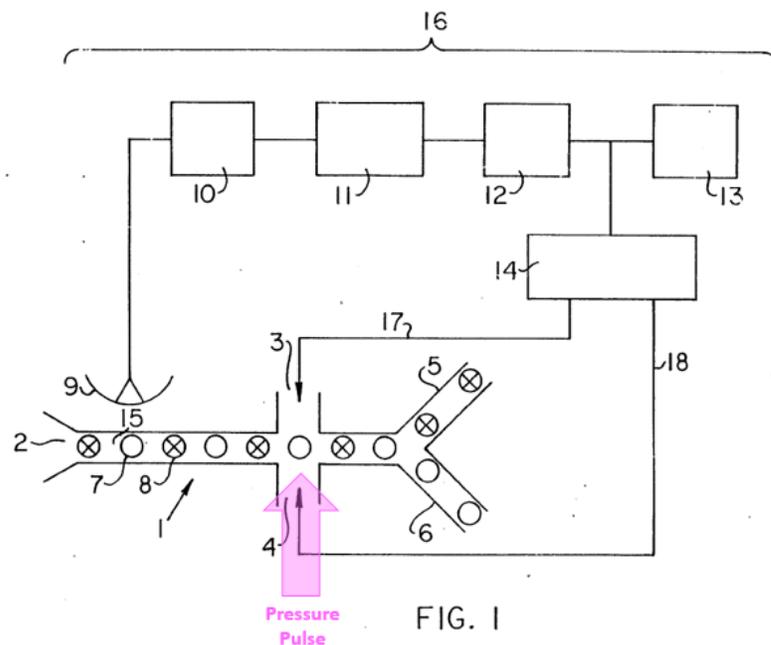
fluidic logic element “may be composed of semi-conductor materials, such as silicon and gallium arsenide.” *Id.* (explaining also that, in “order for the machine vision apparatus to capture an image of the particles flowing therethrough, the top surface cover over the fluidic logic device is composed of a transparent material”). Thus, Marcus teaches the formation of a microfluidic flow channel using micromachining technology in a substrate such as, *e.g.*, silicon, wherein the microfluidic flow channel is covered with a transparent material. Indeed, a POSA would have recognized that fabrication of microfluidic flow channels formed in a substrate was conventional at the relevant time. EX1002, ¶¶222-26 (citing EX1017, 330-31); *see* Sections IX, X.B.i above.

Thus, Marcus in view of Anderson discloses flowing a sample through a microfluidic flow channel formed in a substrate as recited in element **1.a**. EX1002, ¶¶221-26.

[1.b] propagating a pressure pulse across the microfluidic flow channel in a crosswise direction; and

Marcus and Anderson teach propagating a pressure pulse across the microfluidic flow channel in a crosswise direction. Marcus teaches deflecting a particle in the stream of particles to facilitate sorting of a sample. For example, detection of a selected particle (*e.g.*, particle A, labelled number 8 in Figure 1) triggers the fluidic controller device 14 to signal fluidic element control port (4) to

processing of a sample would have been further obvious in view of Anderson. *See, e.g.,* Sections IX, X.B.i; EX1002, ¶¶232-35 (discussing EX1014, 4; EX1016, FIG. 2; EX1018, 341-42; EX1020, 1:42-64, 2:31-3:17; EX1022, 107; EX1023, ¶¶0026, 0032). Indeed, as Dr. Weigl explains, it would have been natural for a POSA to look to other references, if needed, for specific teachings regarding such components. EX1002, ¶232.



See EX1005, FIG. 1 (annotated by Dr. Weigl), EX1002, ¶234.

As discussed above, Anderson discloses conventional actuators and pumps that were adopted by microfluidic devices during the relevant time. *See* Analysis of Ground 2 above; EX1012, 2:29-34; *see also id.*, 28:1-29 (noting that “[m]icrofabrication of microfluidic devices...has been discussed in detail in” the prior art), 34:5-21, 37:13-28; *see also* EX1006, 43:14 (citing Anderson’s teachings

regarding pumps for use in microfluidic devices). Specifically, 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. As a specific 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, 44:28-46:44. As Dr. Weigl, explains, a POSA would have recognized these conventional actuators were suitable for implementing Marcus’s microsorter teachings. EX1002, ¶¶228-29. The use of Anderson’s conventional pumps would provide for a pressure pulse propagated pulse across the microfluidic flow channel of Marcus in a crosswise direction. Marcus and Anderson thus teach propagating a pressure pulse across the microfluidic flow channel in a crosswise direction, as recited in claim element **1.b**. EX1002, ¶¶227-36; *see* Sections X.B.i, X.C.i above

[1.c] dampening or absorbing the pressure pulse using a first reservoir in fluid communication with the microfluidic flow channel,

Marcus discloses dampening or absorbing the pressure pulse using a first reservoir in fluid communication with the microfluidic flow channel. For example, Marcus Figure 1 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 vision camera lens 9. EX1005, 3:28-62; *see also*, ¶¶39-45, above (discussing the term “reservoir”); EX1042, 9-10, 18, 20 (construing “reservoir”); EX1043, ¶¶25-27, 31, 33-34 (same), 44, 48 (construing “chamber”); *see also*, ¶¶46-47, above (discussing the terms “absorbing,” and “dampening”); EX1043, ¶¶37-38, 40-43 (construing “buffer”), 50-52 (construing “absorbing”), 56-57 (construing “dampening”); EX1042, 13-14, 18-19 (same); EX1045, 8-10, 18-20.

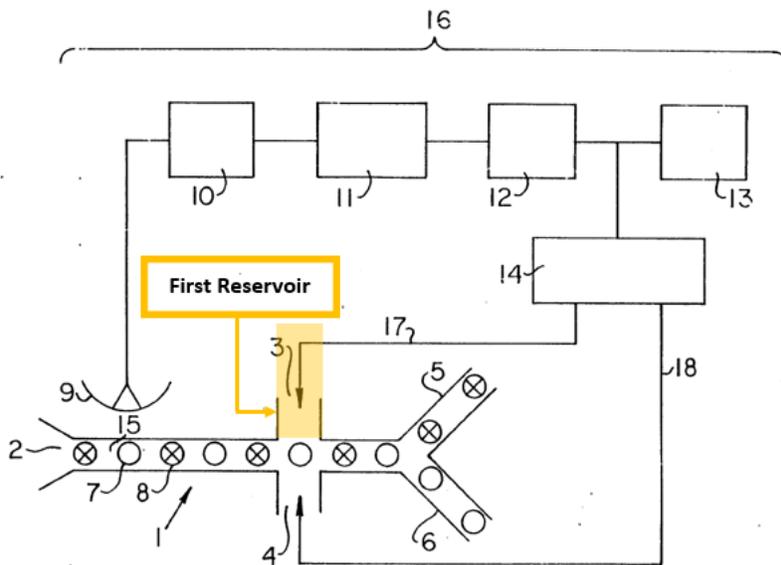
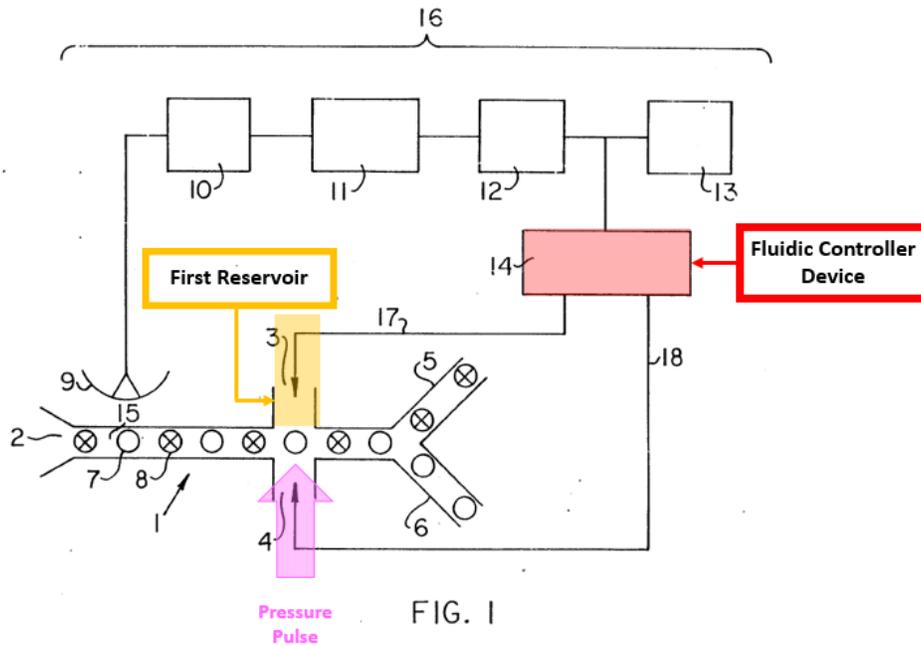


FIG. 1

See EX1005, FIG. 1 (annotated by Dr. Weigl); EX1002, ¶¶237-39.

A POSA would recognize Marcus and Anderson as teaching a pressure pulse propagated from one of the opposed sorting microchannel structures (flow from fluidic control port 4) and toward the non-actuated, opposed sorting microchannel structure (3). EX1005, 3:28-62, FIG. 1; EX1012, 5:11-31, 20:6-24, 28:3-29, 38:1-

39:4, 46:25-51:30, 62:18-67:6; EX1002, ¶240. Thus, Figure 1 (annotated below by Dr. Weigl) of Marcus discloses to a POSA that the opposing microchannel structure is, in each case, a physical structure that contains fluid, in fluid communication with the flow channel, and receives and dampens or absorbs a pressure pulse.



See EX1005, FIG. 1; EX1002, ¶239.

As Dr. Weigl explains, 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, ¶¶241-42 (citing EX1016, 5:44-54, FIG. 1; EX1018, 341-42; EX1032, 8:4-8; EX1033, 196; EX1034, 2:23-34, 39:25-34, 40:20-25; EX1035, 377, 383);

see Section IX, X.B.i, X.C.i above. A POSA would thus recognize the disclosures of Marcus and Anderson as teaching dampening or absorbing the pressure pulse using a first reservoir in fluid communication with the microfluidic flow channel, as recited in claim element **1.c.** EX1002, ¶¶237-43.

[1.d] wherein the pressure pulse is used to sort one or more particles suspended within the sample.

As discussed above relative to elements **1.a**, **1.b**, and **1.c**, Marcus discloses the use of a pressure pulse for sorting different particles in a sample being analyzed into one of two microchannels output port A (5) and output port B (6). *See, e.g.*, EX1005, 3:49-62, FIG. 1; *see* Section X.C.ii above.

For example, in Figure 1, the pressure pulse is propagated in a crosswise direction across the opposing microchannel structure and “particles 7 and 8 are then sorted through output port A and output port B, 5 and 6.” EX1005, 3:43-48; *see also, e.g.*, EX1012, 5:11-31, 20:6-24, 28:3-29, 38:1-39:4, 46:25-51:30, 62:18-67:6, discussed above as to element **1.b**. That is, the pressure pulse applied across the microfluidic flow channel in Figure 1 is used to sort one or more particles.

Marcus also teaches that the particles being sorted are suspended within the sample. Specifically, Marcus’s devices and methods sort particle populations “utilize[] a continuous flow of suspended materials or particles in a liquid means.” EX1005, 1:37-53; *see also id.*, 1:37-53 (utilizing “continuous flow of suspended

materials or particles in a liquid means”), 2:49-66 (utilizing an apparatus can “identify and interpret different images suspended in a fluid medium”).

Thus, Marcus and Anderson teach methods wherein a pressure pulse is used to sort one or more particles suspended within the sample. EX1002, ¶¶244-48.

As discussed above, Marcus and Anderson teach each element of claim 1 in the claimed configuration and provides a POSA with good reason to employ the claimed combination of elements with a reasonable expectation of success. Marcus and Anderson thus renders claim 1 obvious as a whole. EX1002, ¶248.

iii. Independent Claim 5

5. A microfluidic device adapted to facilitate analysis or processing of a sample, the microfluidic device comprising:

Marcus in view of Anderson discloses a microfluidic device adapted to facilitate analysis or processing of a sample. *See also* Section X.C.ii, above. Marcus discloses “a fluidic sorting device for the separation of two or more visually different materials.” EX1005, Abstract; EX1002, ¶249. Marcus’s fluidic sorting device sorts “a particle or material” based on a machine vision apparatus that decides whether an individual particle should be selected. EX1005, Abstract; *see also id.*, 1:62-68, 2:15-66, 3:65-4:3, FIG. 1. Marcus discloses the fluidic sorting component may be used to “sort different cells” and may be prepared “using conventional micromachining technology or any other conventional means...so as

to accommodate the sizes of the particles to be sorted.” *Id.*, 1:22-24, 1:62-68, 2:14-30. A POSA would thus recognize that Marcus teaches a microfluidic device adapted to facilitate analysis or processing of a sample. Accordingly, Marcus and Anderson teach the preamble of claim 5. EX1002, ¶¶249-51.

[5.a] a microfluidic flow channel formed in a substrate, the flow channel having a width and a length that exceeds the width; and

Marcus discloses a microfluidic flow channel formed in a substrate, the flow channel having a width and a length that exceeds the width. EX1002, ¶252. As Marcus explains, and as is depicted in Marcus Figure 1, its microfluidic device includes a microfluidic flow channel that “comprises one input port, two control ports and two output ports.” EX1005, 2:14-15.

Marcus’s microfluidic flow channels are formed in a substrate. For instance, the fluidic logic element of Marcus’s microfluidic device may be “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. Further, the substrate of the fluidic logic element “may be composed of semi-conductor materials, such as silicon and gallium arsenide.” *Id.* Thus, a POSA would understand Marcus as teaching the formation of a microfluidic flow channel using micromachining technology in a substrate such as, *e.g.*, silicon, wherein the microfluidic flow channel is covered with a transparent material. As set forth in

Accordingly, Marcus and Anderson teach a microfluidic device comprising a microfluidic flow channel formed in a substrate, the flow channel having a width and a length that exceeds the width, as recited in element **5.a**.

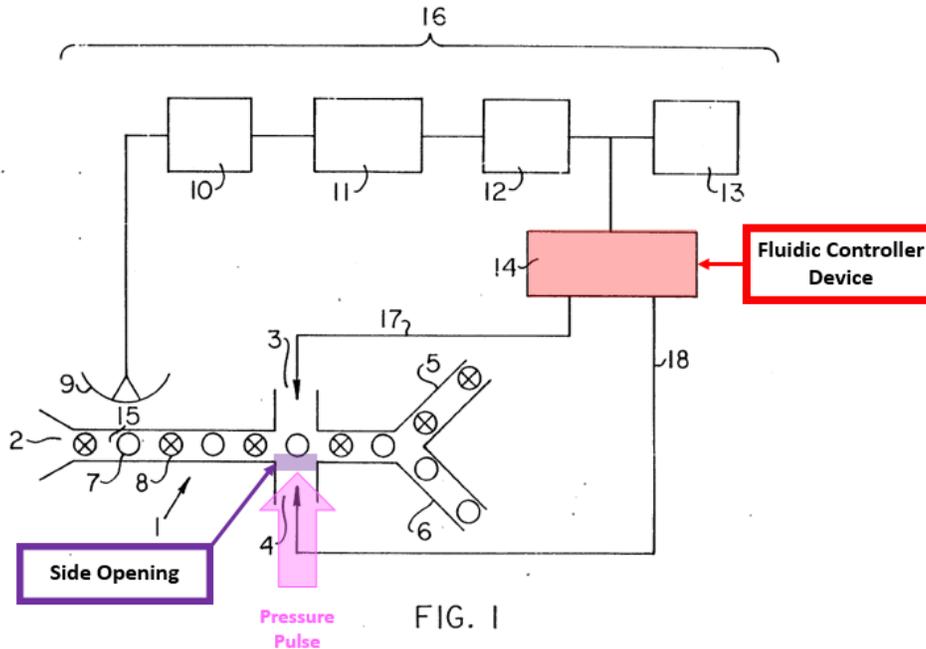
[5.b] a first reservoir in fluid communication with the flow channel adapted for dampening or absorbing a pressure pulse propagated across the width of the flow channel,

As discussed above for claim elements **1.b** and **1.c**, Marcus and Anderson teach a first reservoir in fluid communication with the flow channel adapted for dampening or absorbing a pressure pulse propagated crosswise across the microfluidic flow channel. *See* Section X.C.ii above; EX1005, FIG. 1; EX1012, 5:11-31, 20:6-24, 28:3-29, 38:1-39:4, 46:25-51:30, 62:18-67:6. Thus, Marcus and Anderson teach a first reservoir in fluid communication with the flow channel adapted for dampening or absorbing a pressure pulse propagated across the width of the flow channel, as recited in claim element **5.b**, for the same reasons discussed above. EX1002, ¶¶256-57.

[5.c] wherein the first reservoir is otherwise sealed from an exterior environment.

Marcus suggests the first reservoir be in fluid communication with the flow channel via a side opening and otherwise sealed from an exterior environment, as recited in claim element **5.c** of the '797 patent. *E.g.* EX1005, 22:23-23:18, FIG. 1; EX1002, ¶¶258-59. Marcus Figure 1 (annotated below by Dr. Weigl) depicts a

fluid direction component comprising a particle sorting microchannel (e.g., 4) and at least one actuator (e.g., fluidic controller device 14). EX1005, 3:28-62, FIG. 1.



See EX1005, FIG. 1; EX1002, ¶259.

The particle sorting microchannel (4) is in fluid communication with the microfluidic flow channel via a side opening upstream of the outlet channels but downstream of the detector (machine vision camera lens 9). EX1005, 3:28-62, FIG. 1. A POSA would have understood that it was conventional for the first reservoir of Marcus's Figure 1 (3) to be otherwise sealed from an external environment to perform its stated function. Though, Marcus Figure 1 does not depict a terminus of either oppositely-faced sorting microchannel (3, 4), it depicts and describes these microchannels as being in fluid connection with only the main microfluidic flow channel, and further tethered to the actuator (fluidic controller device 14) through

electronic leads 17 and 18. EX1005, 3:43-48, FIG. 1. Marcus also explains that the fluidic logic element can be micromachined into the substrate and subsequently sealed by placing a covering on top of the substrate over the fluidic logic element. EX1005, 2:20-30 (noting that “the top surface cover over the fluidic logic device is composed of a transparent material”). EX1002, ¶¶260-61.

Moreover, as discussed above as to element **1.b**, a POSA would have had good reason to look to Anderson for more specific disclosures of actuators and actuating mechanisms. EX1002, ¶¶262-63; *see* Sections X.B.i, X.C.i above. Specifically, a POSA would have had good reason to employ a first reservoir that is in fluid communication with the flow channel and otherwise sealed from an exterior environment as disclosed in Marcus Figure 1. Accordingly, Marcus and Anderson teach a first reservoir in fluid communication with the flow channel and otherwise sealed from an external environment. EX1002, ¶¶258-66.

As discussed above, Marcus and Anderson teach each element of claim 5 in the claimed configuration and provides a POSA with good reason to employ the claimed combination of elements with a reasonable expectation of success. Marcus and Anderson thus render claim 5 obvious as a whole. EX1002, ¶¶214-66.

iv. Dependent Claims 2, 13, 16, and 18-19

Claims 2, 13, 16, and 18-19 each depend from either claims 1 or 5. The analysis above with respect to claims 1 or 5 are included here for each of their

respective dependent claims as discussed above. Marcus and Anderson also render obvious the subject matter of claims 2, 13, 16, and 18-19, as discussed in detail below. EX1002, ¶¶267-69.

2. The method of claim 1, wherein the pressure pulse is used to selectively control or otherwise affect the flow of the sample through the flow channel.

As discussed above in claim element **1.d**, Marcus and Anderson teach using a pressure pulse to sort one or more particles suspended within a sample. The pressure pulse selectively controls or otherwise affects the flow of the sample through the flow channel. EX1002, ¶¶270-71; *see* Section X.C.ii above. Marcus specifically teaches that its systems detect a signal produced by a selected member of the particle population in a microfluidic flow channel in which a sample comprising particles (*e.g.*, 7 and 8) in a carrier fluid (*e.g.*, 15) are flowed, upstream of the side openings of the fluidic control ports (*e.g.*, 3 and 4), and selectively applies a pressure pulse across the microfluidic flow channel in a crosswise direction via these fluidic control ports to selectively control or otherwise affect the flow of particles (*e.g.*, 5 and 6) conveyed through the flow channel. EX1005, Abstract, 3:49-62, 4:4-7; EX1012, 5:11-31, 20:6-24, 28:3-29, 38:1-39:4, 46:25-51:30, 62:18-67:6, discussed above as to element **1.b**. Therefore, claim 2 is obvious in view of Marcus and Anderson. EX1002, ¶¶270-72.

13. The device of claim 5, further comprising an actuator or pressurizer operatively associated with flow channel and adapted for generating the pressure pulse across the width of the flow channel.

As discussed relative to claim elements **1.b**, **1.c**, and **5.b**, Marcus and Anderson teach generating a pressure pulse using an actuator (fluidic controller device 14) that is operatively associated with the microfluidic flow channel through control ports 3 and 4. EX1005, Abstract, 2:49-66, 3:49-62; EX1012, 5:11-31, 20:6-24, 28:3-29, 38:1-39:4, 46:25-51:30, 62:18-67:6. Specifically, the pressure pulse propagates across the microfluidic flow channel in a crosswise direction (*i.e.*, actuation of control port 4 results in a cross-channel pulse moving from the bottom to the top of the microfluidic flow channel depicted in Figure 1). EX1002, ¶¶273-75; *see* Section X.C.ii above

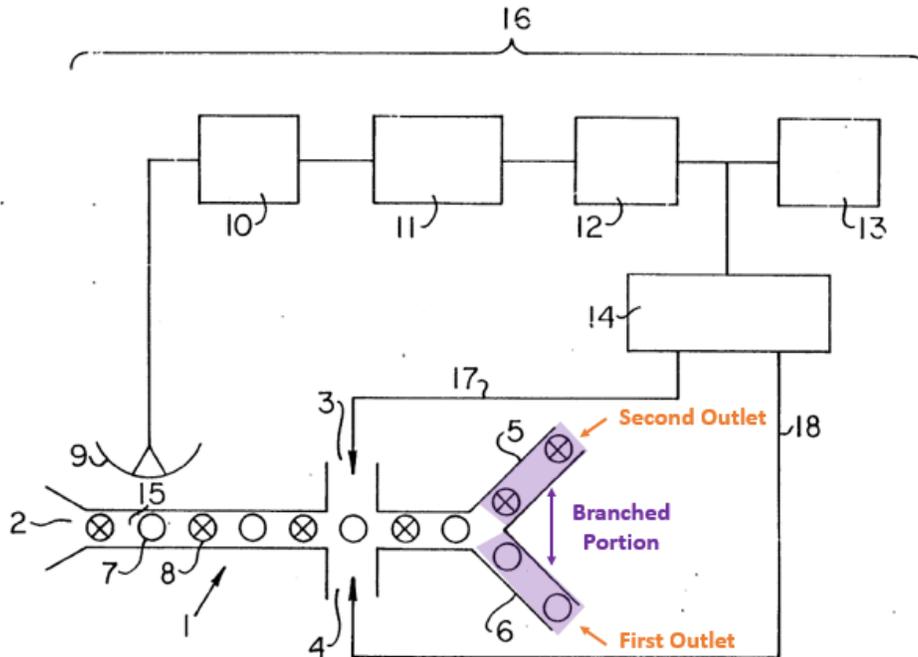
In use, detection of a selected particle (*e.g.*, particle A, labelled number 8 in Figure 1) triggers the actuator to redirect the selected particle from the stream of particles into a selected outlet channel (5) via a pressure pulse that is propagated across the microfluidic flow channel in a crosswise direction. In contrast, a non-selected particle (*e.g.*, particle B, labelled number 7) flows into the outlet for the non-selected particles (6). EX1005, Abstract, 2:49-66, 3:49-62, 5:13-6:2.

Since the actuator or pressurizer provides a pressure pulse in a crosswise direction relative to the microfluidic flow channel, the actuator or pressurizer is

therefore operatively associated with microfluidic flow channel. Indeed, the association as well as the direction of the pressure pulse are depicted in Figure 1. EX1005, Figure 1. Marcus and Anderson therefore teach a microfluidic device further comprising an actuator or pressurizer operatively associated with flow channel and adapted for generating the pressure pulse across the width of the flow channel. Thus, claim 13 is obvious in view of Marcus and Anderson. EX1002, ¶¶273-76.

16. The device of claim 5, wherein the flow channel includes a branched portion, wherein the pressure pulse is used to sort one or more particles suspended within the sample into a selected branch of the branched portion.

Marcus discloses sorting particles into one of two microchannels (*e.g.*, outlet channel A (5, top of fluidic logic element) and outlet channel B (6, bottom), 2422). *See, e.g.*, EX1005, 3:49-62, FIG. 1. A POSA would have recognized that the two microchannels constitute a branched portion of the flow channel, and that the pressure pulse as taught by Marcus and Anderson sorts a particle into a selected branch of the branched portion. EX1002, ¶¶277-78; *see* Section X.C.ii above. Indeed, such branched portions are depicted in Figure 1 Marcus (annotated below by Dr. Weigl).



See EX1005, FIG. 1; EX1002, ¶277.

A POSA would recognize that as a result of the pressure pulse, “particles 7 and 8 are then sorted through output port A and output port B, 5 and 6.” EX1005, 3:43-48; *see also, e.g.*, EX1012, 5:11-31, 20:6-24, 28:3-29, 38:1-39:4, 46:25-51:30, 62:18-67:6, discussed above as to element **1.b**, **1.c**, and **5.b**. That is, the pressure pulse applied across the flow channel in Figure 1 is used to sort one or more particles into a selected branch of the branched portion. Accordingly, Marcus in view of Anderson teaches the microfluidic device of claim 5, wherein the flow channel includes a branched portion, wherein the pressure pulse is used to sort one or more particles suspended within the sample into a selected branch of the branched portion. Therefore, claim 16 is obvious in view of Marcus and Anderson. EX1002, ¶¶277-79.

[18.a] A method comprising: providing the microfluidic device of claim 5;

As discussed above, Marcus and Anderson teach every element of the microfluidic device of claim 5 and that microfluidic device would have been obvious in view of Marcus and Anderson. It thus would have been obvious to provide that device in order to use it in the manner described. EX1002, ¶280; *see* Section X.C.ii above.

[18.b] flowing a sample through the microfluidic flow channel;

Claim element **18.b** largely mirrors claim element **1.a**, discussed above. For at least the same reasons discussed relative to claim element **1.a**, claim element **18.b** is also obvious in view of Marcus and Anderson. EX1002, ¶281; *see* Section X.C.ii above.

[18.c] propagating the pressure pulse across the width of the flow channel; and

Claim element **18.c** largely mirrors claim element **1.b**, discussed above. For at least the same reasons discussed relative to claim element **1.b**, claim element **18.c** is also obvious in view of Marcus and Anderson. EX1002, ¶282; *see* Section X.C.ii above.

[18.d] dampening or absorbing the pressure pulse using the first reservoir in fluid communication with the flow channel.

Claim element **18.d** largely mirrors claim element **1.c**, discussed above. For at least the same reasons discussed relative to claim element **1.c**, claim element **18.d** is also obvious in view of Marcus and Anderson. In view of the above, Marcus and Anderson teach every element of claim 18. Accordingly, claim 18 as a whole would have been obvious in view of Marcus and Anderson. EX1002, ¶¶283-84; *see* Section X.C.ii above.

19. The method of claim 18, wherein the pressure pulse is used to sort one or more particles suspended within the sample.

As discussed above, the method of claim 18 would have been obvious in view of Marcus and Anderson. EX1002, ¶¶280-84; *see* Section X.C.ii above. As discussed relative to claim element **1.d** and claim 2, Marcus and Anderson teach using a pressure pulse to sort one or more particles suspended within a sample. EX1005, 3:28-62, FIG. 1; *see also, e.g.*, EX1012, 5:11-31, 20:6-24, 28:3-29, 38:1-39:4, 46:25-51:30, 62:18-67:6, discussed above as to element **1.b**, **1.c**, and **5.b**. Indeed, the title of Marcus explicitly notes that the Marcus disclosure is a “*fluidic sorting device for two or more materials suspended in a fluid.*” EX1005, Title.

Marcus and Anderson teach a method wherein a pressure pulse is used to selectively control or otherwise affect the flow of the sample through the flow

channel. For instance, Marcus teaches that its 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), the pressure pulse otherwise described above in claim 1 is short-lived, *i.e.*, transient. EX1005, Abstract; *see also id.*, FIG. 1 (depicting particles in the suspension medium flowing through the flow channel before reaching the branched portion; selected particles are sorted into selected particle output A (5) while non-selected particles instead flow into non-selected particle output B (6)). That is, the pressure pulse sorts particles suspended in a sample through the microfluidic flow channel. Therefore, claim 19 is obvious in view of Marcus and Anderson. EX1002, ¶¶285-87.

XI. CONCLUSION

For the reasons set forth above, claims 1-2, 5, 13, 16, and 18-19 of the '797 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

/ Michael T. Rosato /

Michael T. Rosato, Lead Counsel

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 13,964 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. 9,011,797 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. 9,011,797 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	<i>Zeng, 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	<i>Zengerle, et al., 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	<i>Veenstra, et al., 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. 9,011,797 (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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