UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INSTRUMENTATION LABORATORY COMPANY

Petitioner

v.

HEMOSONICS LLC

Patent Owner

Inter Partes Review Case No. Unassigned

Patent 9,410,971

PETITION FOR *INTER PARTES* REVIEW OF

U.S. PATENT NO. 9,410,971 B2

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I. INTRODUCTION

Instrumentation Laboratory Company ("Petitioner") requests *inter partes* review ("IPR") of claims 1-20 (the "IPR Claims") of U.S. Patent No. 9,410,971 ("the '971 Patent") (Ex. 1002), which public records indicate is assigned to HemoSonics LLC ("Patent Owner"). This Petition demonstrates by a preponderance of the evidence that the IPR Claims are unpatentable and should be canceled, based on the prior art references applied herein.

II. MANDATORY NOTICES UNDER 37 C.F.R § 42.8(a)(1)

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

Petitioner, Instrumentation Laboratory Company is the real party-in-interest. Related entities, C A Casyso AG and Werfen USA, LLC, have interests represented by Petitioner.

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

Other pending related applications and patents may be affected by a decision in this proceeding. Specifically, U.S. Patent No. 9,272,280 ("the '280 Patent") (Ex. 1001), of which the '971 Patent is a continuation, is also the subject of an *inter partes* review petition, which Petitioner filed concurrently herewith ("'971 IPR"). Further, U.S. Patent App. Nos. 15/202,059 and 15/357,492 may be affected by the requested review.

C. Lead And Back-Up Counsel and Service Information Under 37 C.F.R. §§ 42.8(b)(3) & (4)

Lead Counsel	Back-Up Counsel
Stephen Y. Chow (Reg. No. 31,338) Burns & Levinson LLP 125 Summer Street Boston, MA 02110 Telephone: (617) 345-3263 Fax: (617) 345-3299 Email: schow@burnslev.com	Gabriel Goldman (Reg. No. 61,343) Ronda Moore (Reg. No. 44,244) Burns & Levinson LLP 125 Summer Street Boston, MA 02110 Telephone: (617) 345-3304, -3221 Fax: (617) 345-3299 Email: ggoldman@burnslev.com; rmoore@burnslev.com

III. GROUNDS FOR STANDING UNDER 37 C.F.R. § 42.104(a)

Petitioner certifies that: (1) the '971 Patent is eligible for *inter partes* review; and (2) Petitioner is not barred or estopped from requesting *inter partes* review of any claims of the '971 Patent on the grounds identified herein.

IV. FEES UNDER 37 C.F.R. §§ 42.15 & 42.103

The required fees are submitted herewith from Deposit Account No. 03-2410 (Order No. 51310-05007). If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. Deposit Account No. 03-2410 (Order No. 51310-05007).

V. STATEMENT OF THE PRECISE RELIEF REQUESTED AND THE REASONS THEREFOR UNDER 37 C.F.R. §§ 42.22(a) & 104(b)

Petitioner requests *inter partes* review under 37 C.F.R. § 42.108 as to the IPR Claims and cancelation of these claims as unpatentable based on one or more grounds under 35 U.S.C. § 102 or 35 U.S.C. § 103 in view of the following prior art patents and publications:

Exhibit	Reference	Priority	Publication	Type
1005	U.S. Patent No. 6,221,672 B2 ("the '672 Patent")	4/30/96	4/24/01	§ 102(a), -(b)
1006	U.S. Patent App. Pub. No. US 2010/0154520 A1 ("the '520 Publication")	12/17/09	6/24/10	§ 102(a), -(e)(1)
1007	U.S. Patent No. 6,016,712 B2 ("the '712 Patent)	9/18/1997	1/25/2000	§ 102(a), -(b)
1008	Lang, T., et al., "Different effects of abciximab and cytochalasin D on clot strength in thrombelastography," Journal of Thrombosis and Haemostasis, 2: 147-153 (2004), PubMed P.M.I.D.: 14717978 ("Lang 2004")		1/9/2004	§ 102(b)
1012	Viola, F., Mauldin Jr., W, Lin-Schmidt, X., Haverstick, D.M., Lawrence, M.B., Walker, W.F., A Novel Ultrasound-Based Method to Evaluate hemostatic Funtion of Whole Blood. Clin Chim Acta. 2010 Jan; 411(1-2): 106–113., Published online 2009 Oct 25, PubMed Central P.M.C.I.D. PMC2791922 ("Viola 2009")		10/25/2009	§ 102(b)

1013	U.S. Patent No. 5,504,011 B2 ("the '011 Patent")	10/21/1994	4/2/1996	§ 102(a), -(b)
1014	U.S. Patent No. 6,613,286 B2 ("the '286 Patent")	12/21/2000	9/2/2003	§ 102(a), -(b)
1015	U.S. Patent No. 5,888,826 B2 ("the '826 Patent")	6/30/1994	3/20,1999	§ 102(a), -(b)
1016	U.S. Patent No. 6,046,051 B2 ("the '051 Patent")	6/27/1997	4/4/2000	§ 102(a), -(b)
1017	U.S. Patent App. Pub. No. 2003/0199082 A1 ("the '082 Publication")	4/15/2002	10/23/2003	§ 102(a), -(b)

Petitioner requests cancelation of the IPR Claims on the following specific grounds:

Ground	IPR Claims	Art	Basis
1	1, 2, 6, 7, 15 and 16	'672 Patent	§ 102(a), -(b)
2	1, 2, 6, 7, 8, 15, and 16	'520 Publication	§ 102(a), -(e)(1)
3	3 and 4	'672 Patent and Viola 2009	§ 103(a)
4	3 and 4	'520 Publication and Viola 2009	§ 103(a)
5	5	'672 Patent and '011 Patent	§ 103(a)
6	5	'520 Publication and '011 Patent	§ 103(a)
7	8, 12 and 13	'672 Patent and '286 Patent	§ 103(a)
8	8, 12 and 13	'520 Publication and '286 Patent	§ 103(a)
9	9, 10 and 11	'672 Patent, '286 Patent, '826 Patent, '051 Patent and '082 Publication	§ 103(a)

10	9, 10 and 11	‘520 Patent, ‘286 Patent, ‘826 Patent, ‘051 Patent and ‘082 Publication	§ 103(a)
11	14	‘672 Patent and ‘712 Patent	§ 103(a)
12	14	‘520 Publication and ‘712 Patent	§ 103(a)
13	17, 18, 19 and 20	‘672 Patent and of Viola 2009	§ 103(a)
14	17, 18, 19 and 20	‘712 Patent, Lang 2004 and Viola 2009	§ 103(a)

Detailed claim charts applying the foregoing prior art for each of the IPR Claims are provided herein. Additional explanation and support for each ground is set forth in the Declaration of Dr. Patrick D. Mize (“Mize Decl.,” Ex. 1003). *See also* Appendix (List of Exhibits).

VI. OVERVIEW OF THE ‘971 PATENT

A. State of the Art Prior to February 15, 2011

The field of devices for evaluating hemostasis – blood clotting – was well-developed prior to the earliest priority date of the ‘971 Patent, the filing date of the provisional application, 61/443,088, February 15, 2011. Dr. Mize’s testimony, offered as an expert in the field, describes in detail the state of the art (Ex. 1003, ¶¶ 17-55). More particularly, Dr. Mize begins by providing a background on hemostasis, platelet activation and coagulation cascade (*id.* ¶¶ 17-21, Fig. 1). Next Dr. Mize proceeds with a historical overview of the development of different types of coagulations tests and reagent combination. (*id.* ¶¶ 18-42). Following the

historical overview of different types of coagulation tests, Dr. Mize also provides a detailed overview of some of the known techniques and devices for detecting coagulation including optical, mechanical, electrical, magnetic and acoustic techniques. (*id.* ¶¶ 43-55). The devices discussed by Dr. Mize are summarized in Ex. 1010, "Table of Prior Art Devices."

B. What the '971 Patent Claims

From a high level perspective, claim 1 of the '971 Patent essentially recites a multi-chamber device including an interrogation device for measuring a viscoelastic property of a test sample, where each chamber includes an activator of coagulation and where one of the chambers further includes abciximab, cytochalasin D or both.

The second independent claim (claim 17) is similar to claim 1 except that it further recites limitations related specifically to acoustic interrogation.

VII. PERSON OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the art ("POSA") in the field of devices for evaluating hemostasis would hold a bachelor's or advanced degree in chemistry, biochemistry, mechanical engineering, or a related discipline, with at least four years of experience in an academic research institution, a hospital research laboratory or medical device company designing or creating devices for evaluating hemostasis. A POSA would also have a knowledge base relating to medical applications for and point-of-care use of devices for evaluating hemostasis including familiarity with medical testing in general. This would include knowledge of clinical conditions, therapy, and how tests will respond to these different conditions. *See* Mize Decl. (Ex.

1003, ¶¶ 14-16).

VIII. CLAIM CONSTRUCTION UNDER 37 C.F.R. § 42.104(b)(3)

A. Claim Construction Standard

A claim subject to IPR is given its broadest reasonable interpretation ("BRI") in light of the specification as it would be understood by a POSA. 37 C.F.R. § 42.100(b); *In re Morris*, 127 F.3d 1048, 1054-55 (Fed. Cir. 1997). Indeed, "claim terms must be interpreted as broadly as their terms reasonably allow." *In re Zletz*, 893 F.2d 319, 321 (Fed. Cir. 1989). Accordingly, when given their BRI in light of the specification, the IPR Claims are anticipated and/or rendered obvious by the identified prior art.

B. "test chamber configured to receive blood of a test sample"

This limitation would be construed by a POSA as meaning "any constrained space or cavity structurally capable of receiving a blood sample." (Ex. 1003, ¶ 71.)

Notably the term "test" refers to an intended use of the chamber. As used in the claim, the term "test" does not implicate any meaningful structural constraints with respect to the chamber. (*Id.*, ¶ 72)

Moreover, the functional language "configured to" is interpreted as not actually requiring loading of a blood sample within the test chamber. Rather, the test chamber merely must be structurally capable of receiving a blood sample. (*Id*.)

Dr. Mize has further construed the term "blood" as including any of fresh (whole) blood, venous or arterial blood, preserved blood, platelet rich or poor plasma

blood or any other blood-based component of derivative. (*Id.*)

C. "configured to be interrogated to determine a hemostatic parameter of the blood"

This limitation would be construed by a POSA as meaning that the test chamber must be "capable of being interrogated in order to determine a hemostatic parameter of the blood." (*Id.*, ¶ 73)

As described in great detail by Dr. Mize, there are many different interrogation techniques which may be utilized to asses a hemostatic parameter (*Id.* ¶¶ 43-55; *see also*, Ex. 1010, "Table of Prior Art Devices."). Many of these interrogation techniques do not require any unique structural configuration of the chamber in order to implement.

D. "activator of coagulation"

An activator of coagulation would be construed by a POSA as being any of an intrinsic activator (such as celite, kaolin, silica, ellagic acid or another charged surface), an extrinsic activator (such as tissue factor or thromboplastin), a protein of the clotting cascade (such as Thrombin or Factor IIa), a co-factor in the clotting cascade (such as calcium), or an activator of a protein in the clotting cascade such as, but not limited to, the snake venoms reptilase, ecarin, and Russell's Viper Venom (RVV). (*Id.*, ¶ 69.)

E. "a first chamber of the plurality comprising a first reagent of a first combination of reagents" and "a second chamber of the plurality comprising a second combination of reagents"

It is noted that these limitations do not specify any specific temporal or

structural constraints regarding when and how the reagents are loaded into the chambers. Thus, these limitations could cover instances where the reagents are preloaded into the chambers, e.g., prior to the chambers receiving the blood sample, as well as instances where the reagents are loaded together with or subsequent to the blood sample. (*Id.*, ¶ 70.)

Petitioner applies the BRI standard to the remaining claim terms.

IX. SPECIFIC GROUNDS FOR UNPATENTABILITY UNDER 37 C.F.R. § 42.104(b)

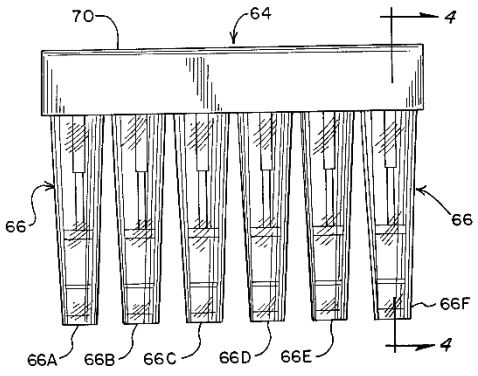
Petitioner requests *inter partes* review of the IPR Claims on the grounds set forth in the table above at Section V, and requests that each of the claims be found unpatentable. Additional explanation and support for each ground of rejection is set forth in the Declaration of Dr. Patrick D. Mize (Ex. 1003).

Provided below is a statement of each ground, and examples of how the recited limitations of the two IPR claims are disclosed in the prior art.

A. Ground 1: The '672 Patent Anticipates IPR Claims 1, 2, 6, 7, 15 and 16.

The '672 Patent (Ground 1), Ex. 1005, prior art to the '280 Patent under both the applicable (pre-AIA) 35 U.S.C. §§ 102(a) and –(b) as patented (April 24, 2001) before the '971 Patent priority date (Feb. 15, 2011) and more than a year before its application date (Feb. 15, 2012), anticipates IPR claims 1, 2, 6, 7, 15 and 16, by disclosing each and every element of the claims, arranged as claimed in a manner enabling to a POSA, as discussed by Dr. Mize in Ex. 1003, ¶¶ 94-100.

The claim chart provided below (reproduced in an abbreviated form from Dr. Mize's Declaration) further evidences how the '672 Patent discloses and enables each and every limitation of claims 1, 2, 6, 7, 15 and 16 of the '971 Patent:

'971 Patent Claims	**'672 Patent (Ex. 1005)**
1. A device for evaluation of hemostasis, comprising:	The '672 Patent teaches in the "Field of Invention" section that "the present invention relates to measuring and determining the effectiveness of antiplatelet reagents or platelet function inhibitors in the coagulation of blood…(and more specifically) on the mechanical activation of platelets. See, e.g., **Col 1; lines 19-25**. Thus, the '672 Patent clearly relates to the evaluation of hemostasis of a patient.
1A. a plurality of test chambers	The assay device (e.g., device 100) disclosed in the '672 patent uses a cartridge (e.g., cartridge 64 or 65) which includes a plurality of test chambers (each characterized by a constrained space or cavity). See, e.g., **Col 2; line 7-12** teaching that "(t)he cartridge includes a plurality of test cells, each of which is defined by a tube-like member having an upper reaction chamber where a plunger assembly is located and where the analytical test is carried out, and a reagent chamber which contains a reagent or reagents." See also, **Col 4, line 45-50**. See also **Fig. 3** depicting a test cartridge 64 for use with device 100 which includes a plurality of test cells 66 (specifically, test cells 66A-E)  FIG. 3

'971 Patent Claims	**'672 Patent (Ex. 1005)**
1Ai. each configured to receive blood of a test sample,	Each of the test cells in the '672 Patent is structurally capable of receiving a blood sample. See, e.g., **Col 4, line 11-12** teaching that "(a)n aliquot of a blood sample is added to each cell," See also, **Col 8, line 50-53** teaching that (t)he apparatus 62 is generally formed of subassemblies. A dispensing subassembly 104 of the apparatus 62 automatically supplies a sample of blood to each test cell 66 of the cartridge 64 or 65.
1Aii. each test chamber comprising a reagent or combination of reagents,	Each of the test cells in the '672 Patent also includes a reagent of combination of reagents. See, e.g., **Col 2; line 7-12** teaching that "(t)he cartridge includes a plurality of test cells, each of which is defined by a tube-like member having…a reagent chamber which contains a reagent or reagents." See also, Fig.4 depicting a reagent composition 80 and contact activator 90 included in each test cell.
1Aiii. wherein each chamber is configured to be interrogated to determine a hemostatic parameter of the blood received therein;	Each of the test cells in the '672 Patent is structurally capable of being interrogated to determine a hemostatic parameter. In particular, the '672 Patent teaches, a mechanical activation of platelets using a plunger assembly 72 in order to detect coagulation. See, also **Col 7, line 42-46**…**Col 8, line 60-64** and **Col 2, line 7-30**.
1B. a first chamber of the plurality comprising a first reagent or a first combination of reagents that interact with the blood received therein, wherein the first reagent, or a reagent included in the first combination of reagents, is an activator of	Each test cell of the '672 Patent includes at least an activator of coagulation which interacts with blood received in the chamber. See, e.g., the **Abstract** teaching that "(a)n aliquot of a blood sample is added to each cell, and the blood sample aliquot, clotting reagent and platelet inactivating agent are mixed." See, also, **Col 2, line 7-14** teaching that "(t)he cartridge includes a plurality of test cells, each of which is defined by a tube-like member having an upper reaction chamber where a plunger assembly is located and where the analytical test is carried out, and a reagent chamber which contains a reagent or reagents. For an activated clotting time (ACT) test, for example, the reagents include an activation reagent to activate coagulation of

‘971 Patent Claims	**‘672 Patent (Ex. 1005)**
coagulation;	the blood**.** See also, **Col 6, line 13-33** teaching a contact activator in the reagent chamber of each test cell 66. See also **Col 6, line 13-33**.
1C. a second chamber of the plurality comprising a second combination of reagents that interact with blood of the test sample received therein, the combination including an activator of coagulation and one or both of abciximab and cytochalasin D.	In addition to each test cell of the ‘672 Patent including an activator of coagulations, as noted above, at least two of the test cells comprise different amounts of a platelet inactivating agent. See, e.g., **Col 6, line 53-55**. As disclosed in **Col 5, line 40-51**, this may include e.g., abciximab: “Two classes of platelet inhibitors exist; the first class comprises compounds that act on platelet membrane sites, broadly known as IIa/IIb inhibitors such as, but not limited to, Abciximab...” See also, **Table 1** depicting cells 66C-66F as including different concentrations of a platelet inhibitor while cells 66A and 66B act as a baseline or control without any platelet inhibitor. **Table 1**, is discussed in **Col 6, line 55-61:** “In the exemplified embodiment shown in FIG. 3, the first two cells 66A and 66B (which represent the “baseline” or non-activated clotting time) contain no platelet inhibiting agent. Each successive cell 66C, 66D, 66E, and 66F includes increasing amounts of platelet inhibiting agent.”
1D. an interrogation device that measures at least one viscoelastic property of the test sample.	The ‘672 Patent discloses an interrogation device for measuring a viscosity change in a liquid such as blood. See, e.g., **Col 2, lines 14-30** teaching: “When the test commences, the contents of the reagent chamber are forced into the reaction chamber to be mixed with the sample of fluid, usually human blood or its components. An actuator, which is a part of the apparatus, lifts the plunger assembly and lowers it, thereby reciprocating the plunger assembly through the pool of fluid in the reaction chamber. The plunger assembly descends on the actuator by the force of gravity, resisted by a property of the fluid in the reaction chamber, such as its viscosity. When the property of the sample changes in a predetermined manner as a result of the onset or occurrence of a coagulation-related activity, the descent rate of the plunger assembly there through is changed. Upon a sufficient change in the descent rate, the

‘971 Patent Claims	**‘672 Patent (Ex. 1005)**
	coagulation-related activity is detected and indicated by the apparatus.”
2. The device of claim 1, further comprising a third chamber comprising a third reagent or combination of reagents that interact with blood of the test sample received therein; a fourth chamber comprising a fourth reagent or combination of reagents that interact with blood of the test sample received therein; and wherein the third and fourth chambers are configured to be interrogated to determine a hemostatic parameter of the test sample.	The ‘672 Patent teaches third and fourth chambers. See, e.g., **Fig. 2** depicting both 4-cell and 6-cell cartridge embodiments (cartridges 65 and 66, respectively). See also, **Col 4, line 27-33** teaching that “FIG. 2 is a perspective view of a 6-channel plunger sensor cartridge, a 4-channel plunger sensor cartridge**,** and a high sensitivity coagulation detection apparatus with which the cartridges are used on selectively alternate basis, all of which comprises an apparatus for measuring and detecting coagulation and coagulation-related factors in fluids, in accordance with the present invention.” As noted above, the ‘672 Patent also teaches that each of the chambers (test cells) in the cartridges includes a reagent or combination of reagents. See, e.g., **Col 2; line 7-12** teaching that “(t)he cartridge includes a plurality of test cells, each of which is defined by a tube-like member having…a reagent chamber which contains a reagent or reagents.” See also, Fig.4 depicting a reagent composition 80 and contact activator 90 included in each test cell. Furthermore, as also noted above, each of the test cells in the ‘672 Patent is structurally capable of being interrogated to determine a hemostatic parameter. In particular, the ‘672 Patent teaches, a mechanical activation of platelets using a plunger assembly 72 in order to detect coagulation. See, e.g., **Col 7, line 42-46** teaching that “the presently preferred embodiment of an apparatus 62 and a plunger sensor cartridge 64 may be used together in order to evaluate the effectiveness of antiplatelet reagents or platelet inhibitors on the mechanical activation of platelets.” See also, **Col 8, line 60-64** and **Col 2, line 7-30.** See also generally **Col 7, line 21-29**.
6. The device of claim 1**,** wherein each	Each of the test cells in the ‘672 patent is defined by a tube-like housing. See, e.g., **Col 2; line 7-12** teaching

‘971 Patent Claims	**‘672 Patent (Ex. 1005)**
test chamber of the plurality of test chambers is at least partially defined by a housing.	that “(t)he cartridge includes a plurality of test cells, each of which is defined by a tube-like member having an upper reaction chamber where a plunger assembly is located and where the analytical test is carried out, and a reagent chamber which contains a reagent or reagents.” Notably, the tube like member 68 of the test wells 66 forms part of the outer housing of the cartridge 64 or 65 as well. See, e.g., **Figs. 2 and 3**.
7. The device of claim 6**,** wherein the device is configured for use with a single test sample.	The ‘672 Patent teaches using a single sample with the multi-chamber cartridge and analyzer. “[t]he apparatus 62 is generally formed of subassemblies. A dispensing subassembly 104 of the apparatus 62 automatically supplies a sample of blood to each test cell 66 of the cartridge 64 or 65.” See **Col 8, line 50-53.** The sample is divided up and portions of the sample are loaded into each of the test wells. See, e.g., **Abstract** teaching that [a]n aliquot of a blood sample is added to each cell.” See also, **claim 11**
15. The device of claim 1, wherein the second chamber comprises a combination of reagents that includes a reagent comprised by the first chamber.	As noted above, each test cell of the ‘672 Patent includes at least an activator of coagulation which interacts with blood received in the chamber. See, e.g., the **Abstract** teaching that “(a)n aliquot of a blood sample is added to each cell, and the blood sample aliquot, clotting reagent and platelet inactivating agent are mixed.” See, also, **Col 2, line 7-14** teaching that “(t)he cartridge includes a plurality of test cells, each of which is defined by a tube-like member having an upper reaction chamber where a plunger assembly is located and where the analytical test is carried out, and a reagent chamber which contains a reagent or reagents. For an activated clotting time (ACT) test, for example, the reagents include an activation reagent to activate coagulation of the blood**.** See also, **Col 6, line 13-33** teaching a contact activator in the reagent chamber of each test cell 66. See also, **claim 3**, wherein an optimized amount of a same contact activator (kaolin) is placed in each said cell See also **Table 1** teaching that each cell 66A-F includes heparin and that each of cells 66C-F includes a different concentration of a same

‘971 Patent Claims	‘672 Patent (Ex. 1005)
	platelet inhibitor.
16. The device of claim 1, wherein the first chamber comprises a first combination of reagents including one or more of reagents selected from the group consisting of kaolin, celite, glass, thrombin, ellagic acid, and tissue factor, and wherein the second chamber comprises the second combination of reagents including one or more reagents selected from the group consisting of kaolin, celite, glass, thrombin, ellagic acid, and tissue factor.	As noted above, the ‘672 patent teaches that each test cell includes at least a contact activator which may be, e.g., kaolin, diatomaceous earth, powdered glass, silica, or any other particle having a negatively charged surface. See, e.g., **Col 6, line 13-33.**

A.

B. Ground 2: The ‘520 Publication Anticipates IPR Claims 1, 2, 6, 7, 8, 15, and 16

The ‘520 Publication (Ground 2), Ex. 1006, prior art to the ‘971 Patent under both the applicable (pre-AIA) 35 U.S.C. §§ 102(a) and –(e)(1) as published (June 24, 2010) before the ‘971 Patent priority date (Feb. 15, 2011), anticipates IPR claims 1, 2, 6, 7, 8, 15 and 16, by disclosing each and every element of the claims, arranged as claimed in a manner enabling to a POSA , as discussed by Dr. Mize in Ex. 1003, ¶¶

101-106.

The claim chart provided below (reproduced in an abbreviated form from Dr. Mize's Declaration) further evidences how the '672 Patent discloses and enables each and every limitation of claims 1, 2, 6, 7, 8, 15 and 16 of the '971 Patent:

'971 Patent Claims	**'520 Publication**
1. A device for evaluation of hemostasis, comprising:	The '520 Publication discloses a cartridge device that can be used for measuring hemostatic properties. "The present invention is directed to a cartridge device for a measuring system for measuring viscoelastic characteristics of a sample liquid, in particular a blood sample." **Abstract**. See also, **paragraphs 0002-0007 and 0025**.
1A. a plurality of test chambers	The '520 Publication also teaches a plurality of test chambers. See, e.g., **paragraph 0029** teaching that "(i)n a first aspect, the present invention provides a cartridge device for a measuring system for measuring viscoelastic characteristics of a sample liquid, in particular a blood sample, comprising a cartridge body having at least one measurement cavity formed therein and having at least one probe element arranged in said at least one measurement cavity for performing a test on said sample liquid." See also **paragraphs 0081-0082** teaching: "FIG. 6 shows another variation of the first embodiment. Two arrangements of FIG. 4 with only one receiving cavity 16 are arranged in parallel... It is apparent to a person skilled in the art that in order to achieve a maximum benefit for a user different types of tests can be combined in one cartridge device 50. In a preferred embodiment the cartridge device 50 comprises four arrangements of FIG. 4 or 5 having 4 measurement cavities 20, 20'. Thus measurements can be done with different reagents on the same liquid sample or with same reagents as well to check plausibility."
1Ai. each configured to receive blood of a test	The '520 Publication also teaches that each of the test chambers is structurally capable of receiving a blood

‘971 Patent Claims	‘520 Publication
sample,	sample. See, e.g., **paragraph 0081** teaching that the sample liquid 1 is shared among the arrangements in parallel.
1Aii. each test chamber comprising a reagent or combination of reagents,	The ‘520 Publication also teaches that each of the test chambers includes a reagent or combination of reagents. See, e.g., **paragraph 0040** teaching that in some embodiments, “at least one reagent cavity is integrally formed…with the at least one measurement cavity.” Thus, for instances of four parallel measurement cavities, such as taught in **paragraph 82** each of the measurement cavities could have an integrally formed respective reagent cavity. See, also **paragraph 83** teaching: “Regarding e.g. blood coagulation there are different reagents available which activate or suppress different parts of the coagulation cascade. Pentapharm GmbH (Munich, Germany) for example amongst others provide tests for intrinsic and extrinsic activation of a blood sample (INTEM™ or EXTEM™ respectively), and also a test for extrinsic activation in which the thrombocyte function is suppressed by administration of cytochalasin D (FIBTEM™)… It is also possible to combine e.g. an INTEM™, an EXTEM™ and a FIBTEM™ coagulation test with a platelet aggregometry test within one cartridge.” As would be apparent to a person of ordinary skill in the art, each of the cited tests, INTEM™, EXTEM™ and FIBTEM™ implicates a particular reagent combination which would be included for use with a respective measurement cavity.
1Aiii. wherein each chamber is configured to be interrogated to determine a hemostatic parameter of the blood received therein;	Each measurement cavity in the ‘520 Publication is structurally capable of being interrogated to determine a hemostatic parameter. See, e.g., **paragraph 0029** teaching that “[i]n a first aspect, the present invention provides a cartridge device for a measuring system for measuring viscoelastic characteristics of a sample liquid, in particular a blood sample, comprising a cartridge body having at least one measurement cavity formed therein and having at least one probe element

‘971 Patent Claims	‘520 Publication
	arranged in said at least one measurement cavity for performing a test on said sample liquid” In particular, the ‘520 Publication teaches, mechanical activation and optical detection of a sample in the measurement cavity using a pin and cup mechanism. See, e.g., **paragraph 11** teaching that “[a]s the sample liquid 1 begins to coagulate the motion amplitude of the shaft 6 which is detected by the deflection of a light beam from detecting means 10 and a mirror 9 starts to decrease.” See also, paragraph 83 teaching “a probe element 22 arranged in the measurement cavity 20” and **paragraph 88** teaching that “FIG. 7 c shows the sample liquid 1, which has been pumped into the measurement cavity 20. The probe pin 3 of the probe element 22 is immersed in the sample liquid 1 a plunger assembly 72 in order to detect coagulation.”
1B. a first chamber of the plurality comprising a first reagent or a first combination of reagents that interact with the blood received therein, wherein the first reagent, or a reagent included in the first combination of reagents, is an activator of coagulation;	As noted above, the ‘520 Publication teaches that a measurement cavity may include an integrally formed reagent cavity. Moreover, the ‘520 Publication provides examples of different reagents that can be included for performing different assays. See, e.g., **paragraph 0083** teaching “Regarding, e.g., blood coagulation there are different reagents available which activate or suppress different parts of the coagulation cascade. Pentapharrn GmbH (Munich, Germany) for example amongst others provide tests for intrinsic and extrinsic activation of a blood sample (INTEM™ or EXTEM™ respectively), and also a test for extrinsic activation in which the thrombocyte function is suppressed by administration of cytochalasin D (FIBTEM™). The ‘520 Publication also provides that plurality of different assays may be combined in a single cartridge. See, **Ibid.**, teaching that “it is also possible to combine e.g. an INTEM™, an EXTEM™ and a FIBTEM™ coagulation test with a platelet aggregometry test within one cartridge.” As disclosed, this could be achieved by multiple different measurement cavities each associated with a respective assay and its reagents. See, e.g., **paragraph 0082** teaching “it is apparent to a person skilled in the

‘971 Patent Claims	‘520 Publication
	art that in order to achieve a maximum benefit for a user different types of tests can be combined in one cartridge device 50. In a preferred embodiment the cartridge device 50 comprises four arrangements of FIG. 4 or 5 having 4 measurement cavities 20, 20'" Thus, the ‘520 Publication includes teachings that a first measurement cavity in a plurality of measurement cavities can include reagents which “activate different parts of the coagulation cascade” such as intrinsic or extrinsic activators (as would be used in the INTEM™ and EXTEM™ assays, respectively).
1C. a second chamber of the plurality comprising a second combination of reagents that interact with blood of the test sample received therein, the combination including an activator of coagulation and one or both of abciximab and cytochalasin D; and	As noted above, the ‘520 Publication teaches that a measurement cavity may include an integrally formed reagent cavity. Moreover, the ‘520 Publication provides examples of different reagents that can be included for performing different assays including specifically use of an extrinsic activator in combination with cytochalasin D (as is the case with the FIBTEM™ assay) See, e.g., **paragraph 0083** teaching “Regarding, e.g., blood coagulation there are different reagents available which activate or suppress different parts of the coagulation cascade. Pentapharrn GmbH (Munich, Germany) for example amongst others provide tests for intrinsic and extrinsic activation of a blood sample (INTEM™ or EXTEM™ respectively), and also a test for extrinsic activation in which the thrombocyte function is suppressed by administration of cytochalasin D (FIBTEM™).” As noted above, the ‘520 Publication also provides that plurality of different assays may be combined in a single cartridge. See, **Ibid.**, teaching that “it is also possible to combine e.g. an INTEM™, an EXTEM™ and a FIBTEM™ coagulation test with a platelet aggregometry test within one cartridge.” Again, this could be achieved by multiple different measurement cavities each associated with a respective assay and its reagents. See, e.g., **paragraph 0082** teaching “it is apparent to a person skilled in the art that in order to

‘971 Patent Claims	‘520 Publication
	achieve a maximum benefit for a user different types of tests can be combined in one cartridge device 50. In a preferred embodiment the cartridge device 50 comprises four arrangements of FIG. 4 or 5 having 4 measurement cavities 20, 20'.” Thus, the ‘520 Publication discloses embodiments, e.g., where a first measurement cavity can include intrinsic or extrinsic activators (as would be used in the INTEM™ and EXTEM™ assays, respectively), while a second measurement cavity can include an extrinsic activator in combination with cytochalasin D reagents (as would be used in the FIBTEM™ assay.
1D. an interrogation device that measures at least one viscoelastic property of the test sample.	The ‘520 Publication discloses an interrogation device for measuring a viscosity change in a liquid such as blood. See, e.g., **paragraph 0025** teaching “[i]t is a problem underlying the presented invention to provide a cartridge device for a measuring system for measuring viscoelastic characteristics of a sample liquid, in particular a blood sample.” See, also **paragraph 0029** teaching that “[i]n a first aspect, the present invention provides a cartridge device for a measuring system for measuring viscoelastic characteristics of a sample liquid, in particular a blood sample, comprising a cartridge body having at least one measurement cavity formed therein and having at least one probe element arranged in said at least one measurement cavity for performing a test on said sample liquid” See also, **paragraph 31** teaching: “In a third aspect, the present invention provides a method for measuring viscoelastic characteristics of a sample liquid by means of said measuring system, comprising the following steps: a) providing the cartridge device having at least one measurement cavity with at least one probe element arranged therein; b) attaching the cartridge device to said interface element, said shaft being inserted into said probe element; c) filling said measurement cavity of said cartridge device with sample liquid; d) rotating said shaft in an oscillating

‘971 Patent Claims	‘520 Publication
	motion around said rotation axis; and e) measuring viscoelastic characteristics of said sample liquid by detecting the rotation of said shaft by said detecting means. See also, **paragraphs 0006-0009** generally disclosing viscoelastic measurement techniques and apparatus.
2. The device of claim 1, further comprising a third chamber comprising a third reagent or combination of reagents that *interact* with blood of the test sample received therein; a fourth chamber comprising a fourth reagent or combination of reagents that *interact* with blood of the test sample received therein; and wherein the third and fourth chambers are configured to be *interrogated* to determine a *hemostatic parameter* of the test sample.	The ‘580 Publication teaches third and fourth chambers each of which include reagents for performing assays. See, e.g., **paragraph 0082** teaching: “In a preferred embodiment the cartridge device 50 comprises four arrangements of FIG. 4 or 5 having 4 measurement cavities 20, 20′. Thus measurements can be done with different reagents on the same liquid sample or with same reagents as well to check plausibility.” A specific example of a four assay cartridge is also disclosed, wherein each of the assays inherently implicates a particular reagent or reagent combination. See also, **paragraph 0083** teaching that “it is also possible to combine e.g. an INTEM™, an EXTEM™ and a FIBTEM™ coagulation test with a platelet aggregometry test within one cartridge.” As noted above, the ‘520 Publication provides examples of different reagents that can be included for performing different assays. Moreover, the INTEM™, EXTEM™ FIBTEM™ assays and related reagents were well known in the art prior to the priority date of the ‘971 Patent. Similarly, reagents for the ROTEM Platelet Aggregometry assay and reagents were also known in the art.
6. The device of claim 1**,** wherein each test chamber of the plurality of test chambers is at least partially defined by a housing.	Each of the measurement cavities in the ‘580 patent is defined by a housing. See, e.g., **Abstract** teaching “a cartridge body having at least one measurement cavity formed therein…and a cover being attachable on said cartridge body; wherein said cover covers at least partially said at least one measurement cavity. Note that the cartridge body and cover cooperate to form a housing. See, e.g., **Fig. 7B**. See also, **paragraph 0038** teaching that “[t]he cover can be fixed on the cartridge body either by bonding or welding…[or] integrally

‘971 Patent Claims	‘520 Publication
	formed with the cartridge body” and **paragraph 0093** teaching that “the cartridge device 50 comprises two parts: the cartridge body 30 and the cover 31, which are glued or welded together to obtain a leak-proof device.”
7. The device of claim 6**,** wherein the device is configured for use with a single test sample.	The ‘580 Publication teaches using a single sample with a multi-chamber cartridge. See, e.g., **paragraph 0081** teaching with respect to the parallel channel embodiment of **Fig. 6** that “[t]he sample liquid 1 is shared among the arrangements in parallel.” See also, **paragraph 0082** teaching: “In a preferred embodiment the cartridge device 50 comprises four arrangements of FIG. 4 or 5 having 4 measurement cavities 20, 20′. Thus measurements can be done with different reagents on the same liquid sample or with same reagents.” See also **paragraph 0083** teaching combining “an INTEM, an EXTEM and a FIBTEM coagulation test with a platelet aggregometry test within one cartridge” as well as that “[b]y comparison of the results on an EXTEM test of a pathologic sample to those of a FIBTEM test of the same sample it is possible to e.g. precisely determine if a coagulation disorder results from lack of fibrinogen or a malfunction of platelets.”
8. The device of claim 7, further comprising a fluid pathway having an inlet for receiving a test sample, wherein the fluid pathway is in communication with at least one test chamber to deliver the test sample, or a portion thereof, to one or more of the test chambers.	The ‘580 Publication teaches a fluid pathway having an inlet (receiving cavity 16 and branched inlet ducts 13 and 13’) for receiving a test sample (for receiving the sample liquid 1), wherein the fluid pathway is in communication with at least one measurement cavity (sample from inlet 13 flows through intermediate duct 14 reagent cavity 19 and outlet duct 15 and into measurement cavity 20 and sample from inlet 13’ flows through intermediate duct 14’ reagent cavity 19’ and outlet duct 15’ and into measurement cavity 20’) thereby delivering the test sample, or a portion thereof, to one or more of the measurement cavities. See, e.g., **paragraph 81** and **Fig. 6.**

‘971 Patent Claims	‘520 Publication
15. The device of claim 1, wherein the second chamber comprises a combination of reagents that includes a reagent comprised by the first chamber.	As noted above, both the FIBTEM and the EXTEM assays disclosed in **paragraph 0083** include a same extrinsic activator. Thus, the ‘520 Publication teaches embodiments where a first and a second measurement cavity both utilize an extrinsic activator (i.e., tissue factor). See also, **paragraph 0082** teaching with respect to the multi-channel embodiment in Fig. 6 that the “measurements can be done with different reagents on the same liquid sample or with same reagents as well to check plausibility.” As noted above, the EXTEM™ and FIBTEM™ assays and related reagents were well known in the art prior to the priority date of the ‘971 Patent. Similarly, reagents for the ROTEM Platelet Aggregometry assay and reagents were also known in the art. See, e.g., paragraph 39 of this Declaration, *supra*.
16. The device of claim 1, wherein the first chamber comprises a first combination of reagents including one or more of kaolin, celite, glass, thrombin, ellagic acid, and tissue factor and wherein the second chamber comprises the second combination of reagents including one or more reagents selected from the group consisting of kaolin, celite, glass, thrombin, ellagic acid, and tissue factor.	As noted above, the ‘520 Publication teaches that that an extrinsic activator may be used, e.g., in the case of the EXTEM™ assay. Furthermore, **paragraph 0003** explicitly discloses that the process of blood clotting can be activated by extrinsic factors such as tissue factor. Again it is noted that the INTEM™, EXTEM™ and FIBTEM™ assays were well known in the art prior to the priority date of the ‘971 Patent. As such, the ‘520 Publication also inherently teaches utilizing ellegic acid, since it was well known in the art that the INTEM™ assay utilizes ellagic acid activtion. See, e.g., paragraph 39 of this Declaration, *supra*.

C. Ground 3: The '672 Patent in Combination with Viola 2009, Renders Obvious IPR Claims 3 and 4

The '672 Patent (Ex.1005), prior art to the '971 Patent under (pre-AIA) 35 U.S.C. §§ 102(b), in Combination with Viola 2009 (Ex. 1012), also prior art to the '971 Patent under (pre-AIA) 35 U.S.C. §§ 102(b), renders obvious IPR claims 3 and 4, by disclosing each and every element of the claims, arranged as claimed in a manner enabling to a POSA , as discussed by Dr. Mize in Ex. 1003, ¶¶ 107-112.

The claim chart provided below (reproduced in an abbreviated form from Dr. Mize's Declaration) further evidences how Viola 2009 (when viewed in combination with the '672 Patent) discloses and enables each and every limitation of claims 3 and 4 of the '971 Patent:

'971 Patent Claims	**Viola 2009**
3. The device of claim 1, wherein the interrogation device is configured to use acoustic radiation force.	Viola 2009 teaches an interrogation device for measuring a viscoelastic property of a sample that is configured to use acoustic radiation force. See, e.g., **Section 2.1** entitled "Acoustic radiation force" and teaching that Sonorheometry is performed using acoustic radiation force as a means to generate small and localized displacements within a blood sample. Returned echoes are processed to measure the induced displacements and determine viscoelastic properties of the sample. See also, **Section 2.3** teaching that: "The transducer used in the experiments is a 10MHz piston transducer with a 1cm aperture, a 4cm fixed focus, and roughly 50% fractional bandwidth (Olympus NDT Inc., Waltham, MA). Acoustic radiation force is induced by applying ultrasound pulses (each 16 cycles long) at a PRF that is adaptively varied from 25Hz to 12.8KHz.
4. The device of claim 1, wherein the	Viola 2009 teaches an interrogation device for measuring a viscoelastic property of a sample that is

‘971 Patent Claims	Viola 2009
interrogation device is configured to transmit sound into one or more test chamber.	configured to transmit sound into one or more test chambers. In particular, the sonorheometry instrumentation described in **Section 2.3** of Viola 2009 includes a transducer for transmitting sound into cuvettes holding a blood sample. “Blood samples are analyzed using off the shelf polystyrene cuvettes (Fisher Scientific, Pittsburgh, PA). These cuvettes have low acoustic attenuation and acoustic impedance similar to that of blood; combined these properties allow us to deliver enough ultrasound signal within the blood to perform measurements.” **Ibid.**

D. Ground 4: The ‘520 Publication in Combination with Viola 2009, Renders Obvious IPR Claims 3 and 4.

The ‘520 Patent (Ex.1006), prior art to the ‘971 Patent under both the applicable (pre-AIA) 35 U.S.C. §§ 102(a) and –(e)(1), in Combination with Viola 2009 (Ex. 1012), prior art to the ‘971 Patent under (pre-AIA) 35 U.S.C. §§ 102(b), renders obvious IPR claims 3 and 4, by disclosing each and every element of the claims, arranged as claimed in a manner enabling to a POSA , as discussed by Dr. Mize in Ex. 1003, ¶¶ 107-112.

The claim chart provided above with respect to Ground 3 (reproduced from Dr. Mize’s Declaration) further evidences how Viola 2009 (when viewed in combination with the ‘520 Publication) discloses and enables each and every limitation of claims 3 and 4 of the ‘971 Patent:

E. Ground 5: The ‘672 Patent in Combination with the ‘011 Patent, Renders Obvious IPR Claim 5

The ‘672 Patent (Ex.1005), prior art to the ‘971 Patent under (pre-AIA) 35 U.S.C. §§ 102(b), in Combination with the ‘011 Patent (Ex. 1013), also prior art to the ‘971 Patent under (pre-AIA) 35 U.S.C. §§ 102(b), renders obvious IPR claim 5, by disclosing each and every element of the claim, arranged as claimed in a manner enabling to a POSA , as discussed by Dr. Mize in Ex. 1003, ¶¶ 113-117.

The claim chart provided below (reproduced in an abbreviated form from Dr. Mize’s Declaration) further evidences how the ‘011 Patent (when viewed in combination with the ‘672 Patent) discloses and enables each and every limitation of claim 5 of the ‘971 Patent:

‘971 Patent Claims	**The ‘011 Patent**
The device of claim 1, wherein the first reagent and the second combination of reagents are lyophilized prior to interacting with the test samples.	The ‘011 Patent teaches lyophilized reagents for mixing with the test sample. Moreover, the ‘001 Patent relates to lyophilized reagents divided between channels in a multi-channel cartridge/chip. See, e.g., **Abstract** teaching “a portable device for performing coagulation tests on a patient's blood.” “Blood is first drawn from a patient using a lancet. The blood is then supplied to a disposable cuvette placed within the testing device. The blood is drawn into multiple conduits within the cuvette. Each of the conduits contains a dried or lyophilized activation reagent that is rehydrated by the blood.” Ibid.

F. Ground 6: The ‘520 Publication in Combination with the ‘011 Patent, Renders Obvious IPR Claim 5.

The ‘520 Patent (Ex.1006), prior art to the ‘971 Patent under both the applicable (pre-AIA) 35 U.S.C. §§ 102(a) and –(e)(1), in Combination with the ‘011

Patent (Ex. 1013), prior art to the ‘971 Patent under (pre-AIA) 35 U.S.C. §§ 102(b), renders obvious IPR claim 5, by disclosing each and every element of the claims, arranged as claimed in a manner enabling to a POSA , as discussed by Dr. Mize in Ex. 1003, ¶¶ 113-117.

The claim chart provided above with respect to Ground 5 (reproduced from Dr. Mize’s Declaration) further evidences how the ‘011 Patent (when viewed in combination with the ‘520 Publication) discloses and enables each and every limitation of claim 5 of the ‘971 Patent:

G. Ground 7: The ‘672 Patent in Combination with the ‘286 Patent, Renders Obvious IPR Claims 8, 12 and 13

The ‘672 Patent (Ex.1005), prior art to the ‘971 Patent under (pre-AIA) 35 U.S.C. §§ 102(b), in Combination with the ‘286 Patent (Ex. 1014), also prior art to the ‘971 Patent under (pre-AIA) 35 U.S.C. §§ 102(b), renders obvious IPR claims 8, 12 and 13, by disclosing each and every element of the claims, arranged as claimed in a manner enabling to a POSA , as discussed by Dr. Mize in Ex. 1003, ¶¶ 118-123.

The claim chart provided below (reproduced in an abbreviated form from Dr. Mize’s Declaration) further evidences how the ‘286 Patent (when viewed in combination with the ‘672 Patent) discloses and enables each and every limitation of claims 8, 12 and 13 of the ‘971 Patent:

‘971 Patent Claims	The ‘286 Patent
8. The device of claim 7, further comprising a fluid	As noted above, the ‘286 Patent teaches a cartridge which includes generally includes a fluid receiving/dispensing reservoir, one or more fluid-

‘971 Patent Claims	The ‘286 Patent
pathway having an inlet for receiving a test sample, wherein the fluid pathway is in communication with at least one test chamber to deliver the test sample, or a portion thereof, to one or more of the test chambers.	receiving chambers and one or more conduit(s) that permit(s) fluid communication between the fluid receiving/dispensing reservoir and the fluid-receiving chamber(s). See **Abstract**. See also, **Col 8,9, lines 65-67, 1-11**.
12. The device of claim 8**,** wherein the fluid pathway further comprises a channel in communication with a least one test chamber, and wherein sample delivered from the channel into the test chamber results in mixing of at least a portion of the sample and the reagent within the test chamber.	The ‘286 Patent teaches three features which offer improved fluid flow and mixing over a previous iteration of the cartridge/device. These three improvements relate to (i) a constricted passageway into the receiving chamber(s), (ii) tangential flow into the receiving chamber(s) and (iii) a fluid exit conduit. See, .e.g, **Col 4-5, line 16-48.** Notably, the ‘286 Patent teaches that “each of the above noted fluid flow features, in its own right, will help a given test apparatus produce more accurate test results.” **Col 5, line 49-51**. Thus, a POSA would have been motivated implement fluid flow into the receiving chambers which promotes mixing of a sample and reagent.
13. The device of claim 12, wherein the fluid pathway further comprises a channel that opens into at least one test chamber on the side and at a tangent to the test chamber.	As noted above, the ‘286 Patent teaches three features which offer improved fluid flow and mixing over a previous iteration of the cartridge/device. These three improvements relate to (i) a constricted passageway into the receiving chamber(s), (ii) tangential flow into the receiving chamber(s) and (iii) a fluid exit conduit. See, .e.g, **Col 4-5, line 16-48.** Notably, the ‘286 Patent teaches that “each of the above noted fluid flow features, in its own right, will help a given test apparatus produce more accurate test results.” **Col 5, line 49-51**. Thus, a POSA would have been motivated implement tangential flow into the receiving chambers which would inherently promote mixing of a sample and reagent. See also **Fig. 10A** and corresponding disclosure. Note that using tangential flow to increase

‘971 Patent Claims	The ‘286 Patent
	mixing and turbulence would have been readily apparent to a POSA and is even more-so in view of the teachings in the ‘286 Patent..

H. Ground 8: The ‘520 Publication in Combination with the ‘286 Patent, Renders Obvious IPR Claims 8, 12 and 13.

The ‘520 Patent (Ex.1006), prior art to the ‘971 Patent under both the applicable (pre-AIA) 35 U.S.C. §§ 102(a) and –(e)(1), in Combination with the ‘286 Patent (Ex. 1014), prior art to the ‘971 Patent under (pre-AIA) 35 U.S.C. §§ 102(b), renders obvious IPR claims 8, 12 and 13, by disclosing each and every element of the claims, arranged as claimed in a manner enabling to a POSA , as discussed by Dr. Mize in Ex. 1003, ¶¶ 118-123.

The claim chart provided above with respect to Ground 7 (reproduced from Dr. Mize’s Declaration) further evidences how the ‘286 Patent (when viewed in combination with the ‘520 Publication discloses and enables each and every limitation of claims 8, 12 and 13 of the ‘971 Patent:

I. Ground 9: The ‘672 Patent in Combination with the ‘286 Patent and in Further Combination with the ‘826 Patent, the ‘051 Patent and the ‘082 Publication Renders Obvious IPR Claims 9, 10 and 11

The ‘672 Patent (Ex.1005), prior art to the ‘971 Patent under (pre-AIA) 35 U.S.C. §§ 102(b), in Combination with the ‘286 Patent (Ex. 1014), also prior art to

the ‘971 Patent under (pre-AIA) 35 U.S.C. §§ 102(b), and in further combination with the ‘826 Patent (Ex. 1015), the ‘051 Patent (Ex. 1016) and the ‘082 Publication (Ex. 1017), each of with is also prior art to the ‘971 Patent under (pre-AIA) 35 U.S.C. §§ 102(b), renders obvious IPR claims 9, 10 and 11, by disclosing each and every element of the claims, arranged as claimed in a manner enabling to a POSA , as discussed by Dr. Mize in Ex. 1003, ¶¶ 124-129.

The claim chart provided below (reproduced in an abbreviated form from Dr. Mize’s Declaration) further evidences how the ‘826 Patent, ‘051 Patent and ‘082 Publication (when viewed in combination with the ‘672 Patent and the ‘286 Patent) disclose and enables each and every limitation of claims 9, 10 and 11 of the ‘971 Patent:

‘971 Patent Claims	**The ‘826 and ‘051 Patents and the ‘082 Publication**
9. The device of claim 8, wherein the housing defines at least a portion of the fluid pathway, and wherein at least a portion of the housing is thermally conductive.	A POSA would understand that warming the test sample and or reagents to 37° C (body temperature) before initiating reactions is the norm in diagnostic assays and coagulation reactions, in particular. This is due to the complexity of interactions. Ostgaard teaches both the use of housings and thermal transfer **Col 7, line 38-44**) Further, Ostgaard (See also, **Col 5, Line 41-44)** states “[e]fficient thermal transfer to minimize incubation time is accomplished by making the bottom surface of the sample holding chamber from a thin, highly thermal conductive material. Jina comments that “[p]referably, the temperature is maintained at 37° C so that the test results can readily compared to other standardized test results without interpolation”. Jina, US 6,046,051, **Col 5, line 48-50.** Jina further teaches using a thermally conductive substrate from efficient transfer of heat. **Col 5, line 45-48.** Also note that the use of thermally conductive polymers in fluid contact surfaces of

‘971 Patent Claims	The ‘826 and ‘051 Patents and the ‘082 Publication
	housing elements for use with biological assays was well known. See, e.g., the entirety of Miller.
10. The device of claim 9, wherein the thermally conductive portion of the housing defines at least a portion of the fluid pathway.	As noted above, Ostgaard teaches thermal transfer via a thermally conductive material defining part of the fluid path. In particular, Otsgaard teaches that the bottom surface of the sample holding chamber is formed from a thermal conductive material. See **Col 7, line 38-44**). Similarly, Jina teaches that “the thermofoil heater is mounted between or below a substrate such as aluminum or other thermally conductive material for efficient transfer of heat to the test card 16.” **Col 5, line 45-48.** Also as noted above, the use of thermally conductive polymers in fluid contact surfaces of housing elements for use with biological assays was well known. See, e.g., the entirety of Miller.
11. The device of claim 10, wherein the thermally conductive portion comprises a thermally conductive polymer.	It is understood by POSA that thermally conductive materials (such as referenced in Otsgaard and Jina) may include polymers and plastics. Further, Miller clearly discloses biological assay trays which are formed using thermally-conductive polymer compositions.

J. Ground 10: The ‘520 Publication in Combination with the ‘286 Patent and in Further Combination with the ‘826 Patent, the ‘051 Patent and the ‘082 Publication Renders Obvious IPR Claims 9, 10 and 11

The ‘520 Patent (Ex.1006), prior art to the ‘971 Patent under both the applicable (pre-AIA) 35 U.S.C. §§ 102(a) and –(e)(1), in Combination with the ‘286 Patent (Ex. 1014), also prior art to the ‘971 Patent under (pre-AIA) 35 U.S.C. §§ 102(b), and in further combination with the ‘826 Patent (Ex. 1015), the ‘051 Patent

(Ex. 1016) and the ‘082 Publication (Ex. 1017), each of with is also prior art to the ‘971 Patent under (pre-AIA) 35 U.S.C. §§ 102(b), renders obvious IPR claims 9, 10 and 11, by disclosing each and every element of the claims, arranged as claimed in a manner enabling to a POSA , as discussed by Dr. Mize in Ex. 1003, ¶¶ 124-129.

The claim chart provided above with respect to ground 9 (reproduced from Dr. Mize’s Declaration) further evidences how the ‘826 Patent, ‘051 Patent and ‘082 Publication (when viewed in combination with the ‘520 Publication and the ‘286 Patent) disclose and enable each and every limitation of claims 9, 10 and 11 of the ‘971 Patent:

K. Ground 11: The ‘672 Patent in Combination with the ‘712 Patent, Renders Obvious IPR Claim 14.

The ‘672 Patent (Ex.1005), prior art to the ‘971 Patent under (pre-AIA) 35 U.S.C. §§ 102(b), in Combination with the ‘712 Patent (Ex. 1007), also prior art to the ‘971 Patent under (pre-AIA) 35 U.S.C. §§ 102(b), renders obvious IPR claim 14, by disclosing each and every element of the claim, arranged as claimed in a manner enabling to a POSA, as discussed by Dr. Mize in Ex. 1003, ¶¶ 130-134.

The claim chart provided below (reproduced in an abbreviated form from Dr. Mize’s Declaration) further evidences how the ‘712 Patent (when viewed in combination with the ‘672 Patent) discloses and enables each and every limitation of claim 14:

‘971 Patent Claims	**The ‘286 Patent**
14. The device of	The ‘712 Patent teaches the test chamber having a

‘971 Patent Claims	The ‘286 Patent
claim 7, wherein one or more test chamber of the plurality of test chambers further comprises a magnetic stirring structure.	magnetic stirring structure. See, e.g., **Col 11, line 59-66**, teaching “mixing means may be included in the second chambers for mixing the reagents with the sample introduced into the second chambers. A suitable mixing means is a mixing ball or the like. The mixing ball may be made from material susceptible to magnetic influence, such as ferrous material and the like, and caused to move at an appropriate time by application of a magnetic field.”

L. Ground 12: The ‘520 Publication in Combination with the ‘712 Patent, Renders Obvious IPR Claim 14.

The ‘520 Patent (Ex.1006), prior art to the ‘971 Patent under both the applicable (pre-AIA) 35 U.S.C. §§ 102(a) and –(e)(1), in Combination with the ‘712 Patent (Ex. 1007), prior art to the ‘971 Patent under (pre-AIA) 35 U.S.C. §§ 102(b), renders obvious IPR claim 14, by disclosing each and every element of the claim, arranged as claimed in a manner enabling to a POSA , as discussed by Dr. Mize in Ex. 1003, ¶¶ 130-134.

The claim chart provided above with respect to Ground 11 (reproduced from Dr. Mize’s Declaration) further evidences how the ‘712 Patent (when viewed in combination with the ‘672 Patent) discloses and enables each and every limitation of claim 14:

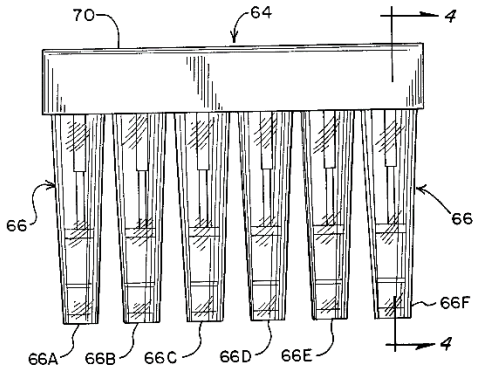
M. Ground 13: The ‘672 Patent in Combination with the Viola 2009 Renders Obvious IPR Claims 17, 18 19 and 20

The ‘672 Patent (Ex.1005), prior art to the ‘971 Patent under (pre-AIA) 35

U.S.C. §§ 102(b), in Combination with Viola 2009 (Ex. 1012), also prior art to the '971 Patent under (pre-AIA) 35 U.S.C. §§ 102(b), renders obvious IPR claims 17, 18, 19 and 20, by disclosing each and every element of the claims, arranged as claimed in a manner enabling to a POSA , as discussed by Dr. Mize in Ex. 1003, ¶¶ 135-142.

The claim chart provided below (reproduced in an abbreviated form from Dr. Mize's Declaration) further evidences how the '672 Patent in combination with Viola 2009 discloses and enables each and every limitation of claims 17, 18 19 and 20 of the '971 Patent:

'971 Patent Claims	**'672 Patent in Combination with Viola 2009**
17. A system for evaluation of hemostasis comprising:	The '672 Patent teaches in the "Field of Invention" section that "the present invention relates to measuring and determining the effectiveness of antiplatelet reagents or platelet function inhibitors in the coagulation of blood…(and more specifically) on the mechanical activation of platelets. See, e.g., **Col 1; lines 19-25**. Thus, the '672 Patent clearly relates to the evaluation of hemostasis of a patient.
17A. a plurality of test chambers	The assay device (e.g., device 100) disclosed in the '672 patent uses a cartridge (e.g., cartridge 64 or 65) which includes a plurality of test chambers (each characterized by a constrained space or cavity). See, e.g., **Col 2; line 7-12** teaching that "(t)he cartridge includes a plurality of test cells, each of which is defined by a tube-like member having an upper reaction chamber where a plunger assembly is located and where the analytical test is carried out, and a reagent chamber which contains a reagent or

‘971 Patent Claims	‘672 Patent in Combination with Viola 2009
	reagents.” See also, **Col 4, line 45-50**. See also **Fig. 3** depicting a test cartridge 64 for use with device 100 which includes a plurality of test cells 66 (specifically, test cells 66A-E)  FIG. 3
17Ai. each configured to receive blood of a test sample,	Each of the test cells in the ‘672 Patent is structurally capable of receiving a blood sample. See, e.g., **Col 4, line 11-12** teaching that “(a)n aliquot of a blood sample is added to each cell,” See also, **Col 8, line 50-53** teaching that (t)he apparatus 62 is generally formed of subassemblies. A dispensing subassembly 104 of the apparatus 62 automatically supplies a sample of blood to each test cell 66 of the cartridge 64 or 65.
17Aii. each test chamber comprising a reagent or combination of reagents;	Each of the test cells in the ‘672 Patent also includes a reagent of combination of reagents. See, e.g., **Col 2; line 7-12** teaching that “(t)he cartridge includes a plurality of test cells, each of which is defined by a tube-like member having…a reagent chamber which contains a reagent or reagents.” See also, Fig.4 depicting a reagent composition 80 and contact activator 90 included in each test cell.
17B. wherein a first chamber of the plurality comprises an *activator* of coagulation that *interact* with the blood	Each test cell of the ‘672 Patent includes at least an activator of coagulation which interacts with blood received in the chamber. See, e.g., the **Abstract** teaching that “(a)n aliquot of a blood sample is

‘971 Patent Claims	‘672 Patent in Combination with Viola 2009
received therein;	added to each cell, and the blood sample aliquot, clotting reagent and platelet inactivating agent are mixed.” See, also, **Col 2, line 7-14** teaching that “(t)he cartridge includes a plurality of test cells, each of which is defined by a tube-like member…where the analytical test is carried out, and a reagent chamber which contains a reagent or reagents. For an activated clotting time (ACT) test, for example, the reagents include an activation reagent to activate coagulation of the blood**.** See also, **Col 6, line 13-33** teaching a contact activator in the reagent chamber of each test cell 66. See also, **Col 6, line 13-33**
17C. wherein a second chamber of the plurality comprises an *activator* of coagulation and one or both of abciximab and cytochalasin D that *interact* with blood of the test sample received therein the combination including an *activator* of coagulation and;	In addition to each test cell of the ‘672 Patent including an activator of coagulations, as noted above, at least two of the test cells comprise different amounts of a platelet inactivating agent. See, e.g., **Col 6, line 53-55**. As disclosed in **Col 5, line 40-51**, this may include e.g., abciximab: “Two classes of platelet inhibitors exist; the first class comprises compounds that act on platelet membrane sites, broadly known as IIa/IIb inhibitors such as, but not limited to, Abciximab….” See also, **Table 1** depicting cells 66C-66F as including different concentrations of a platelet inhibitor while cells 66A and 66B act as a baseline or control without any platelet inhibitor. **Table 1**, is discussed in **Col 6, line 55-61:** “In the exemplified embodiment shown in FIG. 3, the first two cells 66A and 66B (which represent the “baseline” or non-activated clotting time) contain no platelet inhibiting agent. Each successive cell 66C, 66D, 66E, and 66F includes increasing amounts of platelet inhibiting agent.”
17D. wherein the first chamber is configured to be interrogated with ultrasound for a hemostatic parameter of the blood received therein to be determined;	Viola 2009, entitled “Novel Ultrasound-Based Method to Evaluate Hemostatic Function of Whole Blood” is directed towards “a novel ultrasound-based technology, named sonorheometry, which can assess hemostasis function from a small sample of blood. Sonorheometry uses the phenomenon of

‘971 Patent Claims	‘672 Patent in Combination with Viola 2009
17E. wherein the second chamber is configured to be interrogated with ultrasound for a hemostatic parameter of the blood received therein to be determined·	acoustic radiation force to measure the dynamic changes in blood viscoelasticity during clot formation and clot dissolution.” See, Abstract. Viola 2009 further describes implementing sonorheometry in a prototype bench-top instrument (note that a photo of the instrument is available as Supplementary file) **Section 2.3**. This prototype consists of a custom printed circuit board (PCB) controlled by an external laptop computer via USB 2.0 connection. The instrument supports two transmit and 4 receive ultrasound channels….Acoustic radiation force is induced by applying ultrasound pulses (each 16 cycles long) at a PRF that is adaptively varied from 25Hz to 12.8KHz. Blood samples are analyzed using off the shelf polystyrene cuvettes (Fisher Scientific, Pittsburgh, PA). “These cuvettes have low acoustic attenuation and acoustic impedance similar to that of blood; combined these properties allow us to deliver enough ultrasound signal within the blood to perform measurements.” **Ibid.** Viola 2009 further teaches determining a hemostatic parameter based on the ultrasonic interrogation of the cuvette. Hemostatic parameters disclosed include as time to clot (TC_1), fibrin polymerization end (TC_2) clot formation rate (CFR), stiffness (S), initial fibrinolytic phase (TL_1) and final fibrinolytic phase (TL_2). See **Section 2.2**. Essentially, Viola 2009 teaches all the principles and techniques necessary to implement sonoheometry to test a test chamber and detect viscoelasticity through the coagulation process. It would have therefore been obvious to interrogate each of the chambers in the ‘672 Patent using the techniques described in Viola 2009.
17Fi. a *transducer* for transmitting *ultrasound* into one or more test chamber and for receiving reflected	In Viola 2009, the <u>transducer</u> used in the experiments is a 10MHz piston transducer with a 1cm aperture, a 4cm fixed focus, and roughly 50% fractional bandwidth (Olympus NDT Inc., Waltham, MA). Acoustic radiation force is induced by

‘971 Patent Claims	‘672 Patent in Combination with Viola 2009
ultrasound from the chamber and the sample therein; and	applying ultrasound pulses (each 16 cycles long) at a PRF that is adaptively varied from 25Hz to 12.8KHz. **Section 2.3**. Viola 2009 also teaches “[f]uture developments include the use of a second ultrasound transducer at the opposite end of the blood sample under analysis to estimate variation in acoustic properties through the sample. This will allow determining the absolute value of the viscoelastic parameters (rather than indirect relative parameters. See, e.g., **Section 4**.
17Gi. at least one *processor* in communication with the transducer,	In the example bench-top prototype described in Viola 2009 The prototype includes a custom printed circuit board (PCB) controlled by an external laptop computer via USB 2.0 connection. A person of ordinary creativity would understand that this laboratory setup with laptop data analysis could be configured to be a microprocessor controlled sonorheometry coagulation instrument.
17Gii. the *processor* being configured to determine the *hemostatic parameters* from signals transmitted to the processor from the *transducer*.	Viola 2009 teaches that “[t]he raw ultrasound data were transferred from the custom PCB to the laptop computer through USB interface and analyzed in MATLAB …The sonorheometry parameters were calculated by fitting a sigmoidal curve and evaluating the first derivative of the curve, as shown in Fig. 2. For example, the clotting times TC1 and TC2 were calculated based on a threshold value of the derivative curve (20% of the minimum value), whereas the clotting slope CFR is the minimum of the derivative curve. In the results presented here, the stiffness S was estimated using the value of the relative compliance 3 min after TC2. Identical methods and parameters were calculated for the fibrinolytic process.” See **Section 2.6**. A person of ordinary creativity would understand that a laptop computer configured to determine hemostatic parameters such as described by Viola could also be configured to work on a microprocessor based on sonorheometry measurement instrument.

‘971 Patent Claims	‘672 Patent in Combination with Viola 2009
18. The system of claim **17,** wherein the *hemostasis parameters* are selected from the group consisting of TC 1, TC2, clot stiffness, clot formation rate (CFR), TL1, TL2, baseline viscosity, and post lysis viscosity.	As noted above, Viola 2009 teaches the “[t]he sonorheometry parameters were calculated by fitting a sigmoidal curve and evaluating the first derivative of the curve, as shown in Fig. 2. For example, the clotting times TC1 and TC2 were calculated based on a threshold value of the derivative curve (20% of the minimum value), whereas the clotting slope CFR is the minimum of the derivative curve. In the results presented here, the stiffness S was estimated using the value of the relative compliance 3 minutes after TC2. Identical methods and parameters were calculated for the fibrinolytic process.” **Section 2.6**. A person of ordinary creativity would understand that a laptop computer configured to determine hemostatic parameters such as described by Viola 2009 such as TC1, TC2, clot stiffness, etc. could be configured on a microprocessor based on sonorheometry measurement instrument.
19. The system of claim **17,** wherein the processor is further configured to determine a *coagulation factors index*.	As noted, Viola 2009 clearly teaches measurement of time to clot (TC_1) which would be considered a coagulation factors index. See, e.g., **Table 3** of the ‘971 Patent. Moreover, it is noted that the ‘672 Patent likewise teaches calculating a time to clot for each of the assays. It is also noted that a person of ordinary creativity would know that how to combine various measurements into useful indexes. See, e.g., **Abstract** teaching that “Each cell sample is allowed to clot, and the clotting time for each cell is measured.”
20. The system of claim **17,** wherein the processor is further configured to determine at least one *parameter* selected from the group consisting of an intrinsic pathway coagulation factors index, an extrinsic pathway coagulation factors	Viola 2009 teaches that “[i]n a typical experiment, 1 ml of citrated blood was pipette into a 4ml clear polystyrene cuvette along with 0.5 mg of kaolin activator to start coagulation through activation of the intrinsic pathway. Thus, the clotting time TC1 would represent an intrinsic coagulation factor index. See also **Table 3** of the ‘971 Patent. Moreover, TC1, TC2, Clot stiffness could be transformed through normal algebraic

'971 Patent Claims	'672 Patent in Combination with Viola 2009
index, a platelets index, a fibrinogen index, and a fibrinolysis index.	manipulation into indexes that can be derived in a straight forward and logical manner for different parts of hemostasis.

N. Ground 14: The '712 Patent in Combination with Lang 2004 and Viola 2009 Renders Obvious IPR Claims 17, 18 19 and 20

The '712 Patent (Ex.1007), prior art to the '971 Patent under (pre-AIA) 35 U.S.C. §§ 102(b), in Combination with Lang 2004 (Ex. 1008) and Viola 2009 (Ex. 1012, both of which are also prior art to the '971 Patent under (pre-AIA) 35 U.S.C. §§ 102(b), renders obvious IPR claims 17, 18, 19 and 20, by disclosing each and every element of the claims, arranged as claimed in a manner enabling to a POSA , as discussed by Dr. Mize in Ex. 1003, ¶¶ 142-147.

The claim chart provided below (reproduced in an abbreviated form from Dr. Mize's Declaration) further evidences how the '712 Patent in combination with Lang 2004 and Viola 2009 discloses and enables each and every limitation of claims 17, 18 19 and 20 of the '971 Patent:

'971 Patent Claims	'712 Patent in Combination with Lang 2004 and Viola 2009
17. A system for evaluation of hemostasis comprising:	The '712 Patent teaches a cartridge device which may be used to implement any number of different of types of assays including, e.g., coagulation assays. See, e.g., **Col 16, line 59-73**. See also, **Col 2, line 16-31** teaching: See also, **Col 2, lines 40-41**.

‘971 Patent Claims	‘712 Patent in Combination with Lang 2004 and Viola 2009
17A. a plurality of test chambers	The cartridge device in the ‘712 patent clearly includes a plurality of test chambers. See, e.g., second chambers 160a-160d in **Fig. 1**. See also, **Col 9, lines 55-58** teaching “One aspect of the invention concerns a device for receiving and processing a sample. The device comprises a sample receiving element adapted to establish fluid communication with and receive a sample directly from a sample container;” **Col 11, line 8-9** teaching “At least one first chamber is in fluid communication with the sample receiving element;” **Col 11, line 18-19** teaching “The first chamber serves as a staging area for the sample to be processed;” **Col 11, line 41-44** teaching “The device also includes one or more second chambers that are in fluid communication with the first chamber. Fluid communication may occur through a channel or capillary between each of the second chambers and the first chamber;” and **Col 11, line 57-59** teaching “The second chambers are used for conducting further processing of the sample. For example, the second chambers can contain various reagents for conducting an assay.”
17Ai. each configured to receive blood of a test sample,	As described above, each of the second chambers in the cartridge device in the ‘712 Patent are configured for receiving a sample. Example samples, including blood are described, e.g., **Col 7-8, line 64-13**. See also **Col 24, lines 12-15** teaching “where platelet aggregation is to be measured, because of interest in the platelet status of an individual, which may be the natural status or the status resulting from administration of a drug, the sample will be in effect whole blood.”
17Aii. each test chamber comprising a reagent or combination of reagents;	As noted above, each of the second chambers in the cartridge device in the ‘712 Patent includes a reagent or combination of reagents. See, e.g., **Col 11, line 57-59** teaching “The second chambers are

‘971 Patent Claims	‘712 Patent in Combination with Lang 2004 and Viola 2009
	used for conducting further processing of the sample. For example, the second chambers can contain various reagents for conducting an assay.”
17B. wherein a first chamber of the plurality comprises an activator of coagulation that interact with the blood received therein; **17C.** wherein a second chamber of the plurality comprises an *activator* of coagulation and one or both of abciximab and cytochalasin D that *interact* with blood of the test sample received therein the combination including an *activator* of coagulation and;	A POSA would understand that “comprises an activator of coagulation” could mean an activator of coagulation and a number of other reagents that could interact with the blood and affect hemostasis. Lang 2004 entitled “Different effects of abciximab and cytochalasin Don clot strength in thrombelastography” teaches that an intrinsic activator alone and in combination with abciximab and / or cytochalasin D can be used to detect differences between activator alone and those test chambers with activator and platelet inhibitor using the ROTEG analyzer that detects viscoelastic changes through mechanical shear. Viola 2009, entitled “Novel Ultrasound-Based Method to Evaluate Hemostatic Function of Whole Blood” teaches that an intrinsic activator alone and in combination with abciximab can be used to detect differences between activator alone and those test chambers with activator and platelet inhibitor using sonorheometry to detect viscoelastic changes through "sonar echos".
17D. wherein the first chamber is configured to be interrogated with ultrasound for a hemostatic parameter of the blood received therein to be determined; **17E.** wherein the second chamber is configured to be interrogated with ultrasound for a hemostatic parameter of the blood received therein to be determined·	Viola 2009, entitiled “Novel Ultrasound-Based Method to Evaluate Hemostatic Function of Whole Blood” is directed towards “a novel ultrasound-based technology, named sonorheometry, which can assess hemostasis function from a small sample of blood. Sonorheometry uses the phenomenon of acoustic radiation force to measure the dynamic changes in blood viscoelasticity during clot formation and clot dissolution.” See, Abstract. Viola 2009 further describes implementing sonorheometry in a prototype bench-top instrument (note that a photo of the instrument is available as Supplementary

'971 Patent Claims	'712 Patent in Combination with Lang 2004 and Viola 2009
	file) **Section 2.3**. The instrument supports two transmit and 4 receive ultrasound channels. Acoustic radiation force is induced by applying ultrasound pulses (each 16 cycles long) at a PRF that is adaptively varied from 25Hz to 12.8KHz. Blood samples are analyzed using off the shelf polystyrene cuvettes (Fisher Scientific, Pittsburgh, PA). "These cuvettes have low acoustic attenuation and acoustic impedance similar to that of blood; combined these properties allow us to deliver enough ultrasound signal within the blood to perform measurements." **Ibid.** Viola 2009 further teaches determining a hemostatic parameter based on the ultrasonic interrogation of the cuvette. Hemostatic parameters disclosed include as time to clot (TC_1), fibrin polymerization end (TC_2) clot formation rate (CFR), stiffness (S), initial fibrinolytic phase (TL_1) and final fibrinolytic phase (TL_2). See **Section 2.2**.
17Fi. a *transducer* for transmitting *ultrasound* into one or more test chamber and for receiving reflected ultrasound from the chamber and the sample therein; and	In Viola 2009, the transducer used in the experiments is a 10MHz piston transducer with a 1cm aperture, a 4cm fixed focus, and roughly 50% fractional bandwidth (Olympus NDT Inc., Waltham, MA). Acoustic radiation force is induced by applying ultrasound pulses (each 16 cycles long) at a PRF that is adaptively varied from 25Hz to 12.8KHz. **Section 2.3**. Viola 2009 also teaches "[f]uture developments include the use of a second ultrasound transducer at the opposite end of the blood sample under analysis to estimate variation in acoustic properties through the sample. This will allow determining the absolute value of the viscoelastic parameters (rather than indirect relative parameters. See, e.g., **Section 4**.
17Gi. at least one *processor* in communication with the transducer,	In the example bench-top prototype described in Viola 2009 The prototype includes a custom printed circuit board (PCB) controlled by an external laptop computer via USB 2.0 connection.

'971 Patent Claims	'712 Patent in Combination with Lang 2004 and Viola 2009
	A person of ordinary creativity would understand that this laboratory setup with laptop data analysis could be configured to be a microprocessor controlled sonorheometry coagulation instrument.
17Gii. the *processor* being configured to determine the *hemostatic parameters* from signals transmitted to the processor from the *transducer*.	Viola 2009 teaches that "[t]he raw ultrasound data were transferred from the custom PCB to the laptop computer through USB interface and analyzed in MATLAB (MathWorks Inc., Natick, MA)...Pulse to-pulse time delays were estimated using a spline-based estimator [27] with a kernel of echo data of 1.2 mm and a search region of 57 μm along the direction of propagation of ultrasound. The estimated delays were then assembled to generate time–displacement curves, similar to those depicted in Fig. 1B. From these curves we extrapolated the value of the maximum induced displacement, which were then normalized by their corresponding PRF and combined to form a relative compliance curve. The sonorheometry parameters were calculated by fitting a sigmoidal curve and evaluating the first derivative of the curve, as shown in Fig. 2. For example, the clotting times TC1 and TC2 were calculated based on a threshold value of the derivative curve (20% of the minimum value), whereas the clotting slope CFR is the minimum of the derivative curve. In the results presented here, the stiffness S was estimated using the value of the relative compliance 3 min after TC2. Identical methods and parameters were calculated for the fibrinolytic process." See **Section 2.6**.
18. The system of claim **17,** wherein the *hemostasis parameters* are selected from the group consisting of TC 1, TC2, clot stiffness, clot formation rate (CFR), TL1,	As noted above, Viola 2009 teaches the "[t]he sonorheometry parameters were calculated by fitting a sigmoidal curve and evaluating the first derivative of the curve, as shown in Fig. 2. For example, the clotting times TC1 and TC2 were calculated based on a threshold value of the derivative curve (20% of the minimum value),

'971 Patent Claims	'712 Patent in Combination with Lang 2004 and Viola 2009
TL2, baseline viscosity, and post lysis viscosity.	whereas the clotting slope CFR is the minimum of the derivative curve. In the results presented here, the stiffness S was estimated using the value of the relative compliance 3 minutes after TC2. Identical methods and parameters were calculated for the fibrinolytic process." **Section 2.6**.
19. The system of claim **17,** wherein the processor is further configured to determine a *coagulation factors index*.	As noted, Viola 2009 clearly teaches measurement of time to clot (TC_1) which would be considered a coagulation factors index. See, e.g., **Table 3** of the '971 Patent.
20. The system of claim **17,** wherein the processor is further configured to determine at least one *parameter* selected from the group consisting of an intrinsic pathway coagulation factors index, an extrinsic pathway coagulation factors index, a platelets index, a fibrinogen index, and a fibrinolysis index.	Viola 2009 teaches that "[i]n a typical experiment, 1 ml of citrated blood was pipette into a 4ml clear polystyrene cuvette along with 0.5 mg of kaolin activator to start coagulation through activation of the intrinsic pathway. Thus, the clotting time TC1 would represent an intrinsic coagulation factor index. See also **Table 3** of the '971 Patent. Moreover, TC1, TC2, Clot stiffness could be transformed through normal algebraic manipulation into indexes that can be derived in a straight forward and logical manner for different parts of hemostasis.

X. CONCLUSION

For the reasons set forth above, the IPR Claims are anticipated by the applied prior art, and the IPR Claims should be cancelled.

Date: Feb. 3, 2017

Respectfully submitted,
Attorney for Petitioner

/Stephen Y. Chow/
Stephen Y. Chow (Reg. No. 31,338)

CERTIFICATION OF SERVICE (37 C.F.R. § 42.6(e))

The undersigned hereby certifies that the above-captioned Petition for Inter Partes Review of U.S. Patent No. 9,410,971 B2 (and accompanying exhibits), is being served in its entirety on February 4, 2017, upon the following party via Federal Express:

Meunier Carlin & Curfman LLC
999 Peachtree Street NE
Suite 1300
Atlanta GA 30309

Patent owner's correspondence address of record for U.S. Patent No. 9,410,971

/Gabriel Goldman/
Gabriel Goldman (61,343)
Burns & Levinson LLP
125 Summer Street
Boston, MA 02110
(617) 345-3304

APPENDIX – INDEX OF EXHIBITS

Exhibit No.	Description
Ex. 1001	Viola *et al.*, "Device, System and Methods for Evaluation of Hemostasis," U.S. Patent No. 9,410,971 B2 (filed on February 15, 2012; issued on March 1, 2016)
Ex. 1002	Viola *et al.*, "Device, System and Methods for Evaluation of Hemostasis," U.S. Patent No. 9,410,971 B2 (filed on January 21, 2016; issued on August 9, 2016)
Ex. 1003	Declaration of Patrick D. Mize, Ph.D.
Ex. 1004	Curriculum Vitae of Patrick D. Mize, Ph.D.
Ex. 1005	Baugh *et al*., "Method for Determining a Contact Activator for Platelet Activation," U.S. Patent No. 6,221,672 B2 (filed on March 16, 2001; issued on April 29, 2003)
Ex. 1006	Schubert *et al.*, "Cartridge Device for a Measuring System for Measuring Viscoelastic Characteristics of a Sample Liquid, a Corresponding Measuring System, and a Corresponding Method," U.S. Patent Appl. Pub. No. 2010/0154520 (filed Dec. 17, 2007; published June 24, 2010)
Ex. 1007	Warden *et al*., "Device for Receiving and Processing a Sample," U.S. Patent No. 6,016,712 (filed on Sept. 18, 1997; issued on Jan. 25, 2000)
Ex. 1008	Lang, T., *et al*., "Different effects of abciximab and cytochalasin D on clot strength in thrombelastography," *Journal of Thrombosis and Haemostasis*, 2: 147-153 (2004)
Ex. 1009	File history for U.S. Patent No. 9,410,971 B2
Ex. 1010	Table of Prior Art Devices
Ex. 1011	Baugh *et al*., "Method and Device for Testing a Sample of Fresh Whole Blood," U.S. Patent Appl. Pub. No. 2003/0113929 (filed Jan. 20, 2003; published June 19, 2003)
Ex. 1012	Viola, F., Mauldin Jr., W, Lin-Schmidt, X., Haverstick, D.M., Lawrence, M.B., Walker, W.F., A Novel Ultrasound-Based Method

	to Evaluate hemostatic Funtion of Whole Blood. Clin Chim Acta. 2010 Jan; 411(1-2): 106–113., Published online 2009 Oct 25, PubMed Central P.M.C.I.D. PMC2791922
Ex. 1013	Gavin, M. *et al*., "Portable test apparatus and associated method of performing a blood coagulation test," U.S. Patent No. 5,504,011 B2 (filed Oct. 21 1994, issued April 2, 1996)
Ex. 1014	Braun, Sr. *et al*., "Apparatus for Testing Liquid/Reagent Mixtures," U.S. Patent No. 6,613,286 B2 (filed on Dec. 21, 2000, issued on Sept. 2, 2003)
Ex.1015	Ostgaard, R. *et al.*, "Combination reagent holding and test device," U.S. Patent No. 5,888,826 B2 (filed Nov. 25, 1997, issued March 30, 1999)
Ex. 1016	Jina, A., " Method and device for measuring blood coagulation or lysis by viscosity changes," U.S. Patent No. 6,046,051 B2 (filed June 27, 1997, issued April 4, 2000)
Ex. 1017	Miller, J., *et al*., "Thermally-conductive biological assay trays," U.S. Patent App. Pub. No. 2003/0199082 A1 (filed April 8, 2003, published October 23, 2003)
Ex. 1018	Lec, R., *et al*., "Acoustic blood analyzer for assessing blood properties," U.S. Patent App. Pub. No. 2005/0015001 A1 (filed April 16, 2004, published January 20, 2005)
Ex. 1019	Gottumukkala, V.N., Sharma, S.K., Philip, J., Assessing Platelet and Fibrinogen Contribution to Clot Strength using Modified Thromboelastography in Pregnant Women. Anesth. Analg., 1999 Dec.;89(6):1453-5. PubMed P.M.I.D.: 10589626.