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 9,272,280

PETITION FOR *INTER PARTES* REVIEW OF

U.S. PATENT NO. 9,272,280 B2

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I. INTRODUCTION

Instrumentation Laboratory Company ("Petitioner") requests *inter partes* review ("IPR") of claims 1 and 2 (the "IPR Claims") of U.S. Patent No. 9,272,280 ("the '280 Patent") (Ex. 1001), 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, CA 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. 9,410,971 ("the '971 Patent") (Ex. 1002), a continuation of the '280 Patent, is also the subject of an *inter partes* review petition, which Petitioner files 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 '280 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 '280 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. 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 in view of the following prior art patents and publications:

Exhibit	Reference	Priority	Publication
1005	U.S. Patent No. 6,221,672 B2 ("the '672 Patent")	4/30/96	4/24/01
1006	U.S. Patent App. Pub. No. US 2010/0154520 A1 ("the '520 Publication")	12/17/09	6/24/10

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

Ground	IPR Claims	Art	Basis
1	1 and 2	'672 Patent	§ 102(a), -(b)
2	1 and 2	'520 Publication	§ 102(a), -(e)(1)

Detailed claim charts applying the foregoing prior art for each of the IPR Claims are provided herein.[1] Additional explanation and support for each ground

[1] Although it is cited on the face of the '280 Patent, the disclosure of the '672

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 '280 PATENT

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

The field of devices for evaluating hemostasis – blood clotting – was well-developed prior to the earliest priority date of the '280 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, ¶¶ 18-53). More particularly, Dr. Mize begins by providing a background on hemostasis, platelet activation and coagulation cascade (*id.* ¶¶ 18-22, Fig. 1). Next Dr. Mize proceeds with a historical overview of the development of different types of coagulations tests and reagent combination. The historical overview begins with basic coagulation tests utilizing extrinsic and intrinsic activation (*id.* ¶¶ 24-27). Next, Dr. Mize speaks to subsequent developments for testing a patient's hemostatic response to an anticoagulant or anticoagulant antagonist including

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Patent (Ex. 1005), supporting Ground 1 here, was not explicitly considered in the examination, and the anticipating disclosure may have been overlooked by the Examiner in light of the similar figures to, but the different description in, the art (Ex. 1011) actually considered. Mize Decl. (Ex. 1003) ¶¶ 59-63.

development of multi-chamber for testing a patient's response to multiple different concentrations thereof (*id.* ¶¶ 28-30). Dr. Mize also explains how drug-response type testing (including multi-chamber testing) further expanded to examine a patient's response to other drugs including platelet inhibitors, platelet activators and counter-agents to platelet inhibitors (*id.* ¶¶ 31-37). Finally, Dr. Mize discusses the specific implementation of multi-chamber testing to enable isolating factors behind a coagulation problem, such as by comparing assays targeting different pathways or functions of hemostasis (*id.* ¶¶ 38-41). 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.* ¶¶ 41-53). The devices discussed by Dr. Mize are summarized in Ex. 1010, "Table of Prior Art Devices."

Importantly, Dr. Mize's discussion of the state of the art highlights the incorporation of anti-platelet drugs such as abciximab and cytochalasin D into coagulation assays (including specifically multi-channel coagulation assays) and provides details regarding several early devices that implemented such assays. This discussion aligns directly with Dr. Mize's subsequent position regarding the patentability of the '280 claims.

B. What the ‘280 Patent Claims

There is nothing that the ‘280 Patent claims that was not in the **prior** art. The sole independent claim states:

> 1. A device for evaluation of hemostasis, comprising:
>
> a *plurality of test chambers* each *configured to receive blood* of a test *sample*, each test chamber comprising a reagent or combination of reagents, wherein each chamber is *configured to be interrogated to determine a hemostatic parameter of the blood* received therein;
>
> 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*; and
>
> 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.* (Emphasis added.)

From a high level perspective, claim 1 of the ‘280 Patent essentially recites a multi-chamber device where each chamber includes an activator of coagulation and where one of the chambers further includes abciximab, cytochalasin D or both. As evidenced in Dr. Mize’s discussion of the state of the art and further supported by the claim charts produced in Dr. Mize’s Declaration (Ex. 1003) and duplicated herein, many well-known multi-chamber devices existed prior to the ‘280 Patent that utilized reagent combinations as characterized in the claims. In particular,

some of the prior-art multi-channel assays for testing a patient's response to different concentrations of an anti-platelet drug clearly include an activator of coagulation in a first chamber and an activator of coagulation plus abciximab and/or cytochalasin D in a second chamber. Similarly, a number of prior-art assays for isolating factors behind a coagulation problem similarly utilize a first chamber with an activator of coagulation (for testing extrinsic or intrinsic activation) and a second chamber with an activator of coagulation plus abciximab and/or cytochalasin D (for testing fibrinogen function / platelet activation).

Thus, as concluded by Dr. Mize and further reviewed herein, each of the elements of the claim are shown to be present in each of the multi-chamber devices disclosed in the Ground 1 '672 Patent (Ex. 1005) and the Ground 2 '520 Publication (Ex. 1006), including the use of abciximab or cytochalasin D. The only dependent claim simply lists additional reagents well-known in the prior art and present in the devices disclosed in Grounds 1 and 2.

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. In some instances a POSA may be part of a multidisciplinary team and may be able to draw on a wide range of knowledge basis from multiple members of that team. A POSA would also typically be familiar and keep up to date with a current landscape of diagnostic tests and devices for evaluating hemostasis. Finally, in some instances a POSA may be able to draw on experience relating to regulatory practices and best practices standards. *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, ¶ 65.)

"[A]pparatus claims cover what a device *is*, not what a device *does*." *Hewlett-Packard Co.v.Bausch & Lomb Inc.*, 909 F.2d 1464, 1469, 15 USPQ2d 1525, 1528 (Fed. Cir. 1990) (emphasis in original). Functional claim language that is not limited to a specific structure covers all devices that are capable of performing the recited function. See *In re Translogic Technology, Inc.*, 504 F.3d 1249, 1258, 84 USPQ2d 1929, 1935-1936 (Fed. Cir. 2007).

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. Indeed, many tests would not require any unique structural configuration of the chamber in order to implement such and any generic chamber is essentially capable of being used as a test chamber, within the meaning of the claims. (Ex. 1003, ¶ 66)

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*., ¶ 66)

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.*, ¶ 66)

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.*, ¶ 67)

Once again the phrase "configured to" represents a functional limitation. Thus, its meaning is limited to any implicated structure. As described in great detail by Dr. Mize, there are many different interrogation techniques which may be utilized to asses a hemostatic parameter, including, but not limited to, absorbance (light), mechanical (change in pressure or force), magnetic (change in magnetic field), electrical (including changes in potential, impedance, and conductance), or sound (change in response to sound waves). (*Id.* ¶¶ 41-53; *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. Thus, any generic chamber is essentially capable of being interrogated to determine a hemostatic parameter of the blood, within the meaning of the claims. (Ex. 1003, ¶ 68)

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 the IPR Claims

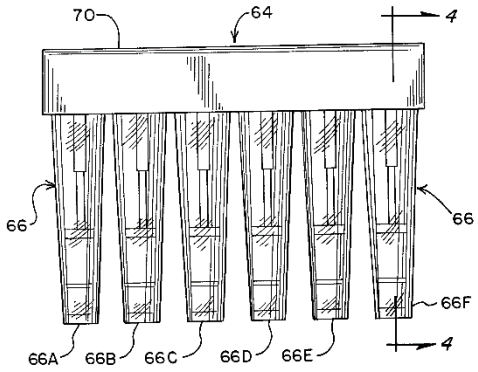
The ‘672 Patent (Ground 1), Ex. 1005, prior art to the ‘280 Patent under both the applicable (pre-AIA) 35 U.S.C. §§ 102(a) and –(b) as patented (April 24, 2001) before the ‘280 Patent priority date (Feb. 15, 2011) and more than a year before its application date (Feb. 15, 2012), anticipates each of the IPR claims, 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, ¶¶ 88-94.

In general, the ’672 Patent, which relates to the HepCon® HMS system, discloses a test cartridge where each of the six test wells includes a contact activator such as kaolin and where a number of the test wells include different amounts of a platelet inactivating agent such as abciximab. In particular, in example embodiments disclosed, two of the chambers are treated as “baseline” assays and contain no platelet inhibiting agent while each of the remaining four chambers includes increasing amounts of the platelet inhibiting agent.

Thus, the HepCon® HMS system clearly teaches a multi-chamber device (a six test well cartridge) where each chambers includes an activator of coagulation (kaolin in each of the test wells) and where one of the chambers further includes abciximab, cytochalasin D or both (four of the test wells include abciximab).

The claim chart provided below (reproduced from Dr. Mize's Declaration) further evidences how the '672 Patent discloses and enables each and every limitation of claims 1 and 2 of the '280 Patent:

'280 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** teaching that "by using different concentrations of a platelet inhibitor in a plurality of test cells, and using an optimized amount of a mechanical contact activator of platelets and/or clotting, the ability of an inhibitor in a selected dose to prevent the mechanical activation of platelets can be assessed." 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)

‘280 Patent Claims	‘672 Patent (Ex. 1005)
	 FIG. 3
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, 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

‘280 Patent Claims	‘672 Patent (Ex. 1005)
	the effectiveness of antiplatelet reagents or platelet inhibitors on the mechanical activation of platelets.” See also, **Col 8, line 60-64** teaching an optical sensing system which “senses the physical descent of the plunger assembly 72 through the blood sample and reagent mixture in the reaction chamber 94 in order to detect coagulation condition. The plunger technique for measuring and detecting coagulation implemented by the device of the ‘380 Patent is further described in the background section thereof. See, e.g., **Col 2, line 7-30** teaching “The 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…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 therethrough is changed. Upon a sufficient change in the descent rate, the coagulation-related activity is detected and indicated by the apparatus.”
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	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

‘280 Patent Claims	**‘672 Patent (Ex. 1005)**
reagent, or a reagent included in the first combination of reagents, is an activator of coagulation; and	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. **Col 6, line 13-33** further provides: The contact activator discussed below and shown in FIG. 4 as contact activator 90) includes an activator (commonly referred to as a surface activator), such as kaolin, to activate platelets and blood Factors XII and/or XI. However, as will be appreciated by those of skill in the art, other contact activators which function in a similar manner to kaolin may be used for the practice of the invention, such as diatomaceous earth, powdered glass, silica, or any other particle having a negatively charged surface. Activators may be chosen by simply performing the method of the present invention with differing activators and comparing the magnitude of clotting time. Kaolin is preferable however, since it is an activator of both coagulation and platelets. If desired, one could also use a contact activator of platelets in combination with a contact activator of coagulation.”
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, which is the Fab fragment of the chimeric human-murine monoclonal antibody 7E3 and sold under the trademark ReoPro™, or 4-(4-(4-(aminoiminomethyl)phenyl)-1-piperazinyl)-1-piperidineacetic acid, hydrochloride trihydrate sold

‘280 Patent Claims	‘672 Patent (Ex. 1005)
	under the trademark GR144053™. The second class comprises compounds that are metabolic inhibitors such as, but not limited to, acetylsalicylic acid or aspirin.” 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.”
2. 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 a second combination of reagents including one or more 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.**

B. Ground 2: The ‘520 Publication Anticipates the IPR Claims

The ‘520 Publication (Ground 2), Ex. 1006, prior art to the ‘280 Patent under both the applicable (pre-AIA) 35 U.S.C. §§ 102(a) and –(e)(1) as published (June 24, 2010) before the ‘280 Patent priority date (Feb. 15, 2011), anticipates each of the IPR claims, 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, ¶¶ 95-100.

In general, the ’520 Publication, which relates to the ROTEM® system, discloses a four channel cartridge which includes, the EXTEM™, INTEM™ and FIBTEM™ assays in three of the respective channels. Notably, the EXTEM™ assay includes an extrinsic activator (such as tissue factor) while the FIBTEM™ assay includes an extrinsic activator in combination with cytochalasin D.

Thus, the ROTEM® system clearly teaches a multi-chamber device (a four assay cartridge) where each one of the chambers includes an activator of coagulation (EXTEM™ includes tissue factor) and where another one of the chambers also includes an activator of coagulation and further includes abciximab, cytochalasin D or both (FIBTEM™ includes tissue factor and cytochalasin D).

The claim chart provided below (reproduced from Dr. Mize’s Declaration) further evidences how the ‘672 Patent discloses and enables each and every limitation of claims 1 and 2 of the ‘280 Patent:

‘280 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, wherein a first inlet duct 13 communicates with a second inlet duct 13' connected to second pump means 18'. A second intermediate duct 14' leads to a second reagent cavity 19' storing a second reagent 21'. A second outlet duct 15' connects the second reagent cavity 19' to the second measurement cavity 20'. FIG. 6 shows only one possible variation of a plurality of different arrangements easily imagined. The sample liquid 1 is shared among the arrangements in parallel. Controlled by the external control apparatus the shared portions of the sample liquid 1 are mixed with different reagents 21, 21' during transport. 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

‘280 Patent Claims	‘520 Publication
	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 sample,	The ’520 Publication also teaches that each of the test chambers is structurally capable of receiving a blood 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 state of the art that it is possible by wise combination of such tests to be able to determine very precisely at which point within the coagulation cascade a problem occurs…Referring to FIG. 6 it is possible and worthwhile to provide different cartridge devices 50 for different typical operations. It is also possible to combine e.g. an INTEM™, an EXTEM™ and a FIBTEM™ coagulation test with a platelet aggregometry test

‘280 Patent Claims	‘520 Publication
	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 arranged in said at least one measurement cavity for performing a test on said sample liquid” In particular, the ‘520 Patent 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	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.,

‘280 Patent Claims	‘520 Publication
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; and	**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 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). Notably, the INTEM™ and EXTEM™ assays were well known in the art prior to the priority date of the ‘280 Patent. See Ex. 1003, ¶¶ 39.
1C. a second chamber of the plurality comprising a second combination of reagents	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

‘280 Patent Claims	‘520 Publication
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.	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 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. Again it is noted that the FIBTEM™ assay, like the previously discussed INTEM™ and EXTEM™ assays were well known in the art prior to the priority date of the ‘280 Patent. See

‘280 Patent Claims	‘520 Publication
	Ex. 1003, ¶¶ 39.
2. 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.	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 ‘280 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 Ex. 1003, ¶¶ 39.

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,
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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. 9,272,280 B2 (and accompanying exhibits), is being served in its entirety on February 3, 2017, upon the following party via Federal Express:

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APPENDIX – INDEX OF EXHIBITS

Exhibit No.	Description
Ex. 1001	Viola *et al.*, "Device, System and Methods for Evaluation of Hemostasis," U.S. Patent No. 9,272,280 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 Platelet Inhibitor Response," U.S. Patent No. 6,221,672 B2 (filed on Jan. 4, 1999; issued on April 24, 2001)
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, 2009; 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. 9,272,280 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)