UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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**INSTRUMENTATION LABORATORY COMPANY**

Petitioner

v.

**HEMOSONICS LLC**

Patent Owner

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*Inter Partes* Review Case No. Unassigned

Patent 9,410,971

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**PETITION FOR *INTER PARTES* REVIEW OF**

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

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# I. INTRODUCTION

Instrumentation Laboratory Company ("Petitioner") requests *inter partes* review ("IPR") of claims 3, 4, 5, 8-14, and 17-20 (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. U.S. Patent No. 9,272,280 ("the '280 patent") (Ex. 1001), of which the '971 patent is a continuation, is subject of an *inter partes* review, petitioned by Petitioner on February 3, 2017 and which was instituted on September 1, 2017 with respect to all claims (claims 1 and 2) of the '280 patent (IPR2017-00852, Paper No. 14). Further, U.S. Patent App. Nos. 15/202,059 and 15/357,492 may be affected by the requested review. The '971 patent is also subject of an earlier

*inter partes* review petition ("the first '971 IPR"), which Petitioner filed on February 4, 2017 and which was instituted on September 1, 2017 with respect to claims 1, 2, 6, 7, 15, and 16 of the '971 patent (IPR2017-00855, Paper No. 14).

### C. Relation to the First '971 IPR

This Petition is directed towards the non-instituted claims of first '971 IPR. Substantially new art and evidence are presented in this Petition different from such of the art and arguments that were substantively considered in the first '971 IPR.

Much of the first '971 IPR was not considered substantively. Patent Owner's Preliminary Response (Paper No. 8) argued that the petition improperly incorporated argument by reference. Petitioner sought to show that the petition cited to specific sections of the expert Declaration of Patrick Mize, Ph.D as evidence and not wholesale adoption of arguments.[1] The Board denied this request (Paper No. 13) and, subsequently, agreeing with Patent Owner that the first '971 IPR petition improperly incorporated arguments and evidence from the declaration relating to each of the obviousness grounds, declined to consider substantively such art and arguments in reaching its institution decision.

Following the institution decision in the first '971 IPR, Petitioner filed a

[1] Petitioner argued that testimony of motivations for a person or ordinary skill in the art to combine references is evidentiary in nature and therefore should be considered.

Request for Rehearing (Paper No. 16) again arguing that evidentiary citations to the Declaration should be substantively considered. Petitioner also requested that, even if it disagreed with Petitioner's arguments, the Board exercise discretion in considering the declaration (for the sake of efficiency and fairness). Petitioner argued that incorporation by reference deficiencies are procedural rather than substantive in nature[2] and accordingly remedial measures are typically afforded Petitioner to correct/address improper incorporation by reference. *See, e.g.*, *Research In Motion Corp. v. Multimedia Ideas LLC*, IPR2013-00036, Paper No. 15 (PTAB March 18, 2013). In *Nike USA, Inc. v. Stirling Mouldings Ltd.*, IPR2014-00428, Paper No. 9 at 2 (PTAB Feb. 24, 2014), the petitioner was granted leave to file a corrected petition after the initial petition was determined to include improper incorporation by reference. The Board in the first '971 IPR denied Petitioner's Request for Rehearing on November 3, 2017 (Paper No. 20), affirming that it would not substantively consider the cited sections of the declaration.

Petitioner respectfully submits this filing of a second petition within a month

[2] A decision to not consider evidence presented in the declaration due to improper incorporation by reference is not a decision on the merits of such evidence but rather is a decision based on formalistic requirements for how such evidence was presented.

of the denial is timely under 35 U.S.C. § 314(a). Indeed, under 35 U.S.C. § 325(d), it would have been improper to file a new petition directed towards the art and arguments supported by the contested sections of the declaration until the Board rendered a final decision on whether it would substantively consider such sections of the declaration in the first '971 IPR.

As the Board did not previously substantively consider the merits of the evidence, the grounds presented herein do not reflect a repackaging of previously considered grounds. Petitioner is not modifying its position/arguments in view of a substantive decision by the Board (as is often the case in bad faith serial/follow-on petitions), but requests initial consideration of art and augments that were not previously considered due to procedural defects. Entering this Petition would be consistent with equitable remedial measures which are typically afforded to address improper incorporation by reference. Finally, since the obviousness grounds of the first '971 IPR were not instituted, no estoppel applies.[3]

[3] In *Shaw Industries Group v. Automated Creel Systems*, 817 F.3d 1293, 1296 (Fed. Cir. 2016), the Federal Circuit held that estoppel does not apply to grounds denied by the PTAB in an IPR because the "IPR does not begin until it is instituted."

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

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

### E. Fees Under 37 C.F.R. §§ 42.15 and 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).

## III. REQUIREMENTS FOR REVIEW UNDER 37 C.F.R. § 42.104

### A. 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.

### B. Statement of the Precise Relief Requested and the Reasons Therefor Under 37 C.F.R. §§ 42.22(a) and 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 ("Baugh") | 4/30/96 | 4/24/01 | § 102(b) |
| 1006 | U.S. Patent App. Pub. No. 2010/0154520 ("Schubert") | 12/23/08 | 6/24/10 | § 102(a), -(e)(1) |
| 1007 | U.S. Patent No. 6,016,712 ("the '712 patent) | 9/18/1997 | 1/25/2000 | § 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 onlines 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 ("the '011 patent") | 10/21/1994 | 4/2/1996 | § 102(b) |
| 1014 | U.S. Patent No. 6,613,286 ("the '286 patent") | 12/21/2000 | 9/2/2003 | § 102(b) |

| | | | | |
|---|---|---|---|---|
| 1015 | U.S. Patent No. 5,888,826 ("the '826 patent") | 6/30/1994 | 3/30,1999 | § 102(b) |

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

| Ground | IPR Claims | Art | Basis |
|---|---|---|---|
| 1 | 8 | Schubert | § 102(a), -(e)(1) |
| 2 | 12 and 13 | Schubert and the '286 patent | § 103(a) |
| 3 | 8, 12 and 13 | Baugh and the '286 patent | § 103(a) |
| 4 | 9-11 | Schubert and the '826 patent | § 103(a) |
| 5 | 9-11 | Baugh, the '286 patent and the '826 | § 103(a) |
| 6 | 5 | Schubert and the '011 patent | § 103(a) |
| 7 | 5 | Baugh and the '011 patent | § 103(a) |
| 8 | 14 | Schubert and the '712 patent | § 103(a) |
| 9 | 14 | Baugh and the '712 patent | § 103(a) |
| 10 | 3, 4, and 17-20 | Schubert and Viola 2009 | § 103(a) |
| 11 | 3, 4, and 17-20 | Baugh and Viola 2009 | § 103(a) |

Detailed claim charts applying the foregoing published prior art references for each of the IPR Claims are provided herein, along with the reasons why a person of ordinary skill in the art would combine the references. Additional explanation and evidence supporting each ground is set forth herein as well as in the Declaration of

Patrick Mize, Ph.D. ("Mize Decl.," Ex. 1003).

## IV. THE '971 PATENT

The '971 patent, according to its abstract, provides "devices, systems and methods for evaluation of hemostasis," as well as "sound focusing assemblies." The claims for which review is sought in this petition broadly claim a known multi-assay cartridge device with known reagents and, in dependent claims, known features for distribution, heating and mixing samples, and pre-loading of lyophilized reagents, as well as the application of acoustic interrogation techniques previous disclosed in prior publications by the inventors of the '971 patent.

### A. The Relevant Art and Ordinary Skill

#### 1. State of the Art Prior to the '971 Patent Application

"Hemostasis is the physiological process which causes bleeding from a damaged blood vessel to slow and stop." Mize Decl. (Ex. 1003) ¶ 18. This involves a combined effect of platelet activation and coagulation. *Id.* Platelet activation is triggered when the endothelium is damaged and results in the binding of platelets to the extracellular matrix. *Id.* ¶ 26. Coagulation "is the process by which blood transforms from a viscoelastic liquid to a viscoelastic solid (blood clotting)." *Id.* ¶ 27. "Coagulation can occur through intrinsic activation by clotting proteins interacting with charged surfaces or through extrinsic activation by tissue factor (TF) and Factor VIIa (a clotting protein)." *Id.* ¶ 28. Thrombin is generated during clotting

activation which among other roles cleaves fibrinogen to form fibrin. *Id.* See also, *Id.* ¶ 29, Fig. 1 (showing the "cascade" of processes).

In basic coagulation testing (e.g., PT and aPTT tests) "a blood sample is mixed with a reagent for activating coagulation and coagulation characteristics such as time-to-coagulation (clot time) are monitored." *Id.* ¶¶ 31-32. The sample would typically be "equilibrated to 37$^{o}$C." *Id.*

The transition from laboratory-based tests to Point of Care (POC) diagnostic tests motivated the development of "test cartridges for automated analysis of coagulation" which included preloaded, often lyophilized, reagents. *Id.* ¶ 33. Advantageously the use of a cartridge based system enabled automated testing using built in microfluidics thereby allowing for "accurate testing in a remote, real-time setting, i.e., POC, by people with limited laboratory experience." *Id.*

Drug-response type tests were also developed which motivated the development of multi-channel/multi-chamber automated testing devices which enabled simultaneously estimating a patient's response to multiple different concentrations of a drug or to different drugs/ drug combinations related to hemostasis (such as anticoagulants, platelet inhibitors, platelet activators and counter-agents to platelet inhibitors). *Id.* ¶¶ 35 and 40-43. For example, the HepCon® HMS system, as disclosed in Baugh") (Ex. 1005), teaches a six chamber test cartridge where each of the test wells includes a contact activator and where

some of the test wells further include different amounts of a platelet inhibitor such as abciximab (*see, e.g.*, Table 1 of Baugh). *Id.* ¶ 44.

Multi-chamber testing was also utilized to enable comparing assays targeting different pathways/functions of hemostasis. *Id.* ¶ 45. As one example, the ROTEM® (Rotational Thromboelastometry) system, as disclosed in U.S. Patent Appl. Pub. No. 2010/0154520 ("Schubert") (Ex. 1006) teaches a four channel cartridge which in preferred embodiments includes a specific combination of assays including EXTEM (extrinsic activator), INTEM (intrinsic activator) and FIBTEM (extrinsic activator plus the platelet inhibitor cytochalasin D) assays. *Id.* ¶ 46.

Many different interrogation techniques have been utilized to assess a hemostatic parameter, including, but not limited to, absorbance, mechanical, magnetic, electrical (potential, impedance, and conductance), or sound. These techniques are generally interchangeable for testing purposes having known configurations and predictable results. *Id.* ¶¶ 53-65.

**2. 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.

Particularly in this field, POSAs are aware of interdisciplinary developments through their colleagues and publications. Mize Decl. (Ex. 1003) ¶¶ 14-16.

**B. The '971 Patent Claims Sought for Review**

Independent claim 1 is reproduced below:

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 second combination including an activator of coagulation and one or both of abciximab and cytochalasin D; and

an interrogation device that measures at least one viscoelastic property of the test sample.

'971 patent 18:62–19:13.

Independent claim 17 recites limitations similar to claim 1, and further requires the chambers to be configured to be interrogated with ultrasound, a transducer for transmitting and receiving ultrasound and a processor configured to determine hemostatic parameters from signals transmitted to the transducer. *Id.*

20:17–41. Claims 3 and 4, each of which depend from claim 1, also recite acoustic interrogation elements. *Id.* 19:24-25 and 19:26-27. Claims 18-20, each of which depend from claim 17, relate to specific parameters and indexes that can be measured via the acoustic interrogation. *Id.* 20:42-52.

Claim 5, which depends from claim 1, recites that the reagents are lyophilized. *Id.* 19:28-30.

Claim 6, which depends from claim 1, recites a housing of the multi-chamber device defining the chambers. *Id.* 19: 31-33. Claim 7, which depends from claim 6, recites use of a single test sample. *Id.* 19:34-35. Claims 8, 12 and 13, which depend from claims 7, 8 and 12, respectively, relate to a fluid pathway for delivery of a sample into a test chamber and promoting reagent mixing. *Id.* 19:36-40, 19:49-53, and 20:1-3.

Claims 9, 10 and 11, which depend from claims 8, 9 and 10, respectively, relate to use of thermally conductive material to facilitate warming of a sample along the fluid pathway. *Id.* 19:41-43, 19:44-46, and 19:47-48.

Claim 14, which depends from the dependency chain of claims 7, 6 and 1, recites a magnetic stirring structure for mixing a sample. *Id.* 20:4-6.

### C. Prosecution History of the '971 Patent

While the standard for review for claim construction under the IPR process is broadest reasonable interpretation by a POSA in light of the specification, to the

extent that the Board considers the prosecution history of the '971 patent, there is substance only in the four-year prosecution history of the '280 patent (Ex. 1009) from which the '971 patent was continued and issued in six months after correcting double patenting issues (15/003,325 file). The history of the '280 patent shows that it was granted solely on the basis of limitations relating to the reagent composition in the test chambers, and specifically on the inclusion of abciximab, cytochalasin D or both in the second chamber; these elements were carried forward as into independent claims 1 and 17 of the '971 patent (Ex. 1002 18:62-19:13 and 20:17-41).[4] As shown below, these tests and reagents were well-known in the prior art.

**D. Claim Construction (37 C.F.R. § 42.104(b)(3))**

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

[4] After 3-1/2 years and 800 pages of prosecution, the '280 patent applicant proposed new claims 79 and 80 including these elements, Ex. 1009 at 103-04, then agreed to cancel the other claims to allow these to issue as claims 1 and 2, *id.* at 31. Dependent claims 2-16 of the '971 patent (19:14-20:17) include subject matter previously presented in the '280 patent prosecution (claims 2, 7-13, 15, 16, and 17, Ex. 1009 at 101-02) and found unpatentable without the reagent limitations.

terms must be interpreted as broadly as their terms reasonably allow." *In re Zletz*, 893 F.2d 319, 321 (Fed. Cir. 1989).

**1. "test chamber configured to receive blood of a test sample"**

As construed by a POSA, "any constrained space or cavity structurally capable of receiving a blood sample." Mize Decl. (Ex. 1003) ¶ 82. The term "test" refers to an intended use of the chamber and does not specify a structural constraints for the chamber. *Id.* ¶ 83. The functional language "configured to" is interpreted as not actually requiring loading of a blood sample within the test chamber. Rather, the test chamber is structurally capable of receiving a blood sample. *Id.*

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

As construed by a POSA, the test chamber is "capable of being interrogated in order to determine a hemostatic parameter of the blood." *Id.* ¶ 84. Many different interrogation techniques may be utilized to assess a hemostatic parameter. *Id.* ¶¶ 53-65; *see also* Ex. 1010 ("Table of Prior Art Devices"). These interrogation techniques often do not require any unique structural configuration of the chamber in order to implement.

**3. "activator of coagulation"**

As construed by a POSA, may include 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.* ¶ 86.

**4. "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"**

As construed by a POSA, these limitations include no specific temporal or structural constraints regarding when and how the reagents are loaded into the chambers. Thus, they would cover instances where the reagents are preloaded into the chambers as well as instances where the reagents are loaded together with or subsequent to the blood sample. *Id.* ¶ 87.

**5. "viscoelastic property"**

As construed by a POSA, a property relating to the viscoelasticity of a sample. The '971 patent specification teaches estimating a variety of parameters relating to viscoelastic properties of the sample. Example parameters include relative elasticity, relative viscosity, a clotting time constant, and maximum displacement. '971 patent (Ex. 1002) 17:34-40. *Id.* ¶ 89.

**6. "thermally conductive polymer"**

As construed by a POSA, a polymer that is capable of conducting heat. *Id.* ¶ 90.

Petitioner submits that the remaining terms do not require construction.

## V. SUMMARY OF THE REFERENCES APPLIED IN THIS PETITION

### A. U.S. Patent Publication No. 2010/0154520 ("Schubert")

Schubert (Ex. 1006) teaches a multi-chamber coagulation device cartridge structure as well as the specific reagent combination of a first coagulation assay with an activation of coagulation and a second coagulation assay with an activator coagulation plus an a platelet inhibitor. The device is for evaluation of hemostasis. Abstract and ¶¶ 0002-0007 and 0025. Schubert is directed towards thromboelastometeters such as ROTEM which allow running four different coagulation tests in parallel so as to isolate the effect of different components of the coagulation pathway. ¶¶ 0013, 0016, 0082, and 0083. Schubert discloses a plurality of test chambers (¶ 0029: "a cartridge body having at least one measurement cavity formed therein"). Also, ¶¶ 0081-0082 teach that "[i]n a preferred embodiment the cartridge device 50 comprises four arrangements of FIG. 4 or 5 having 4 measurement cavities 20, 20'"). Each test chamber is configured for receiving a blood sample (¶ 0081: "the sample liquid 1 is shared among the arrangements in parallel"). Also, each test chamber includes a reagent or combination of reagents (¶ 0040 teaches that in some embodiments the measurement cavity [e.g., measurement cavities 20, 20'] may be integrally formed with a reagent cavity [e.g., reagent cavities 19, 19']; *see also* ¶ 0081 teaching that each reagent cavity 19, 19' includes a reagent 21, 21'). Furthermore, each test chamber is configured to be interrogated to

determine a hemostatic parameter using an interrogation device that measures at least one viscoelastic property of the test sample (¶ 0031 teaching "measuring viscoelastic characteristics of a sample liquid in the measurement cavity;" *see also* ¶¶ 0011, 0083 and 0088, teaching a probe element 22 in the measurement cavity 20 for detecting coagulation based on deflection of a light beam; *see also* ¶ 0029).

Schubert also discloses a preferred four chamber embodiment where INTEM, EXTEM and FIBTEM coagulation tests are combined with a platelet aggregometry test within one cartridge. ¶¶ 0082-0083. These tests are described as examples of "different reagents which activate or suppress different parts of the coagulation cascade."[5] Thus, INTEM is disclosed as including a reagent for intrinsic activation (intrinsic activator), EXTEM is disclosed as including a reagent for extrinsic activation (extrinsic activator) and FIBTEM is disclosed as including reagents for extrinsic activation as well as for suppressing thrombocyte function (extrinsic

[5] ¶ 0083 introduces the Pentapharm GmbH tests, INTEM, EXTEM and FIBTEM, for "intrinsic activation," "extrinsic activation" and 'extrinsic activation in which the thrombocyte function is suppressed," respectively, while referring to the immediately preceding sentence that the tests are provided as examples of "different reagents which activate or suppress different parts of the coagulation cascade."

activator plus cytochalasin D). *Id.*

The trademark terms INTEM, EXTEM and FIBTEM refer to specific well known and industry standard tests at the time of the Schubert publication. In particular, the EXTEM assay was known to include an extrinsic activator (Tissue Factor) as a reagent while the INTEM assay was known to include a contact activator as a reagent (ellagic acid plus phospholipid). Furthermore, the FIBTEM assay was known to combine extrinsic activation (using Tissue Factor) and cytochalasin D (an antiplatelet agent) to help quantitate the contribution of fibrinogen and platelets to clot formation. See Mize Decl. (Ex. 1003) ¶¶ 23, 46, 52, 119 and 120. This is also supported by the literature contemporaneous with Schubert.[6]

### B. Görlinger, K., et al., "Perioperative Coagulation Management and Control of Platelet Transfusion by Point-of-Care Platelet Function Analysis," Transfus Med Hemother 34:396-411 (2007) ("Görlinger 2007")

Görlinger 2007 (Ex. 1020), is discussed here as corroborating the teachings of Schubert with respect the ROTEM system and EXTEM, INTEM and FIBTEM assays. Görlinger 2007 discloses findings of the effectiveness of three different point-of-care platelet function analyzers in assessing perioperative bleeding in cardiac surgery (page 396). One of the analyzers reviewed is ROTEM (Rotational Thromboelastometry) (page 403). ROTEM is described as utilizing a temperature-

[6] *See, e.g.*, Görlinger 2007 (Ex. 1020).

controlled pin and cup mechanism to detect changes in elasticity of a clotting sample (*Id.*). The ROTEM system is disclosed as including "four independent channels which enable the performance of four independent tests at the same time" (*id*.). The ROTEM tests are described as being initiated by adding an activator of the extrinsic or intrinsic coagulation pathway (*id*.). "Thromboplastin (tissue factor) from rabbit brain is used for activation of the extrinsic pathway in ExTEM, FibTEM and ApTEM)…FibTEM contains additional cytochalasin D in order to inhibit platelet activation…In InTEM (intrinsic pathway clotting time) test coagulation is activated by partial thromboplastin (phospholipids) and ellagic acid" (*id*.). The parameters detected by ROTEM include clot formation (CFT = clot formation time in seconds), clot stability (A5, A10, A15 = amplitude at 5, 10 or 15 min; MCF = maximum clot firmness) and lysis ML = maximum lysis in % = reduction of clot firmness in relation to MCF) (*id*.). Clot firmness in EXTEM and FIBTEM are compared to detect a fibrinogen deficiency (*id*.).

### C. 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. ("Gottumukkala 1999")

Gottumukkala 1999 (Ex. 1019) is discussed here as corroborating the teachings of Schubert with respect to an assay combination for a thromboelastography device. Gottumukkala, like Schubert, teaches comparing a

first coagulation test with an activator of coagulation relative to a second coagulation test with an activator of coagulation plus a platelet inhibitor.

Gottumukkala 1999 evaluates tests for assessing platelet and Fibrinogen contribution to clot strength in thromboelastographic devices. Gottumukkala teaches using "thromboelastography with ReoPro® to evaluate the independent contribution of fibrinogen and platelets to clot strength." ReoPro® is a trademark name for the monoclonal antibody fragment c7E3 also known as abciximab.[7] In Gottumukkala 1999, a comparative set of tests were run on respective pin and cup mechanisms loaded with a portions of a blood sample. These tests included a first test with 360 $\mu$L of celite-activated whole blood and a second test with with 5 $\mu$L of (2 mg/mL) ReoPro® added to 355 $\mu$L of celite-activated whole blood. Testing was performed on two separate channels of a preheated Thromboelastograph (TEG®; Hemoscope Corp, Skokie, IL). A platelet index (MAplt) reflecting the contribution of platelets to clot strength was then calculated based on a stiffness (clot strength) differential between the two tests (by subtracting MAfib (maximal amplitude with ReoPro®) from MAwb (maximal amplitude with whole blood). Thus, Gottumukalla

[7] *See, e.g.*, Abstract for Faulds, D. *et al.*, Abciximab (c7E3 Fab). A review of its pharmacology and therapeutic potential in ischaemic heart disease; Drugs 583-98 (1994); PubMed P.M.I.D.: 7528131 ("Faulds 1994") (Ex. 1026).

1999 teaches a first chamber including an activator of coagulation (celite) and a second chamber including an activator of coagulation (celite) and abciximab.

**D. U.S. Patent No. 6,221,672 ("Baugh")**

Baugh (Ex. 1005) teaches a multi-chamber coagulation device cartridge structure as well as the specific reagent combination of a first coagulation assay with an activation of coagulation and a second coagulation assay with an activator coagulation plus an a platelet inhibitor. The assay device in Baugh is for evaluation of hemostasis. Baugh 1:14-20. The assay device (e.g., device 100) uses a cartridge (e.g., cartridge 64 or 65) which includes a plurality of test chambers (each characterized by a constrained space or cavity). 2:7-12 and 4:45-50; *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). "An aliquot of a blood sample is added to each cell" via a dispensing subassembly 104. 4:7-8 and 8:17-20. Each of the test cells is defined by a tube-like member having a reagent chamber which contains a reagent or reagents. 2:2-7; *also* Fig. 4. The test cells are interrogated using a plunger assembly 72 and optical sensing system in order to detect coagulation. 7:21-25; 8:27-31 and 2:2-25. Each test cell includes an activator of coagulation and at least two of the test cells include different amounts of a platelet inactivating agent. 6:1-17, 6:34-41; 5:33-43 and Table 1.

### E. Viola, F., et al., "A Novel Ultrasound-Based Method to Evaluate hemostatic Function of Whole Blood" ("Viola 2009")

Viola 2009 (Ex. 1012) is a prior publication by the inventors teaching one alternative for interrogating the viscoelasticity of a blood clot: "sonorheometry," a self-coined term which is described in the paper as "a novel ultrasound-based technology…which can assess hemostasis function from a small blood sample." Notably, the same self-coined term is used in the '971 patent ("provided are sonorheometric devices for evaluation of hemostasis"). Viola 2009 teaches an acoustic based interrogation system which can be used to run tests in a thromboelastographic device, such as the cartridge of Schubert. In particular 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. Viola 2009 also teaches an interrogation device for measuring a viscoelastic property of a sample that is 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.

Thus, Viola 2009 appears to describe an early prototype of the same type of

acoustic interrogation device used in the '971 patent. Viola 2009 is one of many such papers published by the inventors more than one year prior to the priority date of the '971 patent that relate to ultrasound-based interrogation of hemostatic parameters. Thus, the subject matter from the '971 patent relating to acoustic interrogation had already been made part of the public domain prior to the filing of the '971 patent.

**F. U.S. Patent No. 5,504,011 ("the '011 patent")**

The '011 patent (Ex. 1013) teaches a feature of a coagulation testing device where the reagents are lyophilized prior to interacting with a test sample. Abstract ("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."[8]

**G. U.S. Patent No. 6,613,286 ("the '286 patent")**

The '286 patent (Ex. 1014) teaches a cartridge and analyzer which are used

[8] Similar use of lyophilized reagents in the specific context of ROTEM is disclosed in Rahe-Meyer, N. et al., Multicentric comparison of single portion reagents and liquid reagents for thromboelastometry. Blood Coagul Fibrinolysis 2009 Apr;20(3):218-22. PubMed P.M.I.D.: 19657320 ("Rahe-Meyer 2009") (Ex. 1021).

for detecting changes in viscosity of human blood (1:6-12), disclosing a specific method of distribution of the blood sample. The cartridge includes generally includes a fluid receiving/dispensing reservoir, one or more fluid-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, e.g.*, Abstract and 8:65-9:11. A six-channel configuration (with six fluid-receiving chambers in common communication with a fluid inlet and fluid receiving chamber) is depicted and described with respect to Fig. 2. The '286 further discloses a tangential flow pattern of the conduit(s) opening on the side into the fluid-receiving chamber(s), which is used to promote reagent mixing. 4:16-5:48. This is described as advantageous to producing more accurate test results. 5:49-51.

**H. U.S. Patent No. 5,888,826 ("the '826 patent")**

The '826 patent (Ex. 1015) teaches including a thermally conductive material to effect heat transfer with respect to a fluid pathway in a coagulation test card/cartridge. In particular, it teaches making a bottom surface of the sample holding chamber from a thermal conductive material. 5:34-44. 7:41-44. It teaches that test cartridges with an incubation step of heating the sample to be assayed to a predetermined temperature are particularly suited for testing hemostasis or coagulation function of blood. 3:34-35. The '826 patent further teaches that the design and geometry of the housing and its components is selected based on the

assay to be performed. Thus, when the assay involves an incubation step, a section of the holding chamber contacts heating or cooling elements in the instrument. This section preferably comprises a material which is capable of enhancing the heat transfer. 4:18-27. While the '826 patent does not explicitly disclose that this material is a polymer, it does state that polypropylene is a preferred material for the housing and that other plastics (polymers) are also acceptable. 11:66-12:3.

**I. U.S. Patent No. 6,016,712 ("the '712 patent")**

The '712 patent (Ex. 1007) teaches, in the context of a multi-chamber coagulation testing cartridge (see, e.g, second chambers 160a-160d in Fig. 1, 9:55-58 and 11:18-59), the feature of magnetic mixing means in chambers for mixing the reagents with the sample. In particular, it discloses that a suitable mixing means is a mixing ball or the like 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.[9] 11:59-66. The '712 patent also teaches a fluid path for distributing a sample from an inlet to a plurality of test chambers. Fig. 1 and 14:49-15:2.

[9] Similar magnetic mixing means in coagulation testing are also disclosed in U.S. Patent No. 6,318,191 to Shuqi Chen ("the '191 patent") (Ex. 1023).

Each of the forgoing references are prior art to the '971 patent under the applicable (pre-AIA) 35 U.S.C. §§ 102(b), except for Schubert (Ex. 1006) which is prior art to the '971 patent under the applicable (pre-AIA) 35 U.S.C. §§ (pre-AIA) 35 U.S.C. §§ 102(a) and –(e)(1).

## VI. DETAILED EXPLANATION OF THE 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 III(B), and requests that each of the claims be found unpatentable.

In each of the Grounds set forth below is documentary proof that both a multi-chamber coagulation device cartridge structure as well as the specific reagent combination of a first coagulation assay with an activation of coagulation and a second coagulation assay with an activator coagulation plus an a platelet inhibitor such as abciximab, cytochalasin D or both were well known in the art and disclosed in written publications prior to the '971 patent (including in both Schubert (Ex. 1006) and Baugh (Ex. 1005))[1] The file history (Section IV(C)) shows that the original

[1] Schubert and Baugh include similar teachings applicable to claims of the '971 patent and are largely interchangeable with respect to the grounds for rejections raised herein.

examiner granted the underlying claims of the '280 patent and its '971 patent continuation based on the particular reagent combination, and the Board has instituted IPR2017-00852 and -00855, on the basis that Petitioner has a likelihood of success in defeating the claims distinguished by the use of the reagent combination relative to Baugh. This Petition sets forth the specific Grounds for invalidating the remaining IPR Claims that add little to the clouded patentability of the claims already in review. As shown in Grounds 1-11, dependent claims 8-14 and 18-20, merely (and obviously) add known features (mixing, heating, lyophilizing, etc.) to the multi-hemostasis-assay device disclosed in both Schubert and Baugh and should be rejected and canceled.

The only independent IPR claim, claim 17, consists largely of elements of multi-hemostasis-assay cartridge already being reviewed with the addition of general structure for acoustic interrogation, somewhat specified in claims 18-20 dependent from claim 17 and claims 3 and 4 dependent from claim 1 already being reviewed. But Viola 2009 (Ex. 1012) already put in the public domain the motivation and structure for acoustic interrogation prior to the filing of the '971 patent claims 3, 4, and 17-30 that recite that structure. Thus, Grounds 10 and 11 detailing this mapping should be instituted and the claims cancelled.

### A. Ground 1: Schubert Anticipates IPR Claim 8

Schubert (Ex.1006), described at Section V(A), anticipates claim 8 by

disclosing each and every element of the claim (including each and every element of intervening and base claims 1, 6 and 7), arranged as claimed in a manner enabling to a POSA. Dr. Mize's testimony corroborates the above. Mize Decl. (Ex. 1003) ¶¶ 132-135.

The following claim chart matches each and every limitation of claim 8 (including intervening and base claims 1, 6 and 7) of the '971 patent with the disclosure in Schubert:

| **'971 Patent Claims** | **Schubert (Exhibit 1006)** |
|---|---|
| **1.** A device for evaluation of hemostasis, comprising: | Abstract: "cartridge device for a measuring system for measuring viscoelastic characteristics of a sample liquid, in particular a blood sample." |
| **1A.** a plurality of test chambers | ¶¶ 0081-0082 ("a second reagent cavity 19' storing a second reagent 21'. . . 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'." |
| **1Ai.** each configured to receive blood of a test sample, | ¶ 0081 (sample liquid 1 is shared among the arrangements in parallel). |
| **1Aii.** each test chamber comprising a reagent or combination of reagents, | ¶ 0040 (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 ¶0082, each of the measurement cavities could have an integrally formed respective reagent cavity. Also ¶ 0083 teaching combining INTEM, EXTEM and |

| '971 Patent Claims | Schubert (Exhibit 1006) |
|---|---|
| | FIBTEM coagulation tests with a platelet aggregometry test within one cartridge. |
| **1Aiii.** wherein each chamber is configured to be interrogated to determine a hemostatic parameter of the blood received therein; | ¶¶ 0029 ("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") |
| **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 | ¶¶ 0082 and 0083 teaching combining INTEM, EXTEM and FIBTEM coagulation tests with a platelet aggregometry test within one cartridge.<br>Thus, Schubert teaches a first measurement cavity including reagents which "activate different parts of the coagulation cascade" (intrinsic or extrinsic activators, as would be used in the INTEM and EXTEM assays, respectively) and a second measurement cavity including an extrinsic activator in combination with cytochalasin D reagents (as would be used in the FIBTEM assay.[10, 11] |

[10] *See* Sections V(A) and V(B) discussing Schubert and Görlinger 2007 (Ex. 1020), respectively, as well as discussing trademark terms INTEM, EXTEM and FIBTEM referring to specific well known and industry standard tests at the time of the Schubert publication (where EXTEM includes an extrinsic activator: Tissue Factor; INTEM includes an intrinsic activator: ellagic acid plus phospholipid; and FIBTEM includes an extrinsic activator: Tissue Factor and an antiplatelet agent: cytochalasin D).

[11] Gottumukkala 1999 (Ex. 1019) (discussed in Section V(C)) teaches a similar

| '971 Patent Claims | Schubert (Exhibit 1006) |
|---|---|
| combination of reagents, is an activator of coagulation;<br>**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 | |
| **1D.** an interrogation device that measures at least one viscoelastic property of the test sample. | ¶ 0029 ("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" Also, ¶¶ 0028, 0031 (interrogation by oscillating rotation of pin) and ¶¶ 0006-0009 (viscoelastic measurement techniques and apparatus). |
| **6.** The device of claim 1**,** wherein each | Abstract: "a cartridge body having at least one measurement cavity formed therein…and a cover |

assay combination to Schubert for use with a thromboelastography device comparing a first coagulation test with an activator of coagulation to a second coagulation test with an activator of coagulation plus abciximab.

| '971 Patent Claims | Schubert (Exhibit 1006) |
|---|---|
| test chamber of the plurality of test chambers is at least partially defined by a housing. | being attachable on said cartridge body; wherein said cover covers at least partially said at least one measurement cavity." Fig. 7B (body and cover form housing), ¶ 0038 (bonding or welding…[or] integrally formed with the cartridge body"), and ¶ 0093 ("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. | ¶ 0081, Fig. 6: ("[t]he sample liquid 1 is shared among the arrangements in parallel"); *also* ¶ 0082 ("measurements can be done with different reagents on the same liquid sample or with same reagents"). |
| **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. | ¶ 81 and Fig. 6 (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. |

### B. Ground 2: Schubert in Combination with the '286 Patent Renders Obvious Claims 12 and 13.

Schubert (Ex.1006) in combination with the '286 patent (Ex. 1014) renders obvious claims 12 and 13, by disclosing each and every element of the claims, arranged as claimed in a manner enabling to a POSA. Schubert, summarized at

Section V(A), teaches the base claims 1, 6, 7 and 8 to the multi-assay cartridge device (see Ground 1) but does not teach the particular flow paths of dependent claims 12, and 13 for enhancing mixing. The '286 patent, summarized at Section V(G), teaches such flow paths in an analogous art. A POSA, as defined in Section IV(A)(2), would be motivated to combine these references, at least because the '286 patent (5:49-6:4) teaches the applicability of its disclosed flow paths to assays generally and Schubert ¶ 0081 contemplates different configurations. This is simple application of a known technique to improve similar devices in the same way (with predictable results).

As discussed in V(G) above, the '286 patent discloses a particular way of distributing the blood sample in a coagulation testing cartridge, including a tangential flow into the fluid-receiving chamber(s), which is used to promote reagent mixing. It would have been obvious for a POSA to combine the teachings of the '286 patent with the teachings of Schubert. The '286 patent is intended to be a general construct that can be adapted for any number of different types of tests/assays that involve mixing a sample with a reagent in a receiving chamber. See, e.g., 5:49-6:4 teaching: "Again, applicants have found that each of the above noted fluid flow features [such as the tangential flow feature], in its own right, will help a given test apparatus produce more accurate test results…Moreover, these cumulative improvements appear to be the case, regardless of...the liquid being tested, …the

reagent…[and] the type test performed...Thus, the cartridges of this patent disclosure can be used in virtually any test wherein changes in a property of a liquid/reagent mixture is to be measured…" Moreover, Schubert contemplates the possibility of different types of flow paths. *See, e.g.*, ¶ 0081 teaching that "FIG. 6 shows only one possible variation of a plurality of different arrangements easily imagined." Thus, a POSA would have been motivated to apply teachings in the '286 patent to improve reagent mixing and fluid flow in the cartridge of Schubert.

The '286 patent is analogous art at least since it relates to coagulation testing cartridges/devices. There is nothing in the '286 patent or Schubert that teaches away from their combination, and their combination would have predictable results. Dr. Mize's testimony corroborates the above (Mize Decl. (Ex. 1003) ¶¶ 137-140) and the absence of secondary factors that might show non-obviousness (*Id*. ¶¶ 109-112).

The claim chart provided below tabulates the teachings in the '286 patent that, in combination with the previously discussed teachings in Schubert, disclose and enable each and every limitation of claims 12 and 13 (including intervening and base claims 1, 6 and 7) of the '971 patent:

| **'971 Patent Claims** | **References** |
|---|---|
| **1.** | Schubert teaches claim 1 (see Ground 1, claim 1) |
| **6.** [depends from 1] | Schubert teaches claim 6 (see Ground 1, claim 6) |
| **7.** [depends from 6] | Schubert teaches claim 7 (see Ground 1, claim 7) |

| '971 Patent Claims | References |
|---|---|
| **8.** [depends from 7] | Schubert teaches claim 8 (see Ground 1, claim 8) |
| **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 features which offer improved fluid flow and mixing over a previous iteration of the cartridge/device including using tangential sample flow into the receiving chambers. 4:16-5:48. |
| **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. | The '286 patent teaches tangential flow into the receiving chambers. 4:16-5:48. Such tangential sample flow is noted to produce better mixing and more accurate test results." 5:49-51. Thus, a POSA would have been motivated implement fluid flow into the receiving chambers via a channel which promotes mixing of a sample and reagent. |

### C. Ground 3: Baugh in Combination with the '286 Patent Renders Obvious Claims 8, 12 and 13.

Baugh (Ex.1005) in combination with the '286 patent (Ex. 1014) 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. Baugh, summarized at Section V(D), teaches the base claims 1, 6, and 7 to the multi-assay cartridge device (see

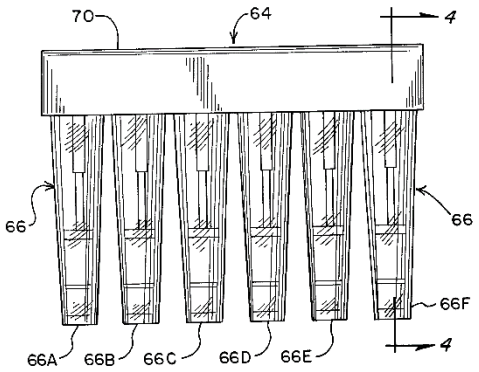
below[12]) but does not teach the particular flow paths of dependent claims 8, 12, and 13 enhancing mixing. The '286 patent, summarized at Section V(G), teaches such flow paths in an analogous art. A POSA, as defined in Section IV(A)(2), would be motivated to combine these references, at least because the '286 patent (5:49-6:4) teaches the applicability of its disclosed flow paths to assays generally and Baugh discloses a dispensing subassembly 104 (8:17-20) that a POSA could substitute for the flow path disclosed in the '286 patent. This is simple application of a known technique to improve similar devices in the same way (with predictable results).

Thus, a POSA would have been motivated to apply teachings in the '286 patent to improve reagent mixing and fluid flow in the cartridge of Baugh. There is nothing in the '286 patent or Baugh that teaches away from their combination, and their combination would have predictable results. Dr. Mize's testimony corroborates the above (Mize Decl. (Ex. 1003) ¶¶ 142-146) and the absence of secondary factors that might show non-obviousness (*id*. ¶¶ 109-112).

The claim chart provided below tabulates the teachings in the '286 patent that, in combination with the previously discussed teachings in Baugh, disclose and

[12] As successfully argued during for institution of claims 1, 6 and 7 in the first '971 IPR, Baugh (discussed in Section VII(D)) teaches each of the elements of claim 7 (including each and every element of intervening and base claims 1 and 6).

enable each and every limitation of claims 8, 12 and 13 (including intervening and base claims 1, 6 and 7) of the '971 patent:

| **'971 Patent Claims** | **References** |
|---|---|
| **1.** A device for evaluation of hemostasis, comprising: | Baugh 1:14-20. |
| **1A.** a plurality of test chambers | Baugh 2:2-7 ("(t)he cartridge includes a plurality of test cells, each of which is defined by a tube-like member..") Also 4:42-47. 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 |
| **1Ai.** each configured to receive blood of a test sample, | Baugh 4:7-8 ("(a)n aliquot of a blood sample is added to each cell,"); also 8:17-20 (dispensing subassembly 104). |
| **1Aii.** each test chamber comprising a reagent or combination of reagents, | Baugh 2:2-7 (each of the test cells includes "a reagent chamber which contains a reagent or reagents." Also Fig. 4 (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; | Baugh teaches each of the test cells in is configured to be interrogated to determine a hemostatic parameter, e.g., by a mechanical activation of platelets using a plunger assembly 72 in order to detect coagulation. 7:21-25; 8:27-31 and 2:2-25. |
| **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;<br>**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. | Baugh Abstract ("the blood sample aliquot, platelet and/or clotting activator and platelet inactivating agent are mixed"); *also*, 2:2-9 ("the reagents include an activation reagent to activate coagulation of the blood"); 6:1-17 (contact activator in the reagent chamber of each test cell 66) 6:34-36 (at least two of the test cells comprise different amounts of a platelet inactivating agent); 5:33-43 (the platelet inactivating agent may be abciximab).<br>Baugh discloses at least two of the test cells comprising different amounts of a platelet inactivating agent. 6:34-36. *Also* 5:1 (depicting cells 66C-66F including different concentrations of a platelet inhibitor while cells 66A and 66B act as a baselines or control without any platelet inhibitor); Table 1, discussed at 6:36-41. |

| | |
|---|---|
| **1D.** an interrogation device that measures at least one viscoelastic property of the test sample. | Baugh 2:10-25 ("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. . . .. Upon a sufficient change in the descent rate, the coagulation-related activity is detected and indicated by the apparatus") |
| **6.** The device of claim 1**,** wherein each test chamber of the plurality of test chambers is at least partially defined by a housing. | Baugh 2:2-7. 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* Figs. 2 and 3. |
| **7.** The device of claim 6**,** wherein the device is configured for use with a single test sample. | Baugh 4:7-8 ("(a)n aliquot of a blood sample is added to each cell"). A dispensing subassembly is used to divide a single blood sample. 8:17-20; *also* Abstract and claim 11. |
| **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 '286 patent teaches a cartridge which includes a fluid receiving/dispensing reservoir, one or more fluid-receiving chambers and one or more conduits that permits fluid communication between the fluid receiving/dispensing reservoir and the fluid-receiving chamber(s). Abstract; *also*, 8:65-9:11. |
| **12.** [depends on 8] | The '286 patent teaches additional elements of claim 12 (see Ground 2, claim 12) |

| | |
|---|---|
| **13.** [depends on 12] | The '286 patent teaches additional elements of claim 13 (see Ground 2, claim 13) |

### D. Ground 4: Schubert in Combination with the '826 Patent Renders Obvious Claims 9-11.

Schubert (Ex.1006) in combination with the '826 patent (Ex. 1015) renders obvious claims 9-11, by disclosing each and every element of the claims, arranged as claimed in a manner enabling to a POSA. Schubert, summarized at Section V(A), teaches the base claims 1, 6, 7 and 8 to the multi-assay cartridge device (see Ground 1) but does not teach a thermally conductive polymer to facilitate heating of the sample along a fluid pathway as characterized in claims 9-11. The '826 patent, summarized at Section V(H), teaches such limitations in an analogous art. A POSA, as defined in Section IV(A)(2), would be motivated to combine these references, at least because the '826 patent (5:49-6:4) teaches the importance of heating in the context of coagulation testing as well as the advantages of integrating heating elements/techniques into coagulation testing cartridges (*i.e.*, to reduce user handling and the potential for error). Moreover Schubert ¶ 0081 contemplates different flow path configurations. This is simple application of a known technique to improve similar devices in the same way (with predictable results).

The '826 patent, summarized in Section V(H), bridges the gap by teaching a distribution path and test chamber made from a thermally conductive material that is heated in the analogous art of a test cartridge for coagulation testing. Although it

does not explicitly state that the material for heat transfer is a "thermally conductive polymer," it states that polypropylene – a polymer – is a preferred material for the housing that conducts heat and that other plastics (polymers) are also acceptable. 11:66-12:3. Thus, it discloses that common plastics are suitable for enhancing heat transfer for test cartridges. It would have been obvious to modify the cartridge in Schubert such that a portion of the fluid path defined by the housing includes a thermally conductive polymer. The motivation for such modifications is provided in the '826 patent which teaches that it is advantageous to incubate the test sample in the same test cartridge in which the assay takes place, thereby reducing user handling and the potential for error. 1:23-28 and 5:37-44. Moreover, as it was well known in the art to heat a sample to 37 degrees Celsius (*in vivo* blood temperature) for coagulation type assays, including specifically for thromboelastometry/ thrombelastography type assays (such as in Schubert).[13]

[13] See, e.g., Delhaye, O.; Wavreille, G.; Tournoys, A.; Garrigue, D.; Tavernier, B., Temperature corrected thromboelastometry in hypothermic trauma patients: 6AP24. European Journal of Anaesthesiology, 2008 May/June, 25:84 ("Delhaye 2008") (Ex. 1024). See also, Douning, L.K., Ramsay, M.A.E., Swygert, T.H., Suit, C.T., Temperature Corrected Thrombelastography in Hypothermic Patients. Anesthesia & Analgesia, 1995 Oct.; 81(3):608 11 Douning 1995") (Ex. 1025). Furthermore, a

Thus, a POSA would have been motivated to utilize the teachings in the '826 patent, to provide improved, in-cartridge heating for the assays in Schubert. There is nothing in the '826 patent or Schubert that would teach away from their combination, and their combination would have predictable results. Dr. Mize's testimony corroborates the above (Mize Decl. (Ex. 1003) ¶¶ 148-152) and the absence of secondary factors that might show non-obviousness (*Id*. ¶¶ 109-112).

The claim chart provided below tabulates the teachings in the '826 patent that, in combination with the previously discussed teachings in Schubert, disclose and enable each and every limitation of claims 9-11 (including intervening and base claims 1, 6, 7 and 8) of the '971 patent:

| **'971 Patent Claims** | **References** |
|---|---|
| **1.** | Schubert teaches claim 1 (see Ground 1, claim 1) |
| **6.** [depends from 1] | Schubert teaches claim 6 (see Ground 1, claim 6) |
| **7.** [depends from 6] | Schubert teaches claim 7 (see Ground 1, claim 7) |
| **8.** [depends from 7] | Schubert teaches claim 8 (see Ground 1, claim 8) |
| **9.** The device of claim 8, wherein the housing defines at least a portion of the fluid | The '826 patent teaches both the use of housings and thermal transfer. **7:38-44.** Further, the '826 patent states **that** "[e]fficient thermal transfer to minimize incubation time is accomplished by making the bottom |

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 due to the complexity of interactions.

| '971 Patent Claims | References |
|---|---|
| pathway, and wherein at least a portion of the housing is thermally conductive. | surface of the sample holding chamber from a thin, highly thermal conductive material. **5:41-44**. |
| **10.** The device of claim 9, wherein the thermally conductive portion of the housing defines at least a portion of the fluid pathway. | The '826 patent teaches thermal transfer via a thermally conductive material defining part of the fluid path. In particular, the '826 patent teaches that the bottom surface of the sample holding chamber is formed from a thermal conductive material. **7**:**8-44**. |
| **11.** The device of claim 10, wherein the thermally conductive portion comprises a thermally conductive polymer. | The '826 patent states that the thermally conductive housing for the cartridge is preferably constructed from a plastic – a polymer – such as polypropylene (11:66-12:3), thus a thermally-conductive polymer. |

### E. Ground 5: Baugh in Combination with the '286 Patent and the '826 Patent Renders Obvious Claims 9-11.

Baugh (Ex.1005) in combination with the '826 patent (Ex. 1015) renders obvious claims 9-11, by disclosing each and every element of the claims, arranged as claimed in a manner enabling to a POSA. Baugh, summarized at Section V(D), teaches the base claims 1, 6, 7 and 8 to the multi-assay cartridge device (see Ground 3) but does not teach a thermally conductive polymer to facilitate heating of the sample along a fluid pathway as characterized in claims 9-11. As noted in Ground 4, the '826 patent, summarized at Section V(H), teaches such limitations in an analogous art and includes explicit motivations for integrating heating

elements/techniques disclosed therein into coagulation testing cartridges. This is simple application of a known technique to improve similar devices in the same way (with predictable results).

It would have been obvious to modify the cartridges in Baugh and the '826 patent such that a portion of the fluid path defined by the housing includes a thermally conductive material such as that disclosed in the '826 patent (which may be polypropyline or other plastic). The motivation for such modifications is provided in the '826 patent as explained in Ground 4 – reducing handling (avoiding errors) and testing at *in vivo* blood temperature.[14]

Thus, a POSA would have been motivated to utilize the teachings in the '826 patent, to provide improved, in cartridge heating. There is nothing in the '826

[14] Other references besides that '826 patent also teach the use of a thermally conductive polymer in the context of a fluid path of a coagulation testing cartridge. For example, "the '357 Publication" (Ex. 1022) teaches fabricating housing portions of a flow path in a coagulation testing device from a material "with good thermal conductivity." Again this may be a polymer as evidence by the '357 publication (Ex. 1022) further teaching that "as for the material of the microchannel it may be fabricated from any suitable microfabricated plastic such as polyester, polycarbonate, polystyrene or polyimide. Preferred polymers are polycarbonates."

patent, Baugh or the '286 patent that would teach away from their combination, and their combination would have predictable results. Dr. Mize's testimony corroborates the above (Mize Decl. (Ex. 1003) ¶¶ 154-157) and the absence of secondary factors that might show non-obviousness (*id*. ¶¶ 109-112).

The claim chart provided below tabulates the teachings in the '826 patent that, in combination with the previously discussed teachings in Baugh in combination with the teachings of the '286 patent, disclose and enable each and every limitation of claims 9-11 (including intervening and base claims 1, 6, 7 and 8) of the '971 patent:

| **'971 Patent Claims** | **References** |
|---|---|
| **1.** | Baugh teaches claim 1 (see Ground 3, claim 1) |
| **6.** [depends from 1] | Baugh teaches claim 6 (see Ground 3, claim 6) |
| **7.** [depends from 6] | Baugh teaches claim 7 (see Ground 3, claim 7) |
| **8.** [depends from 7] | The '286 patent teaches the additional elements of claim 8 (see Ground 2, claim 8) |
| **9.** [depends from 8] | The '826 patent teaches the additional elements of claim 9 (see Ground 4, claim 9) |
| **10.** [depends from 9] | The '826 patent teaches the additional elements of claim 10 (see Ground 4, claim 10) |
| **11.** [depends from 10] | The '826 patent teaches the additional elements of claim 11 (see Ground 4, claim 11) |

### F. Ground 6: Schubert in Combination with the '011 Patent Renders Obvious Claim 5.

Schubert (Ex.1006) in combination with the ‘011 patent (Ex. 1013) renders obvious claim 5, by disclosing each and every element of the claim, arranged as claimed in a manner enabling to a POSA. Schubert, summarized at Section V(A), teaches base claim 1 to the multi-assay cartridge device (see Ground 1) but does not teach that the reagents are lyophilized as recited in claim 5. The ‘011 patent, summarized at Section V(F), teaches such limitations in an analogous art. A POSA, as defined in Section IV(A)(2), would be motivated to combine these references, at least to provide improved reagent storage within the test channel/chamber. This is simple application of a known technique to improve similar devices in the same way (with predictable results).

It would have been obvious for a POSA to combine the teachings of the ‘011 patent with the previously discussed teachings of Schubert. In particular, the relevant teachings in the ‘011 patent (summarized in Section V (F)) provide improved reagent storage within a test channel/chamber via lyophilized reagents. A POSA would therefore have been motivated to include such improved reagent storage within the context of the test chambers in Schubert. The ‘011 patent involves a portable device for performing coagulation tests on a patient's blood. Thus, the ‘011 patent represents analogous art to Schubert. There is nothing in the ‘011 patent or Schubert that would teach away from their combination, as the cartridge structure of Schubert is consistent with the use of lyophilized reagents, and their combination would have

predictable results.[15] Dr. Mize's testimony corroborates the above (Mize Decl. (Ex. 1003) ¶¶ 159-162) and the absence of secondary factors that might show non-obviousness (*id*. ¶¶ 109-112).

The claim chart provided below tabulates the teachings in the '011 patent that, in combination with the previously discussed teachings in Schubert, disclose and enable each and every limitation of claim 5 (including base claim 1) of the '971 patent:

| **'971 Patent Claims** | **References** |
|---|---|
| **1.** | Schubert teaches claim 1 (see Ground 1, claim 1) |
| **5.** 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 in a multi-channel cartridge/chip. **Abstract** teaching a multiple-conduit portable device for performing coagulation tests on a patient's blood, where each of the conduits contains a dried or lyophilized activation reagent that is rehydrated by the blood. |

[15] Rahe-Meyer 2009 (Ex. 1021) corroborates the use of lyophilized reagents within the context of coagulation testing device. Rahe-Meyer 2009 analyzes the efficacy of lyophilized reagents in thromboelastometry (particularly in the context of INTEM, EXTEM and FIBTEM assays. Thus, Rahe-Meyer 2009 provides explicit motivation for using lyophilized reagents in the context of the specific assays disclosed in Schubert.

### G. Ground 7: Baugh in Combination with the '011 Patent Renders Obvious Claim 5.

Baugh (Ex.1005) in combination with the '011 Patent (Ex. 1013) renders obvious claim 5, by disclosing each and every element of the claim, arranged as claimed in a manner enabling to a POSA. Baugh, summarized at Section V(D), teaches base claim 1 to the multi-assay cartridge device (see Ground 3) but does not teach that the reagents are lyophilized as recited in claim 5. The '011 patent, summarized at Section V(F), teaches such limitations in an analogous art. A POSA, as defined in Section IV(A)(2), would be motivated to combine these references, at least to provide improved reagent storage within the test channel/chamber. This is simple application of a known technique to improve similar devices in the same way (with predictable results).

As explained in Ground 6, with the Baugh device substituted for the Schubert device, the '011 patent bridges this gap and provides specific motivation for the POSA to apply to the Baugh device the well-known advantages of lysophilization of pre-loaded reagents.

There is nothing in the '011 patent or Baugh that would teach away from the combination, as the cartridge structure of Baugh is consistent with the use of lyophilized reagents, and their combination would have predictable results. Dr. Mize's testimony corroborates the above (Mize Decl. (Ex. 1003) ¶¶ 164-167) and

the absence of secondary factors that might show non-obviousness (*id*. ¶¶ 109-112).

The claim chart provided below tabulates the teachings in the '011 patent that, in combination with the previously discussed teachings in Baugh, disclose and enable each and every limitation of claim 5 (including base claim 1) of the '971 patent:

| **'971 Patent Claims** | **References** |
|---|---|
| **1.** | Baugh teaches claim 1 (see Ground 3, claim 1) |
| **5.** [depends from 1] | The '011 patent teaches the additional elements of claim 5 (see Ground 6, claim 5) |

### H. Ground 8: Schubert in Combination with the '712 Patent Renders Obvious IPR Claim 14.

Schubert (Ex.1006) in combination with the '712 patent (Ex. 1007) renders obvious IPR claim 14, by disclosing each and every element of the claim, arranged as claimed in a manner enabling to a POSA. Schubert, summarized at Section V(A), teaches base claims 1, 6 and 7 to the multi-assay cartridge device (see Ground 1) but does not teach a magnetic stirring structure recited in claim 14. The '712 patent, summarized at Section V(I), teaches such limitations in an analogous art. A POSA, as defined in Section IV(A)(2), would be motivated to combine these references, at least to provide improved reagent mixing. This is simple application of a known technique to improve similar devices in the same way (with predictable results).

The '712 patent, summarized in Section V(I)), bridges this gap by teaching

the inclusion of magnetic mixing means in chambers for mixing the reagents with the sample in the context of a multi-chamber coagulation testing cartridge. Because the '712 patent teaching provides improved reagent mixing within a test chamber, a POSA would therefore have been motivated to include such improved reagent mixing within the context of the test chambers in Schubert, with predictable results. There is nothing in the '712 patent or Schubert that would teach away from the combination, and their combination would have predictable results. Dr. Mize's testimony corroborates the above (Mize Decl. (Ex. 1003) ¶¶ 168-171) and the absence of secondary factors that might show non-obviousness (*id*. ¶¶ 109-112).

The claim chart provided below tabulates the teachings in the '712 patent that, in combination with the previously discussed teachings in Schubert, disclose and enable each and every limitation of claim 14 (including intervening and base claims 1, 6 and 7) of the '971 patent:

| **'971 patent Claims** | **References** |
|---|---|
| **1.** | Schubert teaches claim 1 (see Ground 1, claim 1) |
| **6.** [depends from 1] | Schubert teaches claim 6 (see Ground 1, claim 6) |
| **7.** [depends from 6] | Schubert teaches claim 7 (see Ground 1, claim 7) |
| **14.** The device of claim 7, wherein one or more test chamber of the plurality of test chambers further | The '712 patent teaches the test chamber having a magnetic stirring structure. 11:**59-66** ("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 |

| '971 patent Claims | References |
|---|---|
| comprises a magnetic stirring structure. | 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"). |

## I. Ground 9: Baugh in Combination with the '712 Patent Renders Obvious Claim 14.

Baugh (Ex.1005) in combination with the '712 patent (Ex. 1007) renders obvious IPR claim 14, by disclosing each and every element of the claim, arranged as claimed in a manner enabling to a POSA. Baugh, summarized at Section V(D), teaches base claims 1, 6 and 7 to the multi-assay cartridge device (see Ground 3) but does not teach a magnetic stirring structure recited in claim 14. The '712 patent, summarized at Section V(I), teaches such limitations in an analogous art. A POSA, as defined in Section IV(A)(2), would be motivated to combine these references, at least to provide improved reagent mixing. This is simple application of a known technique to improve similar devices in the same way (with predictable results).

As explained in Ground 8, with the Baugh device substituted for the Schubert device, the '712 patent bridges this gap and provides specific motivation for the POSA to apply to the Baugh device the known advantages of magnetic in-chamber stirring.

There is nothing in the '712 patent or Baugh that would teach away from their combination, and their combination would have predictable results. Dr. Mize's

testimony corroborates the above (Mize Decl. (Ex. 1003) ¶¶ 173-175) and the absence of secondary factors that might show non-obviousness (*id*. ¶¶ 109-112).

The claim chart provided below tabulates the teachings in the '712 patent that, in combination with the previously discussed teachings in Baugh, disclose and enable each and every limitation of claim 14 (including intervening and base claims 1, 6 and 7) of the '971 patent:

| **'971 Patent Claims** | **References** |
|---|---|
| **1.** | Baugh teaches claim 1 (see Ground 3, claim 1) |
| **6.** [depends from 1] | Baugh teaches claim 6 (see Ground 3, claim 6) |
| **7.** [depends from 6] | Baugh teaches claim 7 (see Ground 3, claim 7) |
| **14.** [depends from 7] | The '712 patent teaches the additional elements of claim 14 (see Ground 8, claim 14) |

### J. Ground 10: Schubert in Combination with Viola 2009 Renders Obvious Claims 3, 4, and 17-20.

Schubert (Ex.1006) in combination with Viola 2009 (Ex. 1012) renders obvious IPR claims 3, 4 and 17-20, by disclosing each and every element of the claims, arranged as claimed in a manner enabling to a POSA. Schubert, summarized at Section V(A), teaches a device for multiple assays of hemostasis with particular reagents, which meets each of the elements of independent claim 1 (Ground 1), and as shown in the following claim chart, most of the elements of independent claim 17, but does not explicitly disclose the acoustic interrogation limitations of claims 3,

4 and 17-20 of the '971 patent. Viola 2009, summarized at Section V(E), teaches such limitations in an analogous art. A POSA, as defined in Section IV(A)(2), would be motivated to combine these references, at least since Viola 2009 teaches better sensitivity and measurement speed via acoustic interrogation. This is simple application of a known technique to improve similar devices in the same way (with predictable results).

Viola 2009, is a prior publication by the '971 patent inventors describing the type of acoustic interrogation device/technique described and claimed in the '971 patent. There was motivation for a POSA to combine the teachings of Viola 2009 of the use of acoustic interrogation of hemostasis function with the teachings of Schubert of a cartridge for multi-assay of hemostasis function. Schubert states that "[t]he present invention is not only suitable for thromboelastometry, thromboeleastography and platelet aggregometry but also for other blood tests usually performed regarding surgery." Schubert ¶ 84. Thus, Schubert explicitly contemplates and provides motivation for modifying the interrogation techniques described therein.

Viola 2009 teaches at Section 1 that its acoustic interrogation techniques described therein are an improvement over mechanical methods (such as described in Schubert:

> In contrast, mechanical methods, such as the Thromboelastogram (TEG) and SonoClot, measure the contribution of all the components

> of hemostasis in whole blood. These methods have been widely studied and shown to offer valuable clinical and scientific insights [17]. However, they utilize complex and expensive mechanical transducers, resulting in instruments that are difficult to operate. In addition, the large mechanical strains (in the range of 8% to 16%) applied to the blood samples have been shown to interfere with clot formation and limit sensitivity and speed of the measurements [18,19].

Thus, Viola 2009 provides motivation for a POSA to replace a mechanical interrogation device with an acoustic interrogation device.

Moreover, the acoustic technique in Viola 2009 provides a measurement of a response curve over time which is comparable to the data provided by the pin and cup technique described in Schubert (compare Fig. 1C to Fig. 6C in Schubert). Thus, replacing a mechanical interrogation device as disclosed in Schubert with an acoustic interrogation device as disclosed in Viola 2009 is a simple substitution of one known element for another to obtain predictable results. Viola 2009 is analogous art at least since it relates to thromboelastography. There is nothing in Viola 2009 or Schubert that would teach away from their combination, and their combination would have predictable results. Dr. Mize's testimony corroborates the above (Mize Decl. (Ex. 1003) ¶¶ 177-183) and the absence of secondary factors that might show non-obviousness (*id*. ¶¶ 109-112).

The claim chart provided below tabulates the teachings in Viola 2009 that, in combination with the previously discussed teachings in Schubert disclose and enable each and every limitation of claims 3, 4 and 17-20 (including base claim 1) of the

‘971 patent:

| **‘971 Patent claims** | **References** |
|---|---|
| **1.** | Schubert teaches claim 1 (see Ground 1, claim 1) |
| **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. **Section 2.1** entitled “Acoustic radiation force” teaches 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. *Also* **Section 2.3** (using a transducer to applying ultrasound pulses thereby inducing an acoustic radiation force). |
| **4.** The device of claim 1, wherein the interrogation device is configured to transmit sound into one or more test chamber. | Viola 2009 teaches an interrogation device for measuring a viscoelastic property of a sample that is configured to transmit sound into one or more test chambers. The sonorheometry instrumentation described in **Section 2.3** 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.” **Id.** |
| **17.** A system for evaluation of hemostasis comprising: | Schubert teaches this element (see Ground 1, claim 1, element 1) |
| **17A.** a plurality of test chambers | Schubert teaches this element (see Ground 1, claim 1, element 1A) |

| '971 Patent claims | References |
|---|---|
| **17Ai.** each configured to receive blood of a test sample, | Schubert teaches this element (see Ground 1, claim 1, element 1Ai) |
| **17Aii.** each test chamber comprising a reagent or combination of reagents; | Schubert teaches this element (see Ground 1, claim 1, element 1Aii) |
| **17B.** wherein a first chamber of the plurality comprises an *activator* of coagulation that *interact* with the blood received therein; | Schubert teaches this element (see Ground 1, claim 1, element 1B) |
| **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; | Schubert teaches this element (see Ground 1, claim 1, element 1C) |
| **17D.** wherein the first chamber is configured to be interrogated with ultrasound for a hemostatic parameter of the blood received therein to be determined;<br>**17E.** wherein the second chamber is | Viola 2009 is directed towards "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." **Abstract**. Viola 2009 further describes implementing sonorheometry in a prototype bench-top instrument. **Section 2.3**. Acoustic radiation force is induced by applying ultrasound pulses to samples in |

| '971 Patent claims | References |
|---|---|
| configured to be interrogated with ultrasound for a hemostatic parameter of the blood received therein to be determined· | cuvettes. The 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." **Id.** Viola 2009 further teaches determining a hemostatic parameter based on the ultrasonic interrogation of the cuvette. *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. *E.g.*, **Section 4**. |
| **17Gi.** at least one *processor* in communication with the transducer, | The bench-top prototype described in Viola 2009 includes a custom printed circuit board (PCB) controlled by an external laptop computer via USB 2.0 connection. **Section 2.6** |
| **17Gii.** the *processor* being configured to determine the *hemostatic parameters* from signals transmitted to the processor from the *transducer*. | Viola 2009 teaches use of a laptop to process the ultrasound data and calculate sonorheometry parameters (for example, clotting times TC1 and TC2) *See* **Section 2.6**. |
| **18.** The system of claim **17,** wherein the *hemostasis parameters* are selected from the group consisting of TC | Viola 2009 teaches calculating sonorheometry parameters including clotting times TC1 and TC2, clotting formation rate CFR and clot stiffness S. **Section 2.6**. |

| ‘971 Patent claims | References |
|---|---|
| 1, TC2, clot stiffness, clot formation rate (CFR), TL1, TL2, baselines viscosity, and post lysis viscosity. | |
| **19.** The system of claim **17,** wherein the processor is further configured to determine a *coagulation factors index*. | Viola 2009 teaches (**Section 2.6**) calculating sonorheometry parameters including clotting times TC1 and TC2 which are coagulation factors indexes according to the ‘971 patent. *E.g.*, **Table 3** of the ‘971 patent 18:40-50. Furthermore, a POSA would know that how to combine various measurements into useful indexes. (Mize Decl. (Ex. 1003) claim ¶ 184 claim chart, claim 19) |
| **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 using kaolin to start coagulation through activation of the intrinsic pathway. **Section 2.5**. Thus, the clotting time TC1 in Viola 2009 is an intrinsic coagulation factor index according to the ‘971 patent. *Compare* **Table 3** of the ‘971 patent 18:40-50. 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. (Mize Decl. (Ex. 1003) claim ¶ 184 claim chart, claim 20) |

### K. Ground 11: Baugh in Combination with Viola 2009 Renders Obvious Claims 3, 4, and 17-20.

Baugh (Ex.1005) in combination with Viola 2009 (Ex. 1012) renders obvious IPR claims 3, 4 and 17-20, by disclosing each and every element of the claims,

arranged as claimed in a manner enabling to a POSA. Baugh, summarized at Section V(D), teaches a device for multiple assays of hemostasis with particular reagents, which meets each of the elements of independent claim 1 (Ground 3), and as shown in the following claim chart, most of the elements of independent claim 17, but does not explicitly disclose the acoustic interrogation limitations of claims 3, 4 and 17-20 of the '971 patent. As explained in Ground 10, with the Baugh device[16] substituted for the Schubert device, Viola 2009 (summarized at Section V(E)) which is analogous art bridges this gap and provides specific motivation (better sensitivity and measurement speed) for the POSA to apply to the Baugh device the Viola 2009-published advantages of acoustic interrogation. This is simple application of a known technique to improve similar devices in the same way (with predictable results).

[16] Baugh explicitly states that:

> [M]any of the details of functionality will be generalized herein with the understanding that the assignee's prior patents and applications disclose many of these details to a greater extent. It is anticipated that similar results and effects as those obtained from using the assignee's plunger sensor technique will also be obtainable by practicing the present invention using other well-known methods and devices.

7:35-41. Thus, Baugh anticipates the assays and apparatus described therein being interrogated using known techniques other than the plunger sensor technique described in Baugh.

As argued above, Viola 2009 (discussed in Section V(E)) describes an early prototype of the same type of acoustic interrogation device used in the '971 patent. It would have been obvious for a POSA to combine the teachings of Viola 2009 relating to acoustic interrogation with the teachings of Baugh. In particular,

There is nothing in Viola 2009 or Baugh that would teach away from the combination, and their combination would have predictable results. Dr. Mize's testimony corroborates the above (Mize Decl. (Ex. 1003) ¶¶ 185-189) and the absence of secondary factors that might show non-obviousness (*id*. ¶¶ 109-112).

The claim chart below tabulates the teachings in Viola 2009 that, in combination with the previously discussed teachings in Baugh, disclose and enable each and every limitation of claims 3, 4 and 17-20 (including base claim 1) of the '971 patent:

| **'971 Patent Claims** | **References** |
|---|---|
| **1.** | Baugh teaches claim 1 (see Ground 3, claim 1) |
| **3.** [depends from 1] | Viola 2009 teaches the additional elements of claim 3 (see Ground 10, claim 3) |
| **4.** [depends from 3] | Viola 2009 teaches the additional elements of claim 4 (see Ground 10, claim 4) |
| **17.** A system for evaluation of hemostasis comprising: | Baugh teaches this element (see Ground 3, claim 1, element 1) |
| **17A.** a plurality of test chambers | Baugh teaches this element (see Ground 3, claim 1, element 1A) |

| '971 Patent Claims | References |
|---|---|
| **17Ai.** each configured to receive blood of a test sample, | Baugh teaches this element (see Ground 3, claim 1, element 1Ai) |
| **17Aii.** each test chamber comprising a reagent or combination of reagents; | Baugh teaches this element (see Ground 3, claim 1, element 1Aii) |
| **17B.** wherein a first chamber of the plurality comprises an *activator* of coagulation that *interact* with the blood received therein; | Baugh teaches this element (see Ground 3, claim 1, element 1B) |
| **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; | Baugh teaches this element (see Ground 3, claim 1, element 1C) |
| **17D.** wherein the first chamber is configured to be interrogated with ultrasound for a hemostatic parameter of the blood received therein to be determined;<br>**17E.** wherein the second chamber is | Viola 2009 teaches these elements (See Ground 10, claim 17) |

| ‘971 Patent Claims | References |
|---|---|
| configured to be interrogated with ultrasound for a hemostatic parameter of the blood received therein to be determined· | |
| **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 | Viola 2009 teaches this element (See Ground 10, claim 17) |
| **17Gi.** at least one *processor* in communication with the transducer, | Viola 2009 teaches this element (See Ground 10, claim 17) |
| **17Gii.** the *processor* being configured to determine the *hemostatic parameters* from signals transmitted to the processor from the *transducer*. | Viola 2009 teaches this element (See Ground 10, claim 17) |
| **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, | Viola 2009 teaches this element (See Ground 10, claim 18) |

| ‘971 Patent Claims | References |
|---|---|
| baselines viscosity, and post lysis viscosity. | |
| **19.** The system of claim **17,** wherein the processor is further configured to determine a *coagulation factors index*. | Viola 2009 teaches this element (See Ground 10, claim 19) |
| **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 this element (See Ground 10, claim 20) |

## VII. 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: November. 30, 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 (and accompanying exhibits), was served in its entirety on November 30, 2017, upon the following party via overnight courier:

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

**CERTIFICATE OF WORD COUNT UNDER 37 C.F.R. § 42.24(a)**

I, the undersigned, do hereby certify that the attached Petition, including footnotes, but not the cover page, exhibit list, table of contents, mandatory notices, and certifications, contains 13,982 words, as measured by the Word Count function of Microsoft Word. This is less than the limit of 14,000 words as specified by 37 C.F.R. § 42.24(a)(i).

/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. 9,272,280 (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 (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 (filed on January 4, 2001; 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 (Parent Case) |
| 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. 30, 2003; published June 19, 2003) |
| 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 Function of Whole Blood. Clin Chim Acta. 2010 Jan; 411(1-2): 106–113., (Also published online 2009 Oct 25, PubMed Central P.M.C.I.D. PMC2791922) |
| 1013 | Gavin, M. *et al*., "Portable test apparatus and associated method of performing a blood coagulation test," U.S. Patent No. 5,504,011 (filed Oct. 21 1994, issued April 2, 1996) |
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| 1015 | Ostgaard, R. *et al.*, "Combination reagent holding and test device," U.S. Patent No. 5,888,826 (filed Nov. 25, 1997, issued March 30, 1999) |
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