UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INSTRUMENTATION LABORATORY COMPANY

Petitioner

v.

HEMOSONICS LLC

Patent Owner

Post-Grant Review Case No. Unassigned

Patent 10,031,144

PETITION FOR POST-GRANT REVIEW OF U.S. PATENT NO. 10,031,144

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I. INTRODUCTION:

Instrumentation Laboratory Company ("Petitioner") requests post-grant review ("PGR") of claims 1-4, 9, 11-14, 16-21, 30, 39, 42, 50, 58, 61 and 63 (the "Challenged Claims") of U.S. Patent No. 10,031,144, issued July 24, 2018 ("the '144 patent") (Ex. 1001), which is assigned to HemoSonics LLC ("Patent Owner"; *see* Real/Frame No. 040856/0895). The '144 patent discloses a single-sample cartridge having multiple test chambers for evaluating hemostasis in a blood sample by a specific acoustic-echo interrogation technique. The specification of the '144 patent is identical to U.S. Patent Nos. 9,272,280, 9,410,971, 9,977,039 and 10,161,944.

The '144 patent claims priority from U.S. Provisional Application No. 61/443,088, which was filed on February 15, 2011 and is a pre-AIA[1] provisional application (Ex. 1004). However, the '144 patent issued from a "transitional" application and the Challenged Claims lack enablement and written description support by any pre-AIA disclosure (Section VII); consequently, the '144 patent is subject to PGR under AIA §§ 3(n)(1) and 6(f)(2)(A). *U.S. Endodontics, LLC v. Gold Standard Instruments, LLC*, Case PGR2015-00019, Paper No. 54, at 7–8 (PTAB Dec. 28, 2016). *Schul International Company LLC v. EMSEAL Joint Systems Ltd.*,

[1] Leahy-Smith America Invents Act, Pub. L. 112-29, 125 Stat. 284, Sept. 22, 2011.

Case PGR2017-00053, Paper No. 10 (PTAB April 9, 2018). *Inguran LLC v. Premium Genetics (UK) Ltd., Case PGR2015-00017*, Paper No. 8 (PTAB Dec. 22, 2015).

This Petition shows that, more likely than not, the Challenged Claims lack both enablement and written description support, as required by 35 U.S.C. § 112(a) (Ground 1), and are indefinite under 35 U.S.C. § 112(b) (Ground 2). The independent Challenged Claims 1, 20, 42 and 61 are based on functional limitations of "interrogation," "transducers" and "processors," untethered to any definite structure, to read on techniques for interrogation and data analysis that far exceed the scope of the '144 patent, which **only** discloses and enables a specific acoustic-echo technique. The "genus" claims 1, 20, 42 and 61 should not stand when at best only a "species" is disclosed. *LizardTech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1344 (Fed. Cir. 2005), held redundant and thus invalid a facially broader claim that was not supported by disclosure beyond the scope of a narrower claims. On that basis, Challenged Claims 1, 20, 42 and 61 fail under 35 U.S.C. § 112.

Furthermore, various dependent claims recite new matter, which has **no basis** in the specification, including (i) premixing of the sample and reagent(s) prior to the sample being introduced to the test chamber (claims 18, 30 and 50) and (ii) the transducer(s) comprising an LED emitter (claims 16, 39, 58 and 63), where the independent claims previously characterize such transducer(s) as being used for

evaluating hemostasis (*i.e.*, in the interrogation of the sample for determining a viscoelastic property or hemostatic parameters).[2]

This Petition also shows that the Challenged Claims (if not limited to the disclosed acoustic-echo technique), are anticipated (Ground 1) under 35 U.S.C. § 102 by Publication No. 2010/0154520 ("Schubert") (Ex. 1005) and, under 35 U.S.C. § 103, as obvious over Schubert in view of the State of the Art (SoA) for TEM / TEG (Ground 4). Even if limited to the disclosed acoustic-echo technique, the Challenged Claims are obvious over Schubert in view of the SoA for acoustic-echo based interrogation and data analysis. (Ground 5.)

These positions are supported by the Declaration of Dr. Frank LaDuca ("LaDuca Decl.") (Ex. 1002).

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 GMBH and Werfen USA, LLC, have interests represented by Petitioner.

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

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[2] The only disclosure of an LED emitter in the '144 patent is for optically monitoring chamber fluid levels (Ex. 1001, 6:40-45) and not for evaluating hemostasis.

All claims of related U.S. Patent No. 9,272,280 ("the '280 patent") were held unpatentable in *Instrumentation Laboratory Co. v. HemoSonics LLP*, IPR2017-00852, Paper No. 47 (PTAB Feb. 13, 2019) ("'852 FWD," Ex. 1028). Additionally, claims 1, 2, 6–8, 15, and 16 of related U.S. Patent No. 9,410,971 ("the '971 patent") were held unpatentable in *Instrumentation Laboratory Co. v. HemoSonics LLP*, IPR2017-00855, Paper No. 55 (PTAB Feb. 13, 2019) ("'971 FWD," Ex. 1029). Specifically, the '280 and '971 patent claims were held unpatentable as anticipated by Schubert.

The '144 patent issued from U.S. Patent Application No. 15/202,059, which is a "transitional" patent application filed on July 5, 2016. U.S. Patent Application No. 15/202,059 ('144 patent) is a continuation of U.S. Patent Application No. 15/003,325 ('971 patent), filed January 21, 2016, which is a continuation of U.S. Patent Application No. 13/397,398 ('280 patent), filed February 15, 2012. Additionally, U.S. Application No. 15/991,677 (now issued as U.S. Patent No. 10,161,944), filed May 29, 2018, is a continuation of U.S. Patent Application No. 15/904,984 (pending), filed February 26, 2018, which is a continuation of U.S. Application No. 15/644,124 (now issued as U.S. Patent No. 9,977,039; currently petitioned for Post Grant Review under PGR2019-00033), filed July 7, 2017, which is a continuation of U.S. Patent Application No. 15/202,059 ('144 patent). Each of these patents, all owned by Patent Owner, claim combinations of features disclosed

in their common specification; therefore, they all may be affected by the requested review. Petitioner's U.S. Patent No. 9,915,671, based on the same disclosure as Schubert, but with claims copied in part from those of Patent Owner, is being reviewed in IPR2018-00950.

C. Lead and Back Up Counsel Under 37 C.F.R. § 42.8(b)(3):

Pursuant to 37 C.F.R. § 42.8(b)(3), lead counsel for this Petition is Stephen Y. Chow (Reg. No. 31,338) and back-up counsel are Gabriel Goldman (Reg. No. 61,343) and Richard Emmons (Reg. No. 68,216). Pursuant to 37 C.F.R. § 42.10(b), Petitioner has filed a power of attorney designating the above-identified counsel.

D. Service Information Under 37 C.F.R. § 42.8(b)(4):

Pursuant to 37 C.F.R. § 42.8(b)(4) service information for the Petition is as follows:

Lead Counsel	Back-Up Counsel
Stephen Y. Chow (Reg. No. 31,338) Hsuanyeh Law Group, PC 11 Beacon Street Boston, MA 02108 Telephone: (617) 886-9288 Fax: (617) 886-9188 Email: stephen.y.chow@hsuanyeh.com	Gabriel Goldman (Reg. No. 61,343) Richard Emmons (Reg. No. 68,216) Burns & Levinson LLP 125 Summer Street Boston, MA 02110 Telephone: (617) 345-3304, -3534 Fax: (617) 345-3299 Email: ggoldman@burnslev.com; rmoore@burnslev.com

Petitioner consents to electronic service at the above-identified email addresses.

III. ADDITIONAL REQUIREMENTS:

A. Payment of Fees Under 37 C.F.R. § 42.15:

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).

B. Timing Under 37 C.F.R. § 42.202:

The present petition for post-grant review is filed within nine months of July 24, 2018, the issue date of the '144 patent.

C. Grounds for Standing Under 37 C.F.R. § 42.204(a):

Petitioner certifies that: (1) the '144 patent is eligible for post-grant review; and (2) Petitioner is not barred or estopped from requesting post-grant review of any claims of the '144 patent on the grounds identified herein.

IV. THE '144 PATENT:

A. Specification of the '144 Patent:

The specification of the '144 patent is directed to "devices, systems and methods for evaluation of hemostasis" as well as "sound focusing assemblies" (Ex. 1001, Title and Abstract). The '144 patent discloses a cartridge device (100) and analysis system (300) for use in evaluation of hemostasis (2:14-15; 2:43-56; 4:18-19; 13:27-14:3, 18:24-19:10; Tables 2 and 3). LaDuca Decl. ¶ 67.

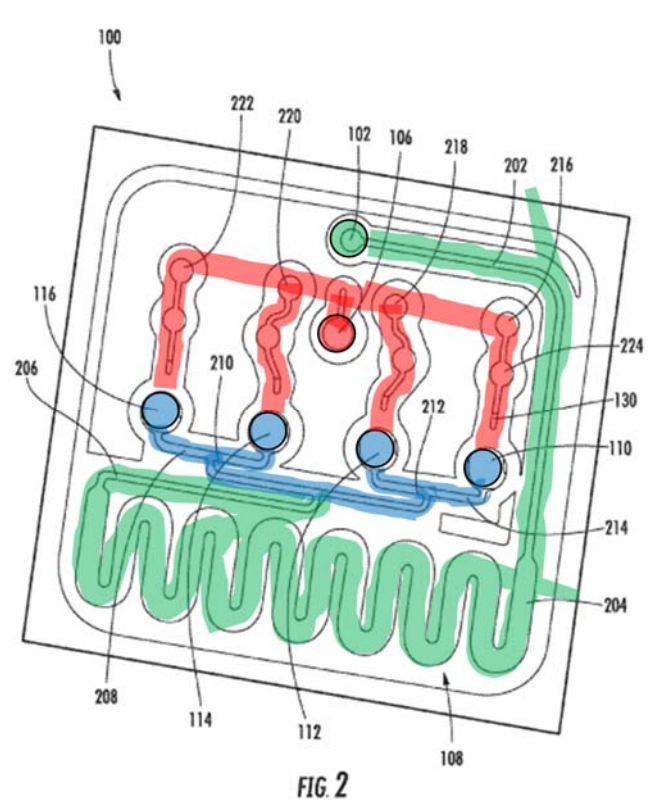
Referring to FIGS. 1A-G, 2-5, 8A-8D and 10B (including annotated FIG. 2, below) of the '144 patent, the cartridge device (100) includes a plurality of test chambers (110, 112, 114, 116) that include a reagent or combination of reagents (Ex. 1001, 2:17-21; 2:37-42, 5:58-63; Table 1) that may be lyophilized (8:47-59). Table 1 provides reagents that can be used in the test wells. LaDuca Decl. ¶ 68.

Test Well 1	Test Well 2	Test Well 3	Test Well 4
0.15 mg of kaolin buffers and stabilizers 0 µl of 2 mg/ml abciximab	0.15 mg of kaolin buffers and stabilizers 12 µl of 2 mg/ml abciximab	0.3 U of thrombin buffers and stabilizers 12 µl of 2 mg/ml abciximab	recombinant tissue factor buffers and stabilizers 0 µl of 2 mg/ml abciximab

Table 1 of the '144 Patent

Test Well 1 includes an intrinsic activator (kaolin), Test Well 2 includes an intrinsic activator (again kaolin) plus abciximab (which is a platelet inhibitor), Test Well 3 includes thrombin plus abciximab and Test Well 4 includes an extrinsic activator (recombinant tissue factor). LaDuca Decl. ¶ 69.

The cartridge device (100) includes a fluid pathway including a plurality of channels (202, 204, 206, 208, 210, 212, 214) for distributing a blood sample from an inlet 102 to the plurality of test chambers (Ex. 1001, 4:18-48). LaDuca Decl. ¶ 70.



Annotated Figure 2 of the '144 patent

The cartridge device (100) is designed to be used in a system comprising a transducer (unidentified part of ultrasonic generating means 502, FIG. 5) that transmits ultrasound into one or more chamber(s) and receives reflected sound from the chamber(s) and the test sample therein (Ex. 1001, 2:43-46, 13:27-35). Cartridge

device (100) is adapted to be positioned into a pocket (302) of an analysis system (300) to enable acoustic coupling with the test chambers (12:17-25 and 13:29-45). Each test chamber in the cartridge includes a sound focusing assembly 131 (also referred to in the '144 patent as a lens assembly or lens) that provides dry ultrasonic coupling both for acoustically exciting the sample and receiving a responsive echo as in SONAR (17:52-53), rigid substrate (132) and couplant (134) in FIGS. 1D and 1F (11:42-12:6). LaDuca Decl. ¶ 71.

The analysis system (300) and cartridge device (100), as described, are specifically designed for acoustic-echo interrogation using an ultrasonic transducer (Ex. 1001, 2:27-29; 2:35-38; 2:43-46; 2:60-65; 12:7-10; 13:19-26, 13:32-45, 15:40-43). The structure of the ultrasonic transducer is not described, but only referred to as part of an "[u]ltrasonic generating means 502" pointed at generally in Fig. 5. (13:31-32.) The system is described to include at least one processor for determining a hemostasis parameter from the received sound (2:46-48). In particular, an ensemble of acoustic pulses is transmitted into a blood sample and the returning echoes are detected and used for time delay estimation (TDE) – an algorithm used in "RADAR, SONAR and medical ultrasound imaging (Doppler)" (17:53-54) – to estimate time-displacement curves for the samples in each test chamber throughout the process of coagulation and fibrinolysis (FIG. 6B; 17:40-50). The time-displacement curves are used to produce a "relative stiffness" versus time curve

using a "modified Voigt-Kelvin model" (of a dashpot and spring representing contributions of the viscous and elastic properties of the viscoelastic subject) and "various parameters relating to the viscoelastic properties of the sample" (including "relative elasticity, relative viscosity, time constant, and maximum displacement"). LaDuca Decl. ¶ 72.

"[Hemostatic] parameters[3]" (Table 2) are generated for each test chamber by analyzing the "relative stiffness" versus time curve. By generating hemostatic parameters for the specific combination of tests in Table 1, "indices" (Table 3) relating to specific aspects of hemostasis (*i.e.*, intrinsic pathway, extrinsic pathway, platelets, fibrinogen and fibrinolysis) are assigned. LaDuca Decl. ¶ 73.

[3] There is no definition for "hemostatic parameter" in the '144 patent, and Table 2 is not so labeled. It is assumed that the parameters mentioned here may be "hemostatic parameters." Nor are "viscoelastic properties" defined, only that they may be "modeled" using the Voigt-Kelvin model (18:56-59).

Parameter	Information provided	Dependent upon
TC_1, TC_2	Measure initial and final fibrin formation	Function of fibrinogen and other coagulation factors
S	Fibrin and platelet activity	Function of fibrin network and platelet aggregation
CFR	Rate of fibrin polymerization	Function of fibrinogen and other coagulation factors
TL_1, TL_2	Clot dissolving process	Function of fibrinolytic proteins of the plasma

Table 2, of the '144 Patent

Output	Method
Coagulation factors Index (Intrinsic Pathway)	Time to clot TC_1 in well #1
Coagulation factors Index (Extrinsic Pathway)	Time to clot TC_1 in well #4
Platelets Index	Stiffness S differential between well #1 and well #2
Fibrinogen Index	Stiffness S in well #3
Fibrinolysis Index	Time to lysis TL_1 in well #4

Table 3, of the '144 Patent

The description of the derivation of the "[hemostatic] parameters" of Table 2 and thus the assigned "indices" of Table 3 is somewhat confused. The description states, "[i]ndices of hemostasis are calculated by fitting a sigmoidal curve to the stiffness-time curve (FIG. 6C) and evaluating the first derivative of the curve" (Ex. 1001, 18:30-32). TC1 and TC2 indicate the beginning and ending phases of fibrin formation, and are "calculated" based on a threshold value (20% of the minimum

value) of the derivative curve. 32-36). No explanation is provided for this threshold value choice. A "clotting slope CFR" indicative of the rate of polymerization is calculated as the maximum of derivative curve (18:36-38). A stiffness parameter S that "depends [in an unstated way] upon platelet function and the final stiffness of the fibrin network" is "estimated" 3 minutes after TC2 (18:39-41). "Identical methods and indices are calculated for the fibrinolytic process" (18:41-43 [emphasis added]). For example, "TL1 and TL2 can be defined to represent the initial and final phases of the fibrinolytic process." (8:42-44 [emphasis added].) These values appear as "parameters" in Table 2 and the "indices" in Table 3 appear to be derived from the parameters determined for the specific combination of tests in Table 1. LaDuca Decl. ¶ 74.

The '144 patent teaches that the processing of the disclosed methods, devices and systems can be performed by software components and that program modules can be used, for example, to cause the transmission of ultrasound having desired transmit parameters and to receive and process ultrasound to evaluate hemostasis indices of a sample from the subject (Ex. 1001, 13:46-14:3). A flow chart of analysis steps performed by the system is described with respect to FIG. 7 (17:20-38). Important components (*e.g.*, Time Delay Estimation step 708 and curve-fitting step 710) are expressly drawn from the prior art. It is stated that "TDE is a common signal processing step in application fields ranging from RADAR, SONAR and medical

ultrasound imaging (Doppler)" and that "[a] variety of 'off-the-shelf' algorithms are available to perform this operation" (17:50-53). In the disclosed interrogation and processing, "[t]he viscoelastic properties of the blood sample during hemostasis is modeled using a modified model of the well-known Voigt-Kelvin mechanical model" (17:56-58 [emphasis added]) also "well validated in the past" (17:61-62). "Each time-displacement curve is fitted to the modified Voigt-Kelvin model to estimate a variety of parameters relating to the viscoelastic properties of the sample" (17:63-66). Other components such as calculating derivatives are common-place algorithms. Processor/instruction components for "directing" operations, interfacing with sub-system devices are "routine and conventional" and dependent on the particular devices. LaDuca Decl. ¶ 75.

The '144 patent only discloses and enables using an acoustic-echo technique for interrogation and data analysis and is completely silent with respect to any non-acoustic-echo techniques. LaDuca Decl. ¶ 76.

B. Challenged Claims of the '144 Patent:

The '144 Patent includes 63 total claims, including independent claims 1, 20, 42 and 61. Claim 1 is an apparatus claim while claims 20, 40 and 61 are system claims. Elements of claims 1, 20, 40 and 61 are specified in Tables A and B below:

Table A: Elements of Apparatus Claim 1

Element	Claim 1
1.1	An apparatus for evaluation of hemostasis, comprising (Ex. 1001, 19:23)
1.2	a housing that is configured to couple to a system, (19:24)
1.3	wherein the system comprises one or more transducers for each of a plurality of test chambers, (19:24-26)
1.4	wherein the system comprises at least one processor and memory having instructions stored thereon, wherein the instructions when executed by the at least one processor cause the at least one processor to direct the one or more transducers associated with each of the plurality of test chambers in the interrogation of the test sample to determine at least one viscoelastic property of the test sample; (19:26-34)
1.5	the plurality of test chambers, including a first test chamber, a second test chamber, and a third test chamber, that are each at least partially defined by the housing; and (19:35-38)
1.6	a fluid pathway having an inlet, defined by the housing, and from which an external vessel establishes fluid communication, to receive a test sample, wherein the fluid pathway is in fluid communication with the first test chamber, the second test chamber, and the third test chamber to deliver the test sample, or a portion thereof, to the first test chamber, the second test chamber, and the third test chamber, (19:39-46)
1.7	wherein each of the plurality of test chambers comprises a reagent or combination of reagents, and (19:47-48)
1.8	wherein each of the plurality of test chambers, including the first, second, and third test chambers, is configured to receive, via the fluid pathway, blood of a test sample to be interrogated to determine a plurality of hemostatic parameters; (19:48-53)

Element	Claim 1
1.9	wherein the first test chamber comprises 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 configured to activate coagulation via extrinsic or intrinsic pathway; (19:54-59)
1.10	wherein the second test chamber comprises a second combination of reagents that interact with blood of the test sample received therein, wherein the second combination of reagents includes i) a reagent, or a combination of reagents, configured to activate coagulation via the extrinsic or intrinsic pathway and ii) a reagent, or a combination of reagents, configured to inhibit platelet contraction; and (19:60-67)
1.11	wherein the third test chambers comprises a third reagent or a third combination of reagents that interact with the blood received therein, wherein the third reagent, or a reagent included in the third combination of reagents, is configured to activate coagulation via the extrinsic or intrinsic pathway. (20:1-6)

Table B: Elements of System Claims 20, 42 and 61:

Element	Claim 20	Claim 42	Claim 61
2.1	A system for evaluation of hemostasis comprising: (Ex. 1001, 21:14)	Same as claim 20 (23:5)	Same as claim 20 (24:52)
2.2	a plurality of test chambers, including a first test chamber and a second test chamber, (21:15-16)	Same as claim 20 (23: 6-7)	Same as claim 20 (24:53-54)

Element	Claim 20	Claim 42	Claim 61
2.3	wherein each of the plurality of test chambers comprises a reagent or combination of reagents, and (21:16-18)	Same as claim 20 (23:7-9)	Same as claim 20 (24:54-56)
2.4	wherein each of the plurality of test chambers is configured to receive blood of a test sample and to be interrogated to determine a hemostatic parameter of the blood received therein; (21:18-21)	Same as claim 20 (23:9-13)	Same as claim 20 (24:56-59)
2.5	one or more transducers for transmitting energy into one or more test chamber and for receiving reflected energy from the chamber and the sample therein; (21:22-24)	Same as claim 20 (23:14-26)	Same as claim 20 (24:60-62)

Element	Claim 20	Claim 42	Claim 61
2.6	at least one processor in communication with the one or more transducers, wherein the processor is configured to determine the hemostatic parameters from signals transmitted to the processor from the one or more transducers; and (21:25-29)	Same as claim 20 (23:17-21)	Same as claim 20 (24:63-67)
2.7	a memory having instructions stored thereon, wherein the instructions when executed by the at least one processor, cause the at least one processor to perform at least three measurements in parallel; (21:30-34)	a memory having instructions stored thereon, wherein execution of the instructions by the at least one processor cause the at least one processor to determine the hemostatic parameters in parallel; (23:22-25)	a memory having instructions stored thereon, wherein the instructions when executed by the at least one processor, cause the at least one processor to determine a curve associated with a viscoelastic property of the blood of each test sample, the curve being generated from the interrogation as a function of time; (25:1-6)

Element	Claim 20	Claim 42	Claim 61
2.8	wherein the first test chamber comprises a first reagent or a first combination of reagents that interact with the blood of the test sample received therein, wherein the first reagent, or at least one reagent included in the first combination of reagents, is an activator of coagulation; and (21:34-39)	Same as claim 20 (23:26-30)	Same as claim 20 (25:7-12)
2.9	wherein the second test chamber comprises a second combination of reagents that interact with blood of the test sample received therein, the second combination of reagents including an activator of coagulation and a reagent, or a combination of reagents, configured to cause a reduction in measurable changes in clot mechanical properties of the test sample when the test sample is interrogated by the one or more transducers. (21:40-47)	wherein the second chamber comprises a second combination of reagents that interact with blood of the test sample received therein, the second combination of reagents including an activator of coagulation and a reagent, or a combination of reagents, configured to inhibit platelet functions. (23:31-36)	wherein the second test chamber comprises a second combination of reagents that interact with blood of the test sample received therein, the second combination of reagents including an activator of coagulation and a reagent, or a combination of reagents, configured to cause a reduction in measurable changes in clot mechanical properties of the test sample when the test sample is interrogated by the one or more transducers. (25:13-20)

Using claim 1 as representative, an apparatus for evaluation of hemostasis is recited [1.1] with a housing to couple to a system [1.2] that includes one or more **transducers** for each of a plurality of test chambers [1.3] where **processor executable instructions** stored in memory cause a **processor to direct the transducer(s) to interrogate** the test sample "**to determine** one or more **viscoelastic properties**" [1.4].

At least first, second, and third test chambers are defined by the housing [1.5] wherein each chamber:

- is in fluid communication with a [single] fluid pathway that receives a [single] test sample via an inlet [1.6]
- receives the blood to be interrogated to determine a plurality of hemostatic parameters [1.8]
- includes a reagent or combination of reagents [1.7] according to the following Table 1:

Table 1: Reagent(s) in the Test Chambers of Apparatus Claim 1:

Test Chamber	**Reagents**
First Test Chamber [1.9]	reagent(s) activate coagulation
Second Test Chamber [1.10]	reagent(s) activate coagulation ***AND*** inhibit platelet contraction
Third Test Chamber [1.11]	reagent(s) activate coagulation

Summarizing system claims 20, 42 and 61 (in comparison to apparatus claim 1), each claim recites a system for evaluating hemostasis [2.1] (claim 1 recites an apparatus instead of a system [1.5]) where the system includes:

- a plurality of test chambers including first and second chambers [2.2] (claim 1 requires three chambers [1.5]) where each test chamber includes reagent(s) [2.3] (comparable to claim 1 [1.7]) and is configured to receive blood and to be interrogated to determine a hemostatic parameter [2.4] (comparable to claim 1 [1.8]).
- **transducer**(s) for "**transmitting energy** into one or more test chamber[s]" and "**receiving reflected energy** from the chamber and the sample therein" [2.5] (claim 1 requires transducers for each chamber but does not require transmitting energy and receiving reflected energy [1.3])
- a **processor configured to determine the hemostatic parameters from the transducer signals** [2.6] (claim 1 requires processor executable instructions for directing the transducer(s) to interrogate the test sample "to determine one or more viscoelastic properties" [1.4])

- **processor executable instructions** in memory [2.7] for implementing functions according to the following Table 2 (claim 1 does not include this element:

Table 2: Processor Executable Instructions of the System Claims:

Limitation	Claim 20	Claim 42	Claim 61
Processor Executable Instruction to:	perform at least three measurements in parallel	determine the hemostatic parameters in parallel;	determine a curve associated with a viscoelastic property of the blood as a function of time

- where the first and second test chambers include reagent(s) according to the following Table 3 (similar to claim 1 [1.9] and [1.10]):

Table 3: Reagent(s) in the Test Chambers of the System Claims:

	Claim 20	Claim 42	Claim 61
First Test Chamber	Reagent(s) activate coagulation	Reagent(s) activate coagulation	Reagent(s) activate coagulation
Second Test Chamber	Reagent(s) activate coagulation ***AND***	Reagent(s) activate coagulation ***AND***	Reagent(s) activate coagulation ***AND***
	Reagent(s) cause a reduction in measurable changes in clot mechanical properties	Reagent(s) inhibit platelet functions	Reagent(s) cause a reduction in measurable changes in clot mechanical properties

Claims 20, 42 and 61 do not require a cartridge-defining housing or a fluid pathway for sample distribution as does claim 1 [1.2], [1.6] and [1.8]. The '144

patent includes dependent claims directed to interrogation based on changes in clot mechanical properties (claim 2), lyophilized beads as reagents (claims 3), the housing forming a cartridge (claim 4), the test chambers being part of a disposable cartridge (claim 9), specific reagents (claims 11 and 12), assessing specific sets of components of hemostasis (claims 13 and 14), the one or more transducers comprising an LED and detector ("LED" claims 16, 39, 58 and 63), use of agonists and antagonists and parallel testing (claim 17), mixing of the reagent and sample upstream from the test chambers ("premixing" claims 18, 30 and 50), inducing displacement of the sample (claim 19), reduced measurable changes in clot mechanical properties caused by a reagent comprising reduced measurable changes in one or more viscoelastic properties (claim 21).

C. Prosecution History of the '144 Patent:

The provisional application upon which priority is claimed provided a set of claims that recited a cartridge with multiple test chambers, where the chambers "are configured to determine a hemostatic parameter of the test samples" (claims 1 and 2, Provisional Application 61/443,008 (Ex. 1004) at 9, also originally filed claims 1 and 2 of Application 15/202,059,'144 file history (Ex. 1003) at 617):

> "wherein the interrogation comprises measurement of at least one viscoelastic property of the test sample" (Claim 3, *id.*)
>
> "wherein the interrogation comprises use of an acoustic radiation force" (Claim 4, *id.*)

"A system comprising the device of claims 1-6, and further comprising:

> "a. a transducer for transmitting ultrasound into one or more chamber and for receiving reflected sound from the chamber and the test sample therein; and
>
> "b. at least one processor configured to determine a hemostasis parameter from the received sound." (Claim 7, Provisional (Ex. 1004) at 10, filed claim 20, '144 file history (Ex. 1003) at 619 [emphasis added])

The applicant entered a preliminary amendment that modified the base configuration of test chambers from "to determine a hemostatic parameter" to "to be interrogated to determine a hemostatic parameter" (claims 1, 13, and 18, Ex. 1003 at 628, 630, and 631) with the recitation of the transducer and processor in two systems claims, generalizing the transducer:

> "a transducer for transmitting energy into one or more test chamber and for receiving reflected energy from the chamber and the sample therein; and
>
> "at least one processor in communication with the transducer, the processor being configured to determine the hemostatic parameters from signals transmitted to the processor from the transducer;" (Amended claims 13 and 18, Ex. 1003 at 630 and 631 [emphasis added])

Applicant represented that "No new matter has been added." (*Id.* at 633.) This context for "transducer" was maintained in claims 86 (*id*. at 209), 91 (*id*. at 211) and 137 (*id*. at 220), ultimately issued as claims 20, 42 and 61, with additional recitations of processor-executable instructions set forth in Table 2 below. Apparatus claim 74, ultimately issued as claim 1, recited "transducers" for each chamber and "memory having instructions [to] cause the at least one processor to direct the one or more transducers . . . to determine at least one viscoelastic property of the test sample." (*Id.* at 305.)

Thus, the "transducers" were generalized from the originally claimed (and disclosed) transducers "transmitting ultrasound" to transducers "for transmitting energy" in the independent system claims 86, 91 and 137 and to merely being "direct[ed by processor-executable instructions] in the interrogation of the test sample to determine at least one viscoelastic property" in independent apparatus claim 1.

V. 37 C.F.R. § 42.204(b)(1)-(2): IDENTIFICATION OF THE CHALLENGE:

A. Statement of Requested Relief:

Pursuant to 37 C.F.R. § 42.204(b), Petitioner respectfully requests post-grant review and cancellation of the Challenged Claims (claims 1-4, 9, 11-14, 16-21, 30, 39, 42, 50, 58, 61 and 63) of the '144 patent under 35 U.S.C. §§ 321-328 and 37 C.F.R. §§ 42.200-42.224.

This request for relief is based on challenges to the claims on the bases of lack of written description/enablement under 35 U.S.C. § 112(a) (**Ground 1**) and indefiniteness under 35 U.S.C. § 112(b) (**Ground** 2) primarily because the core limitations relating to interrogation and data analysis (including "transducers" and "processors/instructions") were improperly generalized (as seen in Section IV(C)) from the only disclosed acoustic-echo method of interrogation and data analysis. The Challenged Claims are also anticipated by Schubert (Ex. 1005) (**Ground 3**) or obvious over Schubert

(i) In view of the SoA for TEM / TEG **(Ground 4)**, as evidenced by:

- U.S. Patent No. 5,777,215 ("Calatzis") (Ex. 1006);
- Ganter, MT and Hofer, CK, Coagulation monitoring: current techniques and clinical use of viscoelastic point-of-care coagulation devices, Anesth Analg. 2008 May;106(5):1366-75 (PMID: 18420846) ("Ganter") (Ex. 1007);
- Hanecke, P and Klouche, M, Thrombelastography Today: Practicability and Analytical Power, Transfusion Medicine and Hemotherapy. 34. 421-428 (2007) ("Hanecke") (Ex. 1008);
- The 510(k) Summary for ROTEM *delta*, FDA clearance No. K083842 ("the 510(k) Summary for ROTEM *delta*") (Ex. 1009);

- The 510(k) Substantial Equivalence Determination Decision Summary for ROTEM *delta*, FDA clearance No. K083842 (the "Decision Summary for ROTEM *delta*") (Ex. 1010);
- User Manual (2007) for TEG 5000 Thrombelastograph Hemostasis System with TEG Analytical Software (TAS) Version 4.2.3 including an addendum (2008) for TEG Analytical Software (TAS) Version 4.3 (the "TEG 5000 User Manual") (Ex. 1011); and
- U.S. Patent No. 6,537,819 ("Cohen") (Ex. 1012);

Or (ii) in view of the SoA for acoustic-echo based interrogation and data analysis **(Ground 5)**, as evidenced by the following prior publication by the inventors of the '144 patent:

- 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., published online 2009 Oct 25, PubMed Central P.M.C.I.D. PMC2791922 ("Viola 2009") (Ex. 1013).

In view of the accompanying prior art references and supporting declaration of Dr. Frank LaDuca (Ex. 1002), Petitioner respectfully requests cancellation of the

Challenged Claims as summarized in the following table (where each of the grounds is applicable to all of the Challenged Claims).

Grounds	**Exhibits**
Ground 1: Failure to meet the written description requirement and lack of enablement under 35 U.S.C. § 112(a)	1001, 1002, 1003
Ground 2: Indefinite under 35 U.S.C. § 112(b)	1001, 1002, 1003
Ground 3: Anticipated by Schubert under 35 U.S.C. § 102	1001, 1002, 1005
Ground 4: Obvious over Schubert in view of the SoA on TEM/TEG under 35 U.S.C. § 103	1001, 1002, 1005, 1006, 1007, 1008, 1009, 1010, 1011, 1012, 1014
Ground 5: Obvious over Schubert in view of the SoA for acoustic-echo based interrogation and data analysis under 35 U.S.C. § 103	1001, 1002, 1005, 1013

B. Person of Ordinary Skill in the Art ("POSA"):

The relevant art of the claimed subject matter of the '144 Patent involves at least POC diagnostic devices and systems for evaluating hemostasis. LaDuca Decl.

¶ 93. A POSA would have a bachelor degree in a relevant science discipline (such as biology, chemistry, natural sciences, engineering or a biomedical engineering discipline) and at least four years of practical experience designing or creating devices/systems for evaluating hemostasis. This characterization of a POSA is supported by the panel's determination of a POSA in the final written decisions for IPR2018-00852 and IPR2018-00855. LaDuca Decl. ¶ 95

In the context of the '144 patent, the applicable POSA standard (as of the February 15, 2011 priority date for the '144 patent) would encompass multiple aspects of system/device development and must account for the knowledge of person(s) of ordinary skill in POC diagnostics in the context of hemostasis. With respect to computer-implemented aspect of the claims, a POSA would be able to define the system requirements for the software elements that are integrated in appropriately programmed computer processors (including memory with executable instructions). A POSA need not have specific skills in software programming, commonly referred to as code writing. LaDuca Decl. ¶ 94

C. Background on the State of the Art:

1. Hemostasis:

An overview of hemostasis is provided in the Declaration of Dr. Frank LaDuca, including discussion of intrinsic and extrinsic pathways (LaDuca Decl.

¶¶ 23-25), thrombin (LaDuca Decl. ¶ 26), platelets (LaDuca Decl. ¶¶ 27-30) and fibrinolysis (LaDuca Decl. ¶¶ 31-33).

2. Hemostatic Testing:

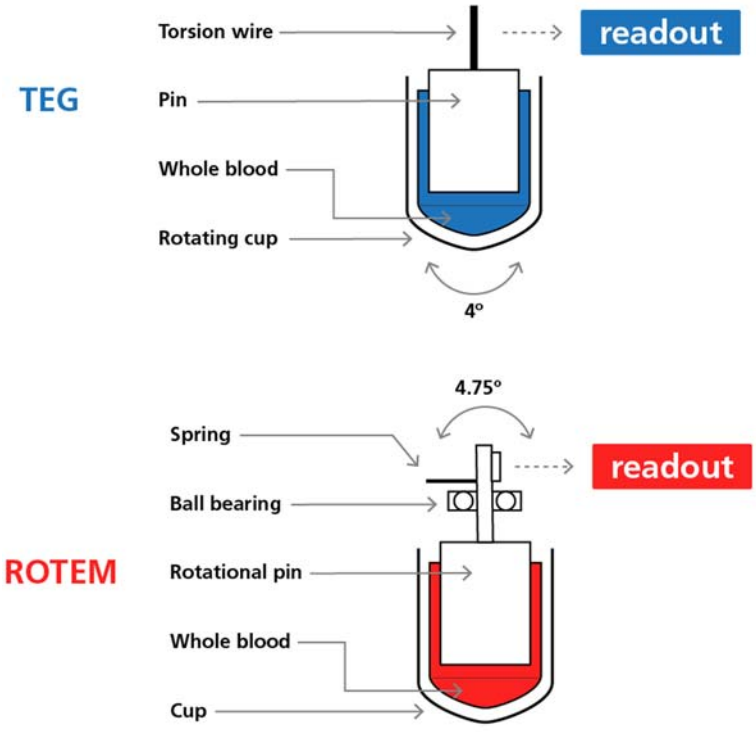
a. Basic Coagulation Tests and Parallel Testing:

Basic coagulation tests included tests for intrinsic and extrinsic activation. LaDuca Decl. ¶ 35-37. These tests expanded to dose-response and titration testing which required conducting multiple tests with different reagents in each test. Dose-response and titration testing demonstrated the importance of being able to conduct multiple test in parallel and were an early driving force in the development of multi-chamber cartridge-based systems for coagulation testing. LaDuca Decl. ¶ 38-32. For example, U.S. Patent No. 6,221,672 ("Baugh") (Ex. 1015) provides an example of dose-response testing for a platelet inhibitor using a cartridge-based system with a plurality of test chambers where each test chamber includes an activator of coagulation and at least two of the test chambers include different amounts of a platelet inactivating agent. LaDuca Decl. ¶ 41.

b. TEM and TEG:

Coagulation time has typically been measured through an increase in blood viscosity. LaDuca Decl. ¶ 43. During later stages of coagulation, however, viscosity may become difficult to measure and other measures (such as clot firmness) become better indicators of changing viscoelastic properties of the sample. LaDuca Decl.

¶ 45. Schubert characterizes "viscoelastic methods" as methods where clot firmness is continuously determined from the formation of the first fibrin fibers until the dissolution of the blood clot by fibrinolysis (Ex. 2005, 2:8-27). LaDuca Decl. ¶ 46. Thromboelastography (TEG) and throboelastometry (TEM) (also known as ROTEM) are example implementations of viscoelastic methods. Both TEG and TEM measure clot firmness using force-response testing. LaDuca Decl. ¶ 47.



In TEG, a cup containing a sample is rotationally oscillated. As the sample coagulates, fibrin creates an elastic linkage between the surfaces of the cup and a probe pin submerged in the sample. This elastic linkage directs rotational force from the cup to the pin. Changes in rotational amplitude of the pin are recorded as a measure of clot firmness over time, generating a characteristic curve reflecting clot

firmness over time (known as a thromboelastogram/thromboelastograph) with various parameters derived therefrom to evaluate hemostasis. LaDuca Decl. ¶ 48.

TEM, similarly to TEG, measures changes in clot firmness over time based on an elastic linkage developed between the surfaces of a cup containing a sample and a probe pin submerged in the sample, and the cup is stationary, which is a key difference relative to TEG. In TEM, a force is applied to the pin via a spring element to cause the pin to rotationally oscillate. As the sample coagulates, the elastic linkage formed between the surfaces of the anchored cup and probe pin impedes the motion of the pin. As with TEG, the rotational amplitude of the pin is recorded as a curve reflecting clot firmness over time and various parameters are derived from the curve in TEM to evaluate hemostasis. LaDuca Decl. ¶ 49.

TEG and TEM curves necessarily (and do) involve computer processing to track and store the many data points of observed maximum rotation. These curves are not based on changing rotational amplitudes observed by the human eye and hand-plotted by data point. LaDuca Decl. ¶ 50.

Lang T, Depka M; Possibilities and limitations of thrombelastometry/-graphy; Hamostaseologie 26:Suppl 1, S20-29, 2006 ("Lang 2006") (Ex. 1016) and Nielson V; A Comparison of the Thrombelastograph and ROTEM", Blood Coagulation and Fibrinolysis 18:3, 247-252, 2007 ("Nielson 2007") (Ex. 1017) describe the clinical

value of different tests that can be run and different parameters that can be measured using TEG and TEM. LaDuca Decl. ¶ 50.

c. Acoustic-Echo Methods:

The '144 patent is generally directed towards devices and systems for viscoelastic methods of testing that utilize an acoustic-echo technique for interrogation and data analysis to determine "clot stiffness" (similar to TEG/TEM "clot firmness"). The force-response generated stiffness over time curves in the '144 patent are similar to the curves in TEG/TEM (*compare* Schubert Fig. 2 *with* '144 patent Fig. 6C). LaDuca Decl. ¶ 53. Importantly, the acoustic-echo technique disclosed in the '144 patent was not new even at the earliest critical date (February 15, 2011). Rather, this type of interrogation and data analysis using ultrasonic transducers and data processing for returned echoes (including time delay estimation and curve fitting), was previously described in earlier publications by the inventors that are prior art to the '144 patent. U.S. Publication No. 2005/0148899 to Walker et al. ("Walker") (Ex. 1018); Viola F, Kramer MD, Lawrence MB, et al., Sonorheometry: A Noncontact Method for the Dynamic Assessment of Thrombosis. Ann Biomed Eng. 2004;32(5):696-705 ("Viola 2004") (Ex. 1019); Viola, et al., "Sonorheometry: A new Method for Assessing Coagulation Potential," IEEE Ultrasonics Symposium, vol. 1, 2007, pp. 1001-1004 ("Viola 2007") "Ex. 1020) and the previously noted Viola 2009 (Ex. 1013). LaDuca Decl. ¶ 54

3. Common Features for Hemostatic Testing Devices:

a. *Automation for Point of Care Testing (POCT):*

POCT devices usually minimize technical procedures to be performed by an operator such as manual pipetting and blood sample application to the device, dividing the blood sample into multiple test chambers or test stations, and adding defined amounts of reagents. Test automation is an important driving force for development of POCT devices. LaDuca Decl. ¶¶ 55-57.

b. ***Sample Distribution:***

Automated sample distribution to a plurality of test chambers was well-known in the SoA. LaDuca Decl. ¶58. Examples of multi-chamber cartridges which implemented automatic sample distribution from an inlet to a plurality of test chambers include: U.S. Patent No. 5,534,226 ("Gavin,") (Ex. 1021, 7:55-64; 8:5-11) (LaDuca Decl. ¶ 59 including annotated Fig. 2 of Gavin), U.S. Patent No. 6,016,712 ("Warden,") (Ex. 1022, 14:49-15:2) (LaDuca Decl. ¶ 59 including annotated Fig. 1 of Warden) and U.S. Patent No. 6,613,286 ("Braun '286") (Ex. 1023, Fig. 2; 8:65-9:11) (LaDuca Decl. ¶ 60).

c. ***Use of Lyophilized Reagents:***

Test cartridges often included lyophilized reagents. LaDuca Decl. ¶¶ 62-63. Lyophilized reagents provided for increased reagent stability during storage and use. Solid state reagents such as beads and pellets were commonly known and

commercially available at the time of the '144 patent. For example, LyoSphere® produced by BioLyph pre-dated the '144 patent based on its inclusion in the disclosure as a commercial source (Ex 1001, Col 8:47-59). As another example, U.S. Patent Application No. 2007/0259348 ("Phadke") (Ex. 1014) teaches "Lyophilized pellets, suitable for use in a microfluidic device…" (Ex. 1014, Abstract). LaDuca Decl. ¶ 64.

d. Using a Processor:

It was common-place well prior to the '144 patent to use a processor for controlling functions of a diagnostic instrument (including interrogation, automation and testing protocol) as well as for data processing and analysis. LaDuca Decl. ¶ 65. Virtually all POCT systems that make precise measurements employ a processor that is associated with some memory to store executable program instructions, base data and acquired data. Many POCT systems also present results graphically (for example, the force-response generated "firmness/stiffness" curves in TEG and TEM and in the '144 patent). Id. For analytical devices, the programming or algorithm(s) can typically extend to include everything that can be gainfully and reasonably automated relative to the test procedure, raw data measurements, analytical process and results output. With regard to the analytical process, the required data collection is device and test specific and generally requires computer processing and programming. By way of example, clot firmness curves in TEG and TEM are clearly

computer-generated from data point acquisition to display. Furthermore, parameters derived from the curve are more precisely (with better reproducibly and standard interpretation between samples) identified as using standard computer analytical programs. LaDuca Decl. ¶ 66

VI. 37 C.F.R. § 42.204(b)(3): CLAIM CONSTRUCTION:

Under 37 C.F.R. § 42.200(b), claims in a post-grant review proceeding are construed using the same claim construction standard that is used to construe claims in a civil action. This includes "construing the claim in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent," *id*., consistent with *Phillips v. AWH Corp.,* 415 F.3d 1303 (Fed. Cir. 2005).

The terms of the Challenged Claims generally do not require construction and should be afforded their ordinary and customary, or "plain" meaning.

A. Claim Construction for Specific Terms:

"transducer" (throughout the claims): This term requires no construction. The plain meaning is consistent with the ordinary meaning of "transducer" as exemplified by Merriam-Webster's Online Dictionary definition provided below:

> Transducer: a device that is actuated by power from one system and supplies power usually in another form to a second system.

(https://www.merriam-webster.com/dictionary/transducer)

A transducer need not transform power (that a POSA would understand to be interchangeable with "energy" or "force" in this definition) into a different form. For example, a transducer can be actuated by mechanical power from one system and supply mechanical power to a second system in the same "form." Transducers can be as varied and numerous as the many different "systems" with which they interact and the many different types of interactions they have with those systems. The term "transducer" does not on its own specify any structure. Rather, the structure of a "transducer" is determined by the structure necessary to interact with two distinct systems – activated by one and transmitting power (or energy or force) to the second. Furthermore, a transducer can comprise a chain or series of several elements or steps for providing power (or energy or force) to a second system based on the actuation by power (or energy or force) from a first system. LaDuca Decl. ¶ 101.

"hemostatic parameter" (throughout the claims): This term requires no construction. This is consistent with the panel reasoning in the Board decisions in IPR2017-00852 and -00855 (Ex. 1028 at 7-10, Ex. 1029 at 9). The plain meaning is a value characterizing some part of the hemostatic process, as consistent with the ordinary meaning of "parameter" as exemplified by Merriam-Webster's Online Dictionary definition provided below:

> Parameter: any of a set of physical properties whose values determine the characteristics or behavior of something.

(https://www.merriam-webster.com/dictionary/parameter)

This is consistent with the non-exhaustive examples of "hemostatic" parameters in the '144 patent (Ex. 1001, Table 2). LaDuca Decl. ¶ 102.

"viscoelastic property" (throughout the claims): This term requires no construction. The plain meaning is a quality or trait of a viscoelastic material. Viscoelastic materials are characterized by both viscous and elastic properties, each of which can be considered a viscoelastic property. This plain meaning is consistent with the ordinary meaning of "property" and "viscoelastic" as exemplified by Merriam-Webster's Online Dictionary definitions provided below:

> Viscoelastic: having appreciable and conjoint viscous and elastic properties.

(https://www.merriam-webster.com/dictionary/property)

> Property: a quality or trait belonging and especially peculiar to an individual or thing.

(https://www.merriam-webster.com/dictionary/viscoelastic)

With respect to viscoelastic properties of a blood sample, as blood coagulates, fibrin formation provides a physiological indication of changing viscoelastic properties of the sample. Early in the clotting process fibrin formation is best indicated by changes in viscosity. As the fibrin strands crosslink and a fibrin mesh

continues to form the blood clot, viscosity may become difficult to measure and other measures (such as clot firmness) become better indicators of the changing viscoelastic properties of the clotted sample. Ultimately as polymerization progresses, with the influence of platelet contractile proteins, the fibrin polymer "contracts" and the result is a characteristic clot retraction which is another indication of changing viscoelastic properties of the clotted sample. LaDuca Decl. ¶ 103.

"clot mechanical properties" (throughout the claims): This term requires no claim construction. The plain meaning is a quality or trait of a clot characterizing reactions to an applied force. This plain meaning is consistent with the ordinary meaning of "mechanical property" as exemplified by Merriam-Webster's Online Dictionary definition provided below:

> Mechanical property: a property that involves a relationship between stress and strain or a reaction to an applied force.

(https://www.merriam-webster.com/dictionary/mechanical%20property)

LaDuca Decl. ¶ 104.

"instructions…cause the at least one processor to direct the one or more transducers…in the interrogation of the test sample to determine at least one viscoelastic property of the test sample" (Element 1.4 of claim 1): This language does not require construction in that it would be understood by a POSA as the plain

meaning of the words. Claim 1, in which the language appears, does not inform a POSA of any particular means of interrogation or any definite structure for the transducers or the processors in how they are programmed (including failing to specify a type of transducer, how the processor uses the transducer to interrogate the sample, how a viscoelastic property is determined, or what the operations of the processor making such a determination might be). Rather, claim 1 appears to cover any type of interrogation using unspecified transducers and unspecified data processing to determine a viscoelastic property. LaDuca Decl. ¶ 105.

This facially broad construction of Element 2.6 of claim 1 is also supported by dependent claims 15 and 16. In particular, claim 15 specifically states that the one or more transducer(s) of claim 1 comprise ultrasonic transducer elements which evidences that claim 1 (as necessarily broader than claim 15) was not intended to be limited to ultrasonic transducer elements. Moreover, claim 16 states that the one or more transducers of claim 1 comprise an LED and a detector which evidences that claim 1 is intended to encompass interrogation of a viscoelastic property using non-ultrasonic traducers (an LED is a not an ultrasonic transducer).

As reviewed in Section IV.A., the ‘144 patent description does not describe the structure of a transducer, only that an “ultrasonic transducer” is used. Aspects of data processing are disclosed (TDE, Voigt-Kelvin model curve-fitting, calculation of derivatives), but these are specific to an acoustic-echo technique for processing

returned echoes. There is no specific disclosure of how the claimed device includes "instructions" that "cause" a disclosed processor to "direct" a disclosed "transducer" in any interrogation (acoustic-echo or otherwise). None of the disclosed embodiments in the '144 patent mention or suggest implementing any technique other than acoustic-echo interrogation for determining a viscoelastic property and there is no invitation to adapt the apparatus and systems to any other technique. LaDuca Decl. ¶ 106.

A POSA would simply not understand the disclosure of the '144 patent to extend to arbitrary methods of interrogation (as currently generalized in claim 1). Moreover, A POSA would not have viewed the inventors of the '144 patent as having enabled or contemplated interrogation techniques for determining a viscoelastic property other than through the use of the disclosed acoustic-echo technique (i.e., using an ultrasonic transducer and data processing for returned echoes). Thus, Element 1.4 is overbroad and not enabled (or supported from the standpoint of the written description requirement) by the '144 patent description. LaDuca Decl. ¶ 107.

"processor is configured to determine the hemostatic parameters from signals transmitted to the processor from the one or more transducers" (Element 2.6 of claims 20, 42 and 61): This language does not require construction in that would be understood by a POSA as the plain meaning of the words. Claims 20, 42 and 61,

in which the language appears, do not inform a POSA of any definite structure for the transducers, the signals or the processors in how they are programmed (including failing to specify a type of transducer, how the hemostatic parameters are determined, or what the operations of the processor making such a determination might be). Rather, claims 20, 42 and 61 appear to cover any type of signal analysis using unspecified transducers and unspecified data processing to determine the hemostatic parameters. LaDuca Decl. ¶ 108.

This facially broad construction of Element 2.6 of claims 20, 42 and 61 is also supported by dependent claims 38, 39, 57, 58, 62 and 63. In particular, claims 38, 57 and 63 (depending from claims 20, 42 and 61, respectively) state that the one or more transducer(s) comprise ultrasonic transducer elements, which evidences that the parent claims (as necessarily broader than the dependent claims) were not intended to be limited to ultrasonic transducer elements. Moreover, claims 39, 58 and 63 (depending from claims 20, 42 and 61, respectively) state that the one or more transducers comprise an LED and a detector, which evidences that the parent claims are intended to encompass determination of hemostatic parameters using signals from non-ultrasonic traducers (an LED is a not an ultrasonic transducer).

As reviewed in Section IV.A., the ‘144 patent discloses the use of TDE applied to echoes from ultrasonic transducers to develop a curve using the Voigt-Kelvin model and to calculate hemostatic parameters according to certain imposed

criteria. These aspects are specific to an acoustic-echo technique for processing returned echoes. None of the disclosed embodiments in the '144 patent, mention or suggest implementing any technique other than this acoustic-echo technique for determining hemostatic parameters and there is no invitation to adapt the apparatus and systems to any other technique. LaDuca Decl. ¶ 109.

A POSA would simply not understand the disclosure of the '144 patent to extend to arbitrary methods of signal analysis (as currently generalized in claims 20, 42 and 61). Indeed, a POSA would not have viewed the inventors of the '144 patent as having enabled or contemplated techniques for determining the hemostatic parameters other than through the use of the disclosed acoustic-echo technique (i.e., using an ultrasonic transducer and data processing for returned echoes). Thus, Element 2.6 is overbroad and not enabled (or supported from the standpoint of the written description requirement) by the '144 patent description. LaDuca Decl. ¶ 110.

"instructions…cause the at least one processor to perform at least three measurements in parallel" (Element 2.7 of claim 20) and "instructions…cause the at least one processor to determine the hemostatic parameters in parallel" (Element 2.7 of claim 42): Although this language does not appear to require construction in that would be understood by a POSA as the plain meaning of the words, there is some vagueness in the term "parallel" – i.e., whether it requires synchronous operation. The only relevant mention of "parallel" in the '144 patent

description is at Ex. 1001, 18:61-65 in connection with comparing hemostatic parameters from parallel tests on the single sample distributed to parallel test chambers with different reagents/tests. From this a POSA would understand "parallel" to mean such conditions as to perform such parallel tests. LaDuca Decl. ¶ 111.

However, there is no disclosure of any "instructions" to cause any "processor" to perform parallel testing. Rather, the specification only generally states that "[t]he processing of the disclosed methods, devices and systems can be performed by software components" (Ex. 1001, 13:46-14:3). Nevertheless, a POSA would be able to specify to a programmer that a given interrogation method supports parallel tests to conduct those parallel tests.[4] LaDuca Decl. ¶ 112.

"instructions…cause the at least one processor to determine a curve associated with a viscoelastic property of the blood of each test sample, the curve being generated from the interrogation as a function of time" (Element

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[4] Schubert has at least the same degree of support as to the '144 patent for implementing parallel measurements. Both Schubert and the '144 patent teach parallel measurements and neither explicitly teaches using a processor to perform such functions.

2.7 of claim 61): his language does not require construction in that would be understood by a POSA as the plain meaning of the words. Read this way, any interrogation that returns any time-curve "associated with a viscoelastic property" would meet Element 2.7 of claim 61. LaDuca Decl. ¶ 113.

Interrogation of a viscoelastic property and curve generation derived therefrom only disclosed in the embodiments of the '144 patent with respect to an acoustic-echo technique for interrogation and data processing (where the curve is generated based on received ultrasound echo signals and applying Time Delay Estimation and curve fitting using the Voigt-Kelvin theoretical model). Thus, Element 2.7 of claim 61 is overbroad and not enabled (or supported from the standpoint of the written description requirement) by the '144 patent description. LaDuca Decl. ¶ 114.

each test chamber being "configured…for interrogation to determine a hemostatic parameter" (Element 1.8 of claim 1 and Element 2.4 of claims 20, 42 and 61): This language does not require construction in that it would be understood by a POSA as the plain meaning of the words. Read this way, any number of interrogation techniques can be imagined, each with many different possible configurations of the test chamber. Indeed, it is unclear how or even if a particular interrogation technique would impact the structural design of the test chamber. LaDuca Decl. ¶ 115.

The only corresponding structure in the embodiments of the '144 patent for the function of the test chamber being configured for interrogation is a sound focusing assembly for dry ultrasonic coupling (Ex. 1001, test chamber cap (132) and lens (134) in FIGS. 1D and 1F; 11:42-12:6). The specification of the '144 patent does not establish or suggest using different test chamber configurations for arbitrary interrogation techniques. Thus, Element 1.8 of claim 1 and Element 2.4 of claims 20, 42 and 61 are overbroad and not enabled (or supported from the standpoint of the written description requirement) by the '144 patent description. LaDuca Decl. ¶ 116.

"a housing that is configured to couple to a system, wherein the system comprises…" (Element 1.2 of claim 1): Claim 1 is directed towards an apparatus for evaluating hemostasis. Claim 1 does not recite that the apparatus includes a system but rather recites that the apparatus includes a housing which is configured to couple to a system. Thus, while claim 1 further describes the system in greater detail (including the system having one or more transducers and a processor and memory which are configured for the interrogation the test sample to determine at least one viscoelastic property), it would have been unclear to a POSA whether the system characterized in claim 1 is an actual element of the claim or merely recited as a functional element of the housing.

"a first of the one or more transducers comprises a light emitting diode (LED) emitter and…a detector" (claims 16, 39, 58 and 63): Claims 16, 39, 58 and 63 depend from claims 1, 20, 42 and 61, respectively. According to claim 1, the one or more transducers are directed by the processor to determine at least one viscoelastic property of the test sample. Similarly, according to claims 20, 42 and 61, the one or more transducers transmit signals to the processor which are used to determine the hemostatic parameters. As reviewed above, however, the '144 patent only discloses an LED emitter and an [optical] detector for monitoring chamber fluid level (Ex. 1001, 6:40-45). Thus, a POSA would **not** have viewed the inventors of the '144 patent as having enabled or contemplated non-ultrasonic techniques for interrogating a viscoelastic property or determining hemostatic parameters. There is nothing in the '144 patent that would provide any indication to a POSA that an LED emitter and a detector would be used in interrogating a viscoelastic property or determining hemostatic parameters and how this could be achieved. LaDuca Decl. ¶ 117.

"prior to being delivered to the first test chamber" (claims 18, 30 and 50): This term requires no claim construction. The plain meaning of claims 18, 30[5] and 50 is that the test sample mixes with reagent(s) before being delivered to the test chamber. Thus, the inference is that the reagents are not pre-loaded into the test chamber (prior to the test chamber receiving the sample) and that the mixing occurs outside of the test chamber. The '144 patent, however, does not teach reagent mixing prior to the sample being delivered to the test chambers. Rather, the '144 patent only teaches embodiments where the reagents are pre-loaded and mixed with the sample in the test chambers. Thus, based on the specification of the '144 patent, a POSA would **not** have viewed the inventors of the '144 patent as having enabled or contemplated mixing of the sample with reagent(s) outside of the test chamber. LaDuca Decl. ¶ 118.

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Grounds for Review Under 37 C.F.R. § 42.204(b)(4)-(5)

[5] Claim 30 has a typographic error where the reagents are recited as mixing with the test chamber instead of, as a POSA would understand the intended meaning to be, with the test sample.

VII. GROUND 1: IT IS MORE LIKELY THAN NOT THAT THE CHALLANGED CLAIMS LACK BOTH ENABLEMENT AND WRITTEN DESCRIPTION UNDER 35 U.S.C. § 112(A):

The Challenged Claims lack enablement and written description support showing possession of invention under 35 U.S.C. § 112(a).

A. As a Matter of Policy, the Challenged Claims Should Not Be Allowed to Use Functional Recitals, Untethered to Any Definite Structure to Preempt Non-Disclosed and Non-Enabled Implementations:

Petitioner contends that the overall policy in this case and related cases (Section II(B)) should be that the '144 patent owner should not be allowed to "claim a genus while disclosing only one species" through broad functional recitals, and, where it has dependent claims that are limited to the species, *LizardTech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336 (Fed. Cir. 2005) should apply to invalidate the independent (genus) claim, rather than construe it narrowly at least for the policy reason that the public should not be deceived by facially broad claims.

The '144 patent is one of multiple continuation applications filed by Patent Owner with claims that exceed the scope of the original disclosure. The pattern is one of claiming generic structure (*e.g.*, "test chamber," "processor," "memory" "instructions" and "transducer") using functional modifiers (*e.g.*, "for," "configured to," "designed to") followed by generic functions (*e.g.*, "interrogation," "determination") relative to imprecise and arbitrary values (*e.g.*, "viscoelastic properties," "hemostatic parameters," "indices of hemostasis"). See generally

Grounds 1 and 2, *Instrumentation Laboratory Co. v. HemoSonics LLC,* Petition for Post-Grant Review of U.S. Patent No. 9,977,039, PGR2019-00033, Paper No. 1 (PTAB filed Feb. 21, 2019) (functional modifiers, primarily "interrogate"). Here, Elements 1.4, 1.8 of claim 1 and Elements 2.4, 2.6 and 2.7 of claims 20, 42 and 61 recite broad functions (such as being configured to be interrogated to determine a hemostatic parameter, causing a processor to direct transducers to interrogate a sample to determine a viscoelastic property, being configured to determine hemostatic parameters from transducer signals, etc.), without any definite claimed structure for achieving those functions. Thus, while the '144 patent specification only teaches structure specific for acoustic-echo interrogation and data analysis (Section IV(A)), the independent Challenged Claims 1, 20, 42 and 61 cover generic non-enabled and non-disclosed alternatives – generalized from the Provisional Application from which it claims priority (Section IV(C)), claiming a genus for which only one species was disclosed.

The '144 patent strategy of claiming functional elements untethered to any discernable definite structure, results in a high degree of ambiguity as to claim scope, and raises significant issues relating to the enablement and written description requirements – and is precisely the reason congress and the Courts have sought to limit the scope of purely functional claiming (*e.g.*, via application of 35 U.S.C. § 112(f), pre-AIA 35 U.S.C. § 112, para. 6). Abstract, innovation-preemptive,

functional claiming based on limited disclosure (such as in the challenged claims of the '144 patent) has long been disallowed. *O'Reilly v. Morse,* 56 U.S. (15 How.) 62, 14 L. Ed. 601 (1853), as explained at *Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1359 (Fed. Cir. 2010). Claim generalization may not exceed the scope of the disclosure. *LizardTech*, 424 F.3d at 1344-45 explained how 35 U.S.C. § 112 applies:

> The "written description" clause of section 112 has been construed to mandate that the specification satisfy two closely related requirements. First, it must describe the manner and process of making and using the invention so as to enable a person of skill in the art to make and use the full scope of the invention without undue experimentation…Second, it must describe the invention sufficiently to convey to a person of skill in the art that the patentee had possession of the claimed invention at the time of the application, i.e., that the patentee invented what is claimed. See O'Reilly v. Morse, 56 U.S. (15 How.) 62, 112–13, 14 L.Ed. 601 (1853) (denying a claim for use of "electro-magnetism, however developed for marking or printing intelligible characters ... at any distances" because others "may discover a mode of writing or printing at a distance ... without using any part of the process or combination set forth in the plaintiff's specification");...

B. The Challenged Claims Lack Both Enablement and Written Description Support:

Under *LizardTech, Inc.*, the Challenged Claims fail under 35 U.S.C. § 112 since the generalization of interrogation and data analysis beyond the acoustic-echo

implementations of the '144 patent (*e.g.*, in Elements 1.4 and 1.8 of claim 1 and Elements 2.4, 2.6 and 2.7 of claims 20, 42 and 61) exceeds the scope of the original disclosure. In *LizardTech, Inc.*, a claim of a broad superset of wave transformation techniques was found unsupported by disclosure only of a particular technique and invalid under 35 U.S.C. § 112, para. 1. The court specifically refused to read in the only disclosure because of duplication of claims scope. 424 F.3d at 1344.

LizardTech explained at 1344-45 the "written description" and "enablement" requirements and noted:

> Those two requirements usually rise and fall together. That is, a recitation of how to make and use the invention across the full breadth of the claim is ordinarily sufficient to demonstrate that the inventor possesses the full scope of the invention, and vice versa...

Both requirements are failed for the Challenged Claims.

For the first requirement, *In re Gosteli*, 872 F.2d 1008, 1012, (Fed. Cir. 1989), posed the question "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed"?

The clear answer is that original disclosure of the '144 patent fails to demonstrate possession by Patent Owner of any implementation other than with respect to acoustic-echo interrogation, which are the only embodiments disclosed in the '144 patent for evaluating hemostasis. Thus, for example, the only type of transducer described for evaluating hemostasis (*i.e.*, by determining a viscoelastic

property or determining hemostatic parameters) is an ultrasonic transducer (Ex. 1001, 2:27-29; 2:35-38; 2:43-46; 2:60-65; 12:7-10; 13:19-26, 13:32-45, 15:40-43). The '144 patent specification focuses extensively on implementing acoustic-echo interrogation – describing sound focusing assemblies (Ex. 1001, test chamber cap (132) and lens (134) in FIGS. 1D and 1F; 11:52-12:16) for the test chambers and ultrasonic transducers and data processing specific to processing reflected ultrasound signals, including performing analytical steps of time delay estimation (TDE) and curve fitting of the TDE using the Voigt-Kelvin theoretical model (Ex. 1001, 12:16-19:10). However, none of the embodiments disclosed in the '144 patent, mention or suggest implementing any other technique for evaluating hemostasis and there is no invitation to adapt the apparatus and systems to any other technique.

The standard for determining if the specification meets the enablement requirement is whether a POSA can make and use the invention without "undue experimentation" as set forth by the Supreme Court in *Minerals Separation Ltd. v. Hyde*, 242 U.S. 261, 270 (1916). *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) set forth the factors that may be considered:

> . . . (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. . . .

Without specifying a particular technique for evaluating hemostasis, it is unknown what quantity of experimentation is necessary under factor (1). Dr. LaDuca, with extensive experience in developing POC hemostasis assay devices, testifies that:

> Alternative techniques for interrogation or data processing, however, may be unlimited in the imagination and limited only by the practicalities of available technology which can continue to evolve and change over the course of the lifetime of a patent. There are many other types of interrogation and interrogation devices implemented in the art for determining a viscoelastic property or hemostatic parameters of a sample. By nature of the specific technical requirements for any interrogation method, virtually all of these techniques and devices require a different structural implementation (i.e., different transducers, different testing protocol, different algorithms for processing data, different test chamber configurations, etc.) than that disclosed in the '144 patent.
>
> While, some technical features of evaluating hemostasis may be straightforward, once a technique is selected, the design or adaptation to that technique requires development and experimentation that typically goes beyond routine experimentation. In my experience, the design or adaptation of apparatus and systems for a new technique of evaluating hemostasis requires multiple iterations, prototypes and refinements. Moreover, the design is likely to vary greatly depending on the type of interrogation applied and subjective choice.

> At times, this means that things like transducers, testing protocol, algorithms for processing data, test chamber configurations, etc., for a particular technique may require experimentation and creativity beyond a POSAs abilities. This is evidenced, for example, by the complexities Patent Owner encountered in developing the apparatus and systems in the '144 patent for acoustic-echo interrogation and data analysis as well as by the complexities described in Schubert with respect to adapting a cartridge for viscoelastic methods of interrogating clot firmness using a pin and cup mechanism (Ex. 1005, 4:38-50).

LaDuca Decl. ¶¶ 119-123.

The '144 patent provided no guidance under *Wands* factor (2) or working examples under factor (3). The breadth of the claim under factor (8) – to adaptation of a cartridge to all present and future methods of interrogating hemostatic parameter – offends patent policy established since at least *O'Reilly v. Morse*.

Thus, the Challenged Claims fail under both subsections (a) and (b) (formerly paragraphs 1 and 2) of 35 U.S.C. § 112.

C. Dependent Claims 16, 18, 30, 39, 50, 58 and 63 Deceptively Broaden Out Claim Scope By Reciting Limitation Which Lack Enablement and Written Description Support:

The over-claiming in the '144 patent is especially evident in dependent claims which broaden the scope of the independent claims by reciting limitations which have ***no*** basis or support in the original disclosure. For example, LED claims 16, 39, 58 and 63 (which depend from claims 1, 20, 42 and 61, respectively) attempt to

establish that the one or more transducers (which in claim 1 are directed by the processor to determine at least one viscoelastic property of the test sample and in claims 20, 42 and 61 transmit signals to the processor which are used to determine the hemostatic parameters) can be an LED and a detector. The '144 patent, however, only discloses an LED emitter and an [optical] detector for monitoring chamber fluid level (Ex. 1001, 6:40-45). Thus, there is no basis or support in the original disclosure for an LED emitter and a detector serving as transducers for in interrogating a viscoelastic property or determining hemostatic parameters.

Similarly, "pre-mix" claims 18, 30 and 50 (which depend from claims 1, 20 and 42, respectively) attempt to establish that the reagents aren't necessarily preloaded into the test chambers and instead can be mixed with the sample prior to the sample entering the test chambers. Again, there is no basis or support in the original disclosure for mixing of the reagents with the sample outside of the test chamber.

VIII. GROUND 2: IT IS MORE LIKELY THAN NOT THAT THE CHALLENGED CLAIMS ARE UNPATENTABLE AS INDEFINITE UNDER 35 U.S.C. § 112(b):

The Challenged Claims are invalid for indefiniteness under 35. U.S.C. 112(b) (formerly para. 2), because they recite limitations that, under *Nautilus, Inc. v. Biosig Instruments*, 134 S. Ct. 2120 (2014), considering the claims as a whole and as informed by the extrinsic record, fail to inform a POSA with reasonable certainty

about the scope of the claimed invention. A patent must be "precise enough to afford clear notice of what is claimed, thereby 'appris[ing] the public of what is still open to them.'" *Id.* at 2129. "Otherwise there would be a zone of uncertainty which enterprise and experimentation may enter only at the risk of infringement claims." *Id.*

A. The Challenged Claims Are Indefinite Due to Functional Claiming Untethered to Any Clear Corresponding Structure:

While functional claiming is permissible, it must always be tethered to structure. Thus, functional claiming must either be linked to sufficiently definite structure in the claims for performing the function (*Williamson v. Citrix Online, LLC*, 792 F.3d 1339, 1349 (Fed. Cir. June 16, 2015) or it is limited based on adequate disclosure of corresponding structure in the specification (*Id.* at 1352). This is the balance struck by Congress in allowing functional claiming. (*Id.* at 1347). Patent Owner should not be allowed to "have its cake and eat it to" by including functional limitations completely untethered to any definite structure.

Apple Inc. v. Motorola, Inc., 757 F.3d 1286 (Fed. Cir. 2014) is highly informative of how "structure" is determined in the context of computer-implemented limitations:

> "Structure" to a person of ordinary skill in the art of computer-implemented inventions may differ from more traditional, mechanical structure. For example, looking for traditional "physical structure" in a

> computer software claim is fruitless because software does not contain physical structures. Indeed, the typical physical structure that implements software, a computer, cannot be relied upon to provide sufficiently definite structure for a software claim lacking "means." Rather, to one of skill in the art, the "structure" of computer software is understood through, for example, an outline of an algorithm, a flowchart, or a specific set of instructions or rules.

Id. at 1298-1299.

Recognizing a degree of similarity between computer-implemented limitations and "circuits," the Court in *Apple Inc*. explained that "structure may also be provided by describing the claim limitation's operation." *Id.* at 1299 (citing to *Linear Tech. Corp. v. Impala Linear Corp.*, 379 F.3d 1311, 1320-1321 (Fed.Cir.2004)). In both *Apple Inc*. and *Linear Tech. Corp.*, determining whether the claims provided sufficiently definite structure hinged on whether the claims provided sufficient recitation of operations so as to connote a definite structure for performing the recited function(s). This is also the analysis applied with respect to "processor" limitations in each of *Ex Parte Smith*, 2012-007631, pages 15-16 (March 14, 2013), *Ex parte Erol*, 2011-001143, page 16 (Mar. 13, 2013) and *Ex parte Lakkala*, 2011-001526, pages 12-13 (Mar. 13, 2013).[6]

[6] All of these cases were designated informative by the USPTO.

The Challenged Claims recite broad functions (such as being configured to be interrogated, causing a processor to direct transducers to interrogate a sample to determine a viscoelastic property, being configured to determine hemostatic parameters from transducer signals, etc.), without any definite claimed structure for achieving those functions. For example, with respect to Element 1.4, claim 1 does not inform a POSA of any particular means of interrogation or any definite structure for the transducers or the processors in how they are programmed (including failing to specify a type of transducer, how the processor uses the transducer to interrogate the sample, how a viscoelastic property is determined, or what the operations of the processor making such a determination might be). Similarly, with respect to Element 2.6, Claims 20, 42 and 61 do not inform a POSA of any definite structure for the transducers, the signals or the processors in how they are programmed (including failing to specify a type of transducer, how the hemostatic parameters are determined, or what the operations of the processor making such a determination might be). Similar deficiencies are discussed in claim construction Section VI.A with respect to Element 1.8 of claim 1 and Elements 2.4 and 2.7 of claims 20, 42 and 61. Thus, the claims fail to provide any definite structure for at least Elements 1.4 and 1.8 of claim 1 and Elements 2.4, 2.6 and 2.7 of claims 20, 42 and 61.

The only corresponding structure in the ‘144 patent specification relates to acoustic-echo interrogation and data analysis (i.e., using ultrasonic transducers to

receive ultrasound echo signals and performing analytical steps of time delay estimation and curve fitting, with respect to Element 1.4 of claim 1 and Elements 2.6 and 2.7 of claims 20, 42 and 61 and sound focusing assemblies for dry ultrasonic coupling with respect to Element 1.8 of claim 1 and Element 2.4 of claims 20, 42 and 61). However, claims 1, 20, 42 and 61 are facially broad and not explicitly limited to acoustic-echo interrogation. Furthermore, dependent claims 15, 16, 38, 39, 57, 58, 62 and 63 evidence (or at the very least deceptively appear to evidence) that the independent claims are not limited to acoustic-echo interrogation and data analysis. Thus, a POSA could not read the claims as limited to the corresponding structure in the specification without this presenting an incongruity with respect to the facial meaning of the claims as further evidenced by the dependent claims.

Accordingly, the Challenged Claims are indefinite for including functional limitations untethered to any definite structure.

B. Element 1.2 of Claim 1 is Indefinite Since It is Unclear Whether "System" is a Positively Recited Element of the Claim:

Claim 1, directed toward an apparatus, does not recite that the apparatus includes a system but rather recites that the apparatus includes a housing which is configured to couple to a system. Thus, as stated in claim construction Section VI.A, while claim 1 describes the system in greater detail, it would have been unclear to a POSA whether the system characterized in claim 1 is an actual element of the claim or merely recited as a functional element of the housing. Both the claims and

specification generally support that the "apparatus" of claim 1 (also characterized as a cartridge device in various dependent claims) is separate from the "[measurement] system" – or at the very least that the "system" is not part of the "apparatus," in claim 1. This is further supported based on the fact that in the specification, the recited structural elements of the "system" in claim 1 – including transducers, memory and a processor – are distinct from the cartridge device. Thus, at least since it would have been unclear to a POSA whether the "system" of claim 1 is part of the claimed apparatus, claim 1 is indefinite.

IX. GROUND 3: IT IS MORE LIKELY THAN NOT THAT THE CHALLENGED CLAIMS ARE UNPATENTABLE AS ANTICIPATED BY SCHUBERT UNDER 35 U.S.C. § 102:

A. Teachings in Schubert:

U.S. Publication No. 20100154520 ("Schubert") (Ex. 1005), published in 2010, discloses a multi-chamber test cartridge for viscoelastic methods of testing. (Fig. 6; ¶¶ 0029, 0081-0082). The cartridge device (50) is used for evaluation of hemostasis (Abstract, ¶¶ 0002-0007; 0025). More particularly, the cartridge device (50) is configured to run different coagulation tests in parallel to isolate the effect of different components of the coagulation pathway. (¶¶ 0013, 0016, 0082, 0083). The cartridge device (50) includes a plurality of test chambers (¶¶ 0029; 0081-0082) where each chamber includes a different reagent or combination of reagents. LaDuca Decl. ¶ 139.

Schubert discloses a preferred four chamber embodiment where INTEM, EXTEM and FIBTEM tests are combined within one cartridge. (Ex. 1005, ¶¶ 0082-0083). These tests utilize different reagents which activate or suppress different parts of the coagulation cascade. INTEM includes a reagent for intrinsic activation (intrinsic activator), EXTEM includes a reagent for extrinsic activation (extrinsic activator) and FIBTEM includes reagents for extrinsic activation and for suppressing thrombocyte function (extrinsic activator plus cytochalasin D) (Id.). The trademark terms INTEM, EXTEM and FIBTEM are technical terms of art known at the time of the Schubert. EXTEM includes an extrinsic activator (Tissue Factor), INTEM includes a contact activator (ellagic acid plus phospholipid) and FIBTEM combines extrinsic activation (using Tissue Factor) and cytochalasin D (an inhibitor of actin polymerization which neutralizes platelet contribution to the viscoelastic response, *i.e.*, clot firmness). This is supported by literature contemporaneous with Schubert. LaDuca Decl. ¶ 140.

As depicted in annotated Fig. 6, below, the cartridge device 50 includes a fluid pathway where branch channels (ducts 13, 14 and 15 and ducts 13' 14' and 15', respectively) connect respective measurement cavities 20 and 20' to a single inlet channel (receiving cavity 16) which in turn is in communication with an inlet (cavity cover 33a). (Ex. 1005, ¶¶ 0047-0048). While Fig. 6 depicts an example embodiment with two arrangements of FIG. 4 or 5, ¶¶ 0081-0082 of Schubert teaches that "[i]n a

preferred embodiment the cartridge device 50 comprises four arrangements of FIG. 4 or 5 having 4 measurement cavities" where "measurements can be done with different reagents on the same liquid sample." A measurement cavity (20, 20') may be integrally formed with a reagent cavity (19, 19') (Ex. 1005, ¶ 0040). LaDuca Decl. ¶ 141.

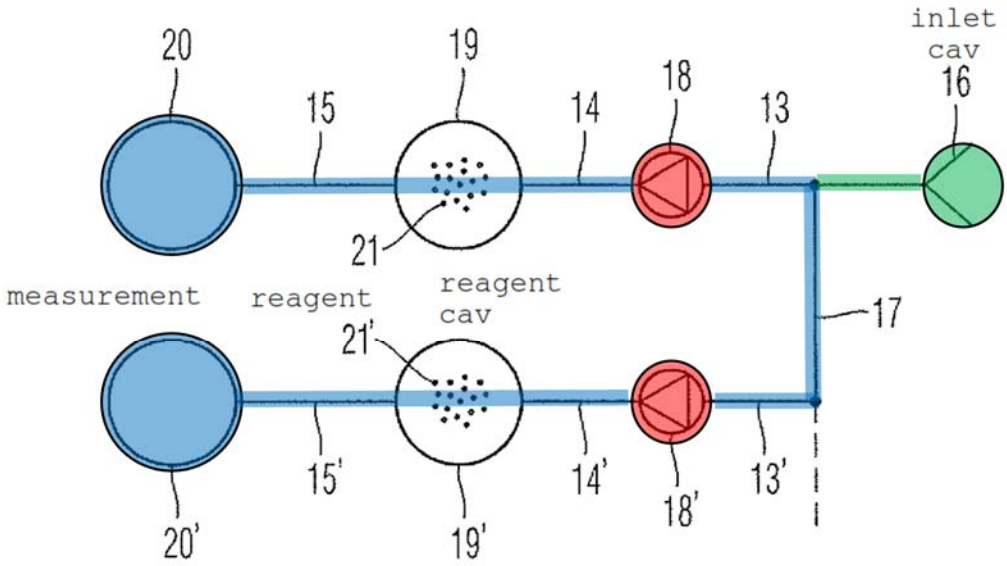
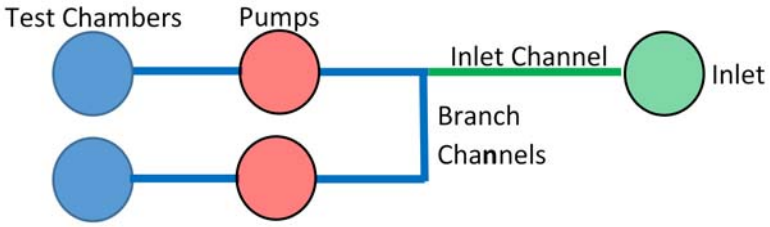


Fig. 6



Schubert further teaches interrogating (Ex. 1005, ¶¶ 0029; 0031; 0011; 0083; 0088) each test chamber to measure changes in the viscoelastic property of the test sample (¶¶ 0006; 0009). Thus, Schubert teaches that cartridge device 50 can be used

with a measuring system to measure a viscoelastic property of the test sample (¶¶ 0002, 0013-0018, 0025-0028 and 0098). LaDuca Decl. ¶ 142.

Schubert, as described herein anticipates each of the Challenged Claims of the '144 patent. In general, the teachings in Schubert are fairly explicit about meeting the claim limitations. However, there are several claim elements where it is useful to provide added explanation with respect to the application of Schubert. LaDuca Decl. ¶ 145.

1. Viscoelastic Methods in Schubert:

Schubert teaches multi-chamber cartridges (e.g., cartridge devices 50) and systems (e.g., measuring system 40) which it generally teaches are "suitable" for implementing thromboelastography (TEG) and thromboelastometry (TEM) (Ex. 1005, ¶ 0077 and ¶ 0084). Schubert further teaches specific embodiments implementing TEM in a measuring system 40 and cartridge (FIGS. 7*a-c* and 13*a-c* and ¶¶ 0085-0088, 0099-0102 and 0106-0163). LaDuca Decl. ¶¶ 145 and 152.

Schubert uses the umbrella term "viscoelastic methods" to refer to the group of diagnostic tests (including TEG and TEM) where "blood clot firmness (or other parameters dependent thereon) is continuously determined, from the formation of the first fibrin fibres [*sic*.] until the dissolution of the blood clot by fibrinolysis" (Ex. 1005, ¶ 0006). LaDuca Decl. ¶ 147. A POSA would understand the curve of FIG. 2 in Schubert to be characteristic of type of clot firmness curves produced for any viscoelastic method (for example, characteristic of the TEG thromboelastogram as well as the similar TEM curve). Furthermore, a POSA would have understood that in order to produce and display such a curve, a processor/computer must necessarily be employed. LaDuca Decl. ¶ 149

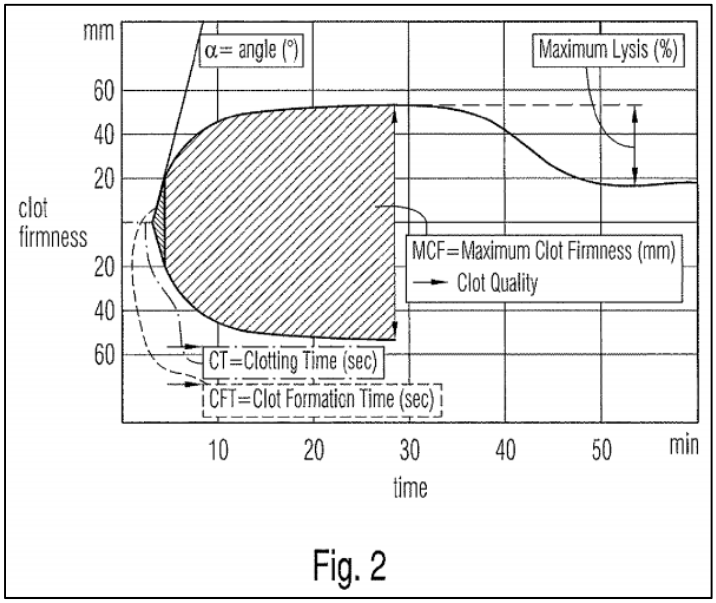


Fig. 2

Schubert also describes example parameters dependent on clot firmness, including: clotting time (CT), clot formation time (CFT); and maximum clot firmness (MCF). Fig. 2 illustrates these parameters as well as two additional parameters, maximum lysis % and α angle. Based on the terminology, a POSA would have recognized that these measurement parameters are TEM parameters. LaDuca Decl. ¶ 150.

The FIELD OF INVENTION section of Schubert describes TEG as the "first viscoelastometric method" (Ex. 1005, ¶ 0008). The basic measurement principles of TEG are then described (FIG. 1 and ¶ 0008). LaDuca Decl. ¶ 148. Schubert characterizes TEM as a modification of TEG. The basic measurement principles of TEM are then described (FIG. 3 and ¶¶ 0010 and 0011) LaDuca Decl. ¶ 151.

In particular, Schubert ¶ 0010 teaches:

> thromboelastometry is based on a cup 2 fixed in a cup holder 12 while the probe pin 3 is actively rotated…[T]he probe pin 3 is attached to a shaft 6 which is suspended by a ball bearing 7 in a base plate 11 and has a spring 9 connected to it. An oscillating motion...induced at the opposite end of the spring is transformed into a periodically rotation of the shaft 6...As the sample liquid 1 begins to coagulate the motion amplitude of the shaft 6 which is detected by the deflection of a light beam from detecting means 10 and a mirror 9 [*sic*., should be 8] starts to decrease.

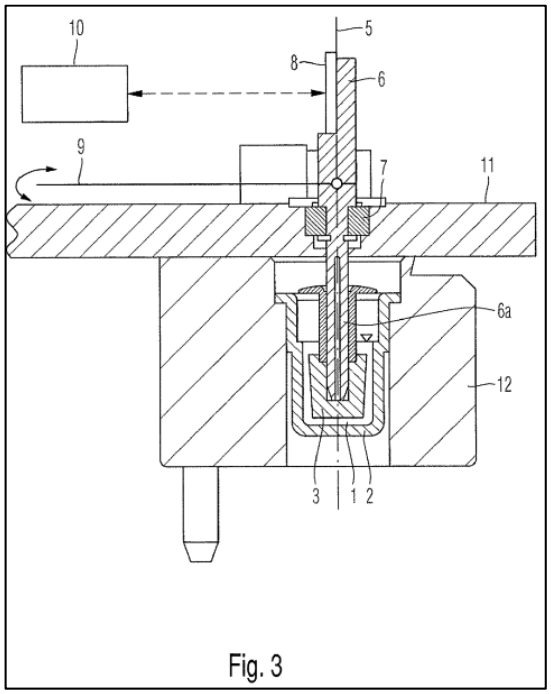


Fig. 3

Schubert cites to Calatzis (Ex. 1006) as teaching TEM. LaDuca Decl. ¶ 151. Consistent with Schubert, Calatzis illustrates (Ex. 1006, FIGS. 6 and 7) and describes (7:25-57) the testing technique for TEM. LaDuca Decl. ¶ 154.

TEM, as implemented by the disclosed embodiments in Schubert, was a well-known diagnostic test in the SoA at the time of Schubert. This is evidenced by TEM being included and characterized in the FIELD OF INVENTION section of Schubert. Furthermore, at the time of Schubert, TEM systems, *e.g.*, ROTEM *delta* (originally, called the ROTEM analyzer), were already on the market and subject to numerous studies, publications, and patents (such as Calatzis). Thus, a POSA's understanding of TEM, as implemented by the disclosed embodiments in Schubert, would include the context provided by this SoA at the time of Schubert. In particular, the SoA would provide context to a POSA to better understand the operation of the interrogation and detection systems in TEM as well as data processing and analysis aspects of TEM. Such context evidences what a POSA would reasonably infer from, and would consider necessarily present in, Schubert's implementation of TEM (such as a processor, memory and relevant transducers). LaDuca Decl. ¶¶ 156-157.

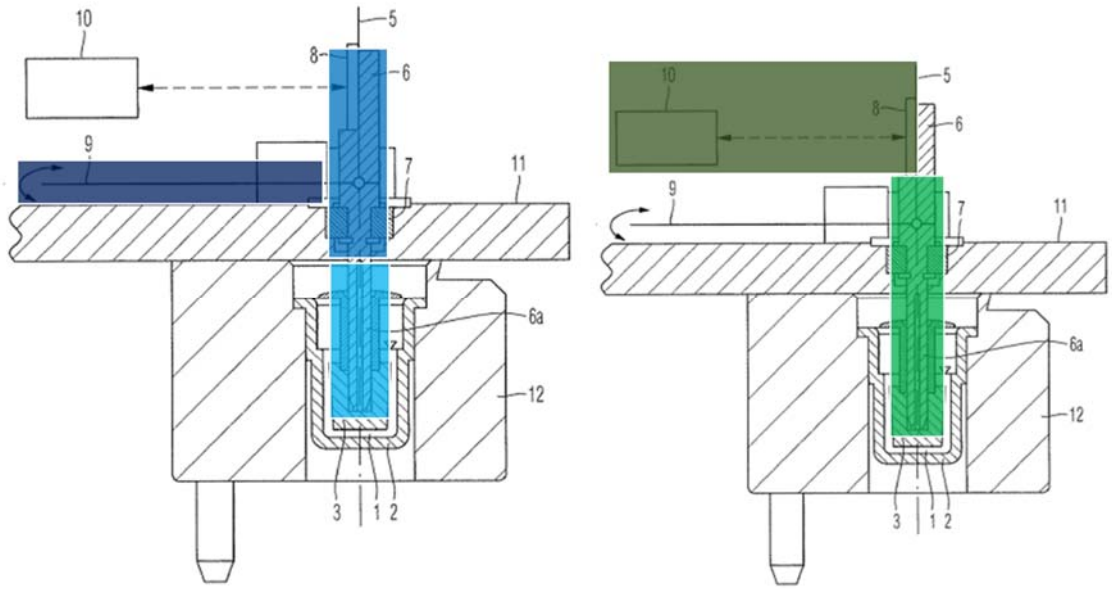
2. Teachings with Respect to Transducers:

With respect to claim 1, Schubert explicitly teaches (i) one or more transducers for each of a plurality of test chambers (Element 1.3) and where the one or more transducers interrogate the test sample to determine at least one viscoelastic property of the test sample (Element 1.4). Similarly, with respect to claims 20, 42 and 61 that Schubert explicitly teaches (i) one or more transducers for transmitting energy into one or more test chambers and for receiving reflected energy from the

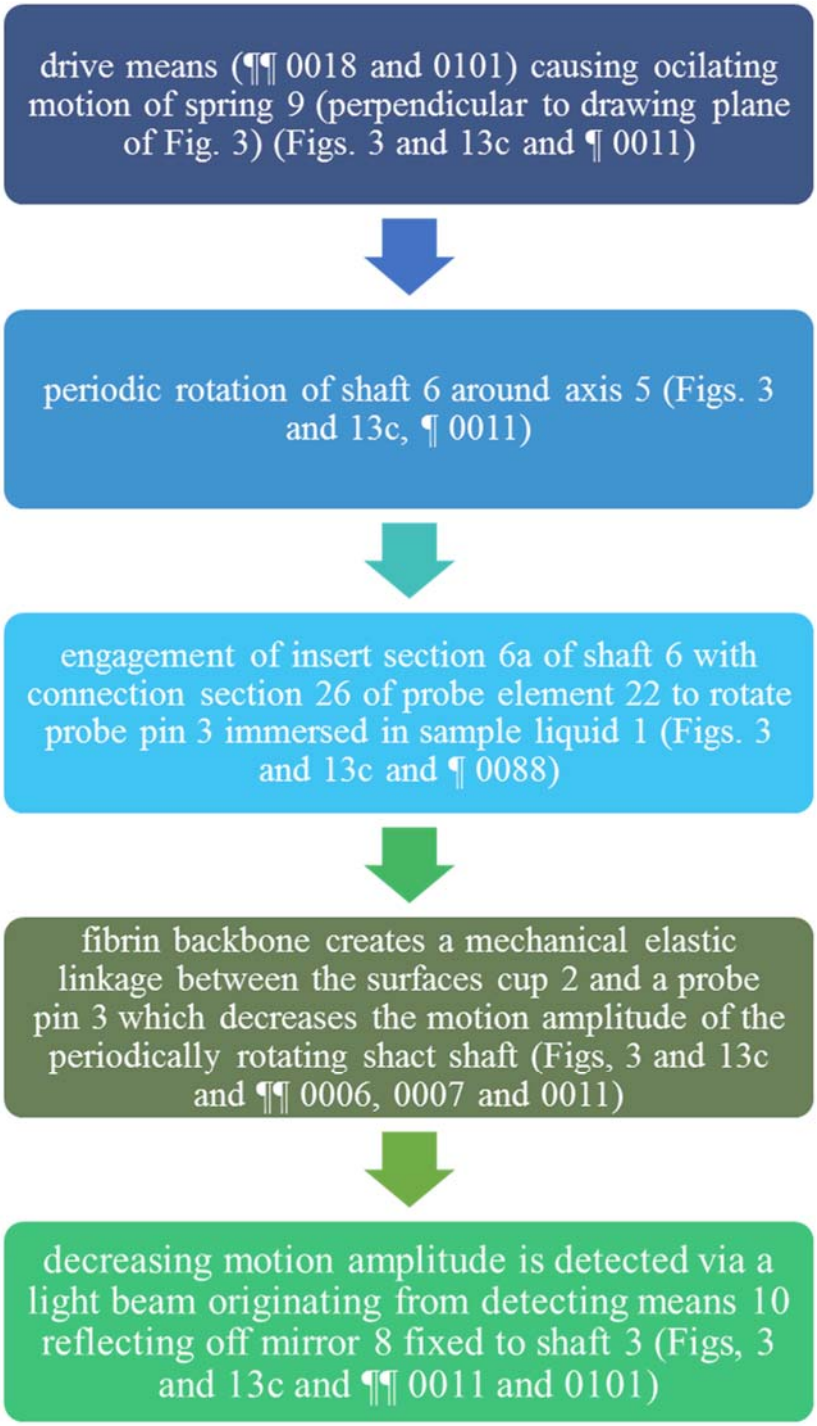
chamber and the sample therein (Element 2.5) and (ii) using transducer signals to determine the hemostatic parameters (Element 2.6). LaDuca Decl. ¶ 158.

TEM, as implemented in the test chambers in Schubert, is a viscoelastic method which determines clot firmness as a function of time based on force-response type testing to assess mechanical elastic linkage between the surfaces of a sample cup and a probe element. LaDuca Decl. ¶ 159. TEM clearly determines viscoelastic properties (acknowledged by the '144 Patent, Ex. 1001, 1:62-67) and hemostatic parameters (Ex. 1005, Fig. 2 and ¶¶ 0006 and 0009). Moreover, as with any force-response type testing, TEM includes transducers which transmit energy into the test chamber and receive energy out of the chamber. LaDuca Decl. ¶¶ 159-160.

Transducers for the TEM implementation in Schubert (Ex. 1005, FIGS. 3, 7a-c, and 13a-c) can include a probe pin and associated elements which (i) induce displacement of the sample by transmitting mechanical energy into the chamber (depicted in shades of blue) and (ii) receive a counter-torque based on reflected energy from the sample resulting from the elastic linkage between the cup and pin) (depicted in shades of green). LaDuca Decl. ¶ 161.

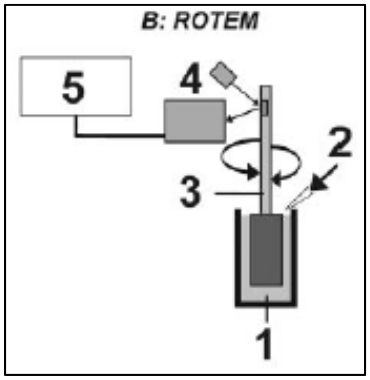


The plain meaning of transducer does not require conversion of power (or energy or force) from one form to another. Thus, transducers in TEM can include the pin to sample interface which both imparts a force and receives a counter-force from the sample. Alternatively, the transducers in TEM can be a chain of elements or components (*e.g.*, a first chain from a drive means to the probe pin and a second chain from the probe pin to the detector – see the flow chart, below with references to Schubert). LaDuca Decl. ¶ 162.



A POSA's understanding of transducers in TEM would also be informed by context provided by the SoA. For example, Calatzis (Ex. 1006) confirms that in

thromboelastometry a motor 38 is used to drive the oscillating motion of the spring through an off-center rotating cam driving a laterally-oscillating base plate that accommodates multiple spring-to-shaft drives (Ex. 1006, 7:25-40). Calatzis further explains that the fibrin fibers result in a counter torque (torque against the rotational movement) which causes the spring to bend and results in the decreased rotational amplitude (7:41-57). Finally, Calatzis describes detection being performed using either a beam generator (*e.g.,* a light-emitting diode) and a CCD-line sensor, preferably using corresponding software (3:20-35). LaDuca Decl. ¶ 163.



Scientific review literature and product literature contemporaneous to Schubert also provides context for a POSA's understanding of TEM in Schubert. Ganter (Ex. 1007) depicts electromechanical signal detection via a light source and mirror mounted on axis (4) (Figure 2B) and discloses that "the signal of the pin suspended in the blood sample is transmitted via an optical detector system" (page 1367). LaDuca Decl. ¶ 164.

Hanecke (Ex. 1008) evidences TEM implementations optically monitoring rotations by means of a mirror, a light source, and a light beam detector and converting such into a real time measurement by an integrated computer system (Motorola 68000s assembler program) (Figs. 1a and 1b and pages 423- 424 ("Principle of Rotational Thromboelastography"). LaDuca Decl. ¶ 165.

Furthermore, the 510(k) Summary for ROTEM *delta*, (Ex. 1009) evidences that a commercial implementation of TEM which uses an "oscillating pin in stationary cup for "signal generation" and "optical 4 CCD chips" for a "signal transducer" (Section 6, Summary of Technological Characteristics of the Product Comparted with the Predicate Device). LaDuca Decl. ¶ 166.

3. Teachings With Respect to Computer-Implemented Components Including Processors, Memory and Processor Executable Instructions:

While Schubert does not explicitly teach using a processor, memory or instructions stored in memory to direct interrogation (Element 1.4) or using a processor to determine the hemostatic parameters from signals transmitted to the processor from the one or more transducers (Element 2.6) (LaDuca Decl. ¶ 167), Dr. LaDuca testifies that these limitations would have been reasonably inferred by a POSA (LaDuca Decl. ¶ 168). In particular, Dr. LaDuca testifies that based on teachings in ¶ 0077 of Schubert a POSA would recognize that most any control apparatus that performs the stated functions of "measurement" (including, "controlling measurement" and "collecting data"), "data analysis," and "user interaction" would use a processor (e.g., a microprocessor, CPU etc.) to implement and/or control such functions. LaDuca Decl. ¶¶ 168-169. Dr. LaDuca further testifies that a POSA would appreciate that data analysis resulting in generation of a clot firmness curve, such as depicted in Fig. 2, clearly requires a processor. LaDuca Decl.

¶169. Thus (based on Ex. 1005, ¶ 0077) a POSA would have reasonably inferred the control apparatus includes a processor for data measurement and data analysis. LaDuca Decl. ¶169.

Turning to (Element 2.7) (Table 2 in Section IV.B.) Schubert explicitly teaches each of (i) performing at least three measurements in parallel (claim 20), (ii) determining the hemostatic parameters in parallel (claim 42) and (iii) determining a curve associated with a viscoelastic property generated from the interrogation as a function of time (claim 61). (Ex. 1005, FIG. 2 and ¶¶ 0008, 0016 and 0053). LaDuca Decl. ¶ 170. It is clear that Schubert does parallel measurements in its multiple different-reagent-chambers, just as disclosed and claimed in the '144 patent. While Schubert does not explicitly teach that these functions are implemented "in parallel" by a processor (*i.e.*, via processor executable instruction) – neither does the '144 patent. Dr. LaDuca testifies that a POSA would have reasonably inferred that a processor would be used to perform measurements in parallel as well as to produce a curve (*e.g.*, the curve of FIG. 2). *Id.* As stated in the preceding paragraph, a POSA would have reasonably inferred (based on Schubert ¶ 0077) that the control apparatus in Schubert includes a processor for data measurement. Furthermore, a POSA would have instantly recognized using a processor for increasing automation (such as performing measurements in parallel). LaDuca Decl. ¶ 171. Also as stated

multiple times herein, it would be self-evident to a POSA that the curve of Fig. 2 is processor-generated; it cannot be human-generated. *Id.*

The '144 patent relies on a similar implicit understand of the use of the processor for performing measurements in parallel in support of the claims. Indeed, the '144 patent does not explicitly describe any instructions or algorithms for performing measurements in parallel. Nor does the original disclosure of the '144 patent suggest that parallel measurements are due to a processor implementation. Rather, the specification merely generally states that "[t]he processing of the disclosed methods, devices and systems can be performed by software components" (Ex. 1001, 13:46-14:3). This is similar to Schubert, which generally teaches that control apparatus of the measurement system contains "mechanical and electronic parts required for measurement, data analysis and user interaction." (Ex. 1005, ¶ 0077). LaDuca Decl. ¶ 172.

A POSA's would also understand TEM (as implemented in Schubert) to include a processor for interrogation and data analysis (including for performing measurements in parallel and generating clot-firmness curves) based on context provided by the SoA. Calatzis (Ex. 1006) explicitly states "preferably using corresponding software" for detection (3:20-35). Ganter (Ex. 1007) evidences TEM as a computer-based system which includes electromechanical transducers (4) and data processing (5), and generates and graphically displays tracings representing

changes in viscoelasticity (Figs. 1-3 and page 1367). Haenecke (Ex. 1008) evidences that TEM includes real time measurement by an integrated computer system (Figs. 1a and 1b and pages 423-24 ("Principle of Rotational Thromboelastography"). The Decision Summary for ROTEM *delta* (Ex. 1010) explicitly discloses for commercial implementations of TEM in ROTEM *delta*, that "Software on the measurement path is used for measurement result calculation, controlling functions, monitoring the measurement process and data analysis…[where] measurement is represented in a graphical picture and as numeric results" (Section O, System Descriptions). LaDuca Decl. ¶ 172.

B. Apparatus Claim 1:

Claim 1 of the '144 patent is anticipated by Schubert at least since each and every element as set forth in the claim is found, either expressly, implicitly or inherently described in Schubert. LaDuca Decl. ¶ 174-182. Claim elements are referenced with respect to Table A (Section IV.B).

Element 1.1 [apparatus for evaluating hemostasis]: Schubert teaches a cartridge device for evaluating hemostasis by measuring viscoelastic characteristics of a blood sample. Abstract and ¶¶ 0006, 0012, 0022, 0024, 0025, 0077, 0083, 0084. Furthermore, the '144 patent acknowledges that TEM (implemented in Schubert) measures the combined effects of all components of hemostasis (Ex. 1001, 1:62-67).

Element 1.2 [housing configured to couple to a system]: Schubert teaches that the cartridge device includes a housing and that the housing is configured to couple to a system. Fig. 13 c, Abstract and ¶¶ 0029, 0038, 0077 and ¶ 0093.

Elements 1.3 and 1.4 [transducer(s) for each test chamber and processing for directing the transducers to interrogate a viscoelastic property]: Schubert explicitly, inherently or implicitly teaches both Elements 1.3 and 1.4. The application of Schubert with respect to (i) viscoelastic methods (such as TEM) (ii) transducers, and (iii) computer-implemented components including processors, memory and processor executable instructions, is described in great detail in the dedicated sections above (Sections IX.A.1-3).

Element 1.5 [first, second and third chambers]: Schubert teaches a preferred embodiment of a cartridge with four measurement chambers (¶¶ 0081-0083) defined by the cartridge (Fig. 13*c*, Abstract and ¶ 0093).

Element 1.6 [fluid pathway for sample distribution via an inlet]: Schubert teaches a fluid pathway with an inlet defined by the housing which receives a test sample from an external vessel, where the fluid pathway is in communication with and distributes the test sample to each of the test chambers. Fig. 6, ¶¶ 0024, 0047, 0048 and 0079. *See* the annotated Fig. 6 of Schubert, above.

Element 1.7 [test chambers having reagent(s)]: Schubert teaches that each of the measurement cavities includes reagents. Figs. 4-6 and ¶¶ 0078-0079 and 0082.

Measurement cavities 20, 20' may be integrally formed with the reagent cavities (19, 19'). ¶¶ 0039-0040 and ¶0080. Thus in some embodiments, the reagents are mixed with the test sample prior to being delivered to the measurement cavities.

Element 1.8 [test chambers being configured to be interrogated to determine hemostatic parameters]: Schubert teaches that the measurement cavities receive blood and are configured for performing a test on the blood sample to determine a plurality of hemostatic parameters. Abstract and ¶¶ 0031 and 0088. Schubert teaches embodiments implementing TEM in a measuring system 40 and cartridge (FIGS. 7a-*c* and 13*a*-*c* and ¶¶ 0085-0088, 0099-0102 and 0106-0163). TEM is further described in the FIELD OF INVENTION section of Schubert (Fig. 3 and ¶¶ 0010-0011) as an example of a "viscoelastic method" which determine clot firmness. Schubert teaches that clot firmness is "a functional parameter, which is important for haemostasis in vivo" (¶¶ 0006; also ¶ 0012, “haemostatic status”). FIG. 2 depicts an example clot firmness curve for TEM and Schubert describes example parameters which can be derived from clot firmness, including "clotting time" CT, clot formation time (CFT) (which is a clot rate parameter) and maximum clot firmness (MCF) (Fig. 2 and ¶ 0009).

Elements 1.9, 1.10 and 1.11 [reagent(s) in each of the test chambers for activating coagulation and reagent(s) in the second test chamber for inhibiting platelet contraction]: Schubert teaches preferred embodiments where each of first

second and third chambers include an activator of coagulation and where the second chamber further includes an inhibitor of platelet contraction. ¶ 0083 teaches combining INTEM, EXTEM and FIBTEM coagulation tests within one cartridge. As stated above (in Section IX.A.), these trademark terms refer to specific well known and industry standard tests at the time of the Schubert publication.[7] INTEM is disclosed as including a reagent for intrinsic activation (intrinsic activator) and was known to include a contact activator as a reagent (ellagic acid plus phospholipid). EXTEM is disclosed as including a reagent for extrinsic activation (extrinsic activator) and was known to include an extrinsic activator (Tissue Factor). FIBTEM is disclosed as including reagents for extrinsic activation as well as for suppressing thrombocyte function (extrinsic activator plus cytochalasin D). FIBTEM assay was known to combine extrinsic activation (using Tissue Factor) and cytochalasin D (an inhibitor of platelet function, specifically platelet contraction).

C. System Claims 20, 42 and 61:

Claims 20, 42 and 61 of the '144 patent are also anticipated by Schubert. LaDuca Decl. ¶ 183-189. Claim elements are referenced with respect to Table B (Section IV.B).

[7] (LaDuca Decl. ¶ 140 as supported by Ex. 1026 and Ex. 1027)

Element 2.1 [system for evaluating hemostasis]: Schubert teaches a system for evaluating hemostasis by measuring viscoelastic characteristics of a blood sample (same support as Element 1.1)

Element 2.2 [first and second test chambers]: Schubert teaches a preferred embodiment of a cartridge with four measurement chambers (same support as Element 1.5)

Element 2.3 [test chambers having reagent(s)]: Schubert teaches that each of the measurement cavities includes reagents (same support as Element 1.7)

Element 2.4 [test chambers configured to receive blood and be interrogated to determine a hemostatic parameter]: Schubert teaches that the measurement cavities receive blood and are configured for performing a test on the blood sample to determine a plurality of hemostatic parameters (same support as Element 1.8)

Elements 2.5, 2.6 and 2.7 [transducer(s) for transmitting energy and receiving reflected energy, processor for determining hemostatic parameters from transducer signals and claim specific processing, i.e., for parallel measurement or curve generation]: Schubert explicitly, inherently or implicitly teaches Elements 2.5, 2.6 and 2.7. The application of Schubert with respect to (i) viscoelastic methods (such as TEM) (ii) transducers, and (iii) computer-implemented components including processors, memory and processor executable

instructions, is described in great detail in the dedicated sections above (Sections IX.A.1-3).

Elements 2.8 and 2.9 [first chamber includes reagent(s) for activating coagulation and second chamber includes reagent(s) for activating coagulation and other claim specific reagent(s), i.e., reagent(s) which reduce changes in clot mechanical properties or reagent(s) which inhibit platelet functions]: Schubert teaches preferred embodiments where each of the chambers include an activator of coagulation and where the second chamber further includes an inhibitor of platelet contraction which would also cause a reduction in changes in clot mechanical properties (*i.e.*, it would prevent clot formation thereby decreasing clot firmness).

D. Dependent Clams:

Dependent claims 2-4, 9, 11-14, 16-19, 21, 30, 39, 50, 58 and 63 are also anticipated by Schubert. LaDuca Decl. ¶ 190-201.

Claim 2 [change in clot mechanical properties]: Schubert teaches interrogation based on a change in clot mechanical properties. ¶ 0011. The '144 Patent (Ex. 1001, 1:62-67) acknowledges that thromboelastography (TEG) and rotational thromboelastometer (ROTEM) are "techniques that monitor the viscoelastic properties of WB [Whole Blood]." Claim 21 evidences that viscoelastic properties are clot mechanical properties.

Claim 3 [lyophilized]: While Schubert does not explicitly teach lyophilized beads, ¶ 0045 does teach that the at least one reagent can be in pulverized, solid or liquid form. Also ¶ 0021 teaches preventing the reaction of the reagents prior to measurement by supplying such in a lyophilized state. A POSA would have understood pulverized to constitute a "powder" form and "solid" to constitute a firm stable shape (such as a bead or pellet). LaDuca Decl. ¶ 192. As such the use of beads or pellets as a solid form would have been implicit based on a POSA's ordinary understanding of reagents in a solid or lyophilized state. In addition, beads and pellets were commonly known and commercially available solid state reagents at the time of Schubert. Id. Use of lyophilized reagents is also discussed in Section V.C.3.c).[8]

[8] For the same reasons it would have been implicit in Schubert, a pellet or bead solid state form would have been an obvious design choice for a POSA. Beads and pellets were commonly known and commercially available solid state reagents at the time of Schubert. Furthermore, a POSA would have understood different forms of solid state reagents could have been used with a reasonable expectation of success. This is supported, *e.g.*, by Phadke teaching that "pellets would, if available, be useful for the practical delivery of reagents in microfluidic systems, where the volumes of

Claim 4 [housing forming cartridge . . .]: Schubert teaches that housing forms a cartridge comprising the plurality of test chambers and the fluid pathway. This is addressed in Elements 1.2 and 1.6 of claim 1.

Claim 9 [disposable cartridge]: Schubert teaches that cartridge device 50 is a disposable part. ¶ 0098.

Claims 11 and 12 [reagents]: As assessed in Elements 1.9, 1.10 and 1.11 of the claim 1, INTEM includes ellagic acid, EXTEM includes tissue factor and FIBTEM includes tissue factor and cytochalasin D. The combination of INTEM or EXTEM along with FIBTEM thus meets claims 11 and 12.

Claims 13 and 14 [assessment of components of hemostasis]: Schubert teaches assessing components of hemostasis that include combined effects of coagulation, platelets, and fibrinolysis as well as assessing components of hemostasis that include plasma coagulation factors, platelets, fibrinogen, and fibrinolytic factors of the plasma. ¶ 0006 teaches assessing clot firmness "from the formation of the first fibrin fibers until the dissolution of the blood clot by fibrinolysis" where "[c]lot firmness results from multiple interlinked processes: coagulation activation, thrombin formation, fibrin formation and polymerization,

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reagents are on the scale of a few microliters, and where reaction chambers are only a few millimeters in dimension" (Ex. 1014, ¶ 0006). LaDuca Decl. ¶ 192, footnote 4.

platelet activation and fibrin-platelet interaction and can be compromised by fibrinolysis." Also ¶ 0083 teaches comparing EXTEM to INTEM to determine "if a coagulation disorder results from lack of fibrinogen or a malfunction of platelets." INTEM and EXTEM test intrinsic and extrinsic coagulation factors, respectively. Comparing EXTEM to FIBTEM assesses platelets and fibrinogen and INTEM and EXTEM are performed through fibrinolysis providing for assessment of fibrinolytic factors.

Claims 16, 39, 58 and 63 [LED emitter + detector]: If these LED claims are not invalidated for clear lack of support (Section VII(C)), they would read on Schubert thus be anticipated. Schubert teaches that as the test sample coagulates, a rotational oscillation amplitude of the shaft decreases and is detected via a light beam originating from detecting means 10. While the light beam in Schubert is not explicitly generated by an LED, Dr. LaDuca testifies that this would have been reasonably inferred by a POSA as a common way for generating a light beam. LaDuca Decl. ¶197. This is supported, for example, by Calatzis explicitly teaching generation of a collimated light beam using a non-collimated light source such as a

diode (Ex. 1006, 3:20-35) in the context of what appears to be the same optical detection system disclosed in Schubert.[9]

Claim 17 [agonists and antagonists; testing in parallel]: Schubert teaches using a combination of agonists and antagonists in a FIBTEM assay and assessing different components of hemostasis by comparing INTEM EXTEM and FIBTEM tests (different tests which activate or suppress different parts of the coagulation cascade). Schubert also teaches conducting such differential tests in parallel. ¶¶ 0006, 0018 and 0083. Furthermore, Schubert teaches a cartridge arrangement for simultaneously distributing a sample to a plurality of measurement cavities to run a series of interrelated tests.

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[9] For the same reasons it would have been implicit, an LED would have been an obvious design choice. In particular, an LED would be an obvious option for a POSA as a light source which can be used in an optical detection system, such as described in Schubert. Again this is supported by Calatzis using a diode (Ex. 1006, 3:20-35) for what appears to be the same optical detection system disclosed in Schubert. Thus, a POSA would have been motivated with a reasonable expectation of success to rely on such teachings. LaDuca Decl. ¶197, footnote 5.

Claims 18, 30 and 50 [upstream mixing]: If these "pre-mix" claims are not invalidated for clear lack of support (Section VII(C)), they would read on Schubert thus be anticipated. In some embodiments in Schubert, the reagent cavity may be upstream from the measurement cavity (rather than integrally formed therewith). See Figs. 4 and 6. Thus, Schubert teaches that the sample may be mixed with the reagent prior to the sample arriving in the measurement cavity.

Claim 19 [induced displacement of sample]: Schubert teaches interrogation based on induced displacement of the test sample produced by the one or more transducers. In particular, the differential motion of the pin relative to the cup while a fibrin mesh attaches to both stretches the fibrin mesh, thus deforming it and displacing portions of the sample. Thus, in the implementation of TEM in Schubert, an oscillating motion of the pin induces displacement of the sample within the meaning of claim 19. See Sections IX.A.1-2.

Claim 21 [clot mechanical properties, measurable changes of which are reduced in claim 20, comprise one or more viscoelastic properties]: Schubert teaches that that the clot mechanical properties interrogated and impacted by the reagents in the second chamber are viscoelastic properties. ¶¶ 0006, 0025-31, 0078.

X. GROUNDS 4 AND 5: IT IS MORE LIKELY THAN NOT THAT THE CHALLENGED CLAIMS ARE UNPATENTABLE AS OBVIOUS OVER SCHUBERT UNDER 35 U.S.C. § 103:

As stated in Section IX., Schubert fails to explicitly teach that using a processor, memory or instructions stored in memory to direct such interrogation (Element 1.4) or that a processor is used to determine the hemostatic parameters from signals transmitted to the processor from the one or more transducers (Element 2.6). Furthermore, with respect to (Element 2.7), Schubert fails to explicitly teach a processor and processor executable instructions for (i) performing at least three measurements in parallel (claim 20), (ii) determining the hemostatic parameters in parallel (claim 42) and (iii) determining a curve associated with a viscoelastic property generated from the interrogation as a function of time (claim 61).

Petitioner submits in Section IX (Ground 3) that these elements are nonetheless anticipated by Schubert because they would have been reasonably inferred from or necessarily implied by Schubert. Should the Board find that this is not the case, the Board may find clearly under Grounds 4 and 5 in this section that any deficiencies in Schubert with respect to these elements would have been obvious over Schubert in view of the SoA. LaDuca Decl. ¶¶ 202-203.

A. GROUND 4: Obviousness over Schubert in view of the State of the Art on TEG and TEM:

In supporting anticipation by Schubert, references including patent literature cited in Schubert for TEM as well as scientific review literature and product

information on TEM (contemporaneous with Schubert) were discussed in Sections IX.A.1-3. These supporting references, also render Elements 1.4 and 2.6 and 2.7 obvious over Schubert (based on at least the same teachings cited in the Sections IX.A.1-3). LaDuca Decl. ¶ 204.

The discussed references all describe implementations of TEM. As previously stated, TEM was a well-known diagnostic test in the SoA at the time of Schubert. Schubert essentially teaches implementing pre-existing TEM diagnostic testing in a novel cartridge-based system. Accordingly, a POSA would have been motivated with a reasonable expectation of success to rely on the robust literature surrounding TEM at the time of Schubert, in the context of such implementation. Also, as noted above, a POSA would clearly rely on teachings relating to TEM from references which are cited to in Schubert for that purpose (*e.g.*, Calatzis). LaDuca Decl. ¶ 205. Furthermore, a POSA would have found Elements 1.4, 2.6 and 2.7 obvious over Schubert in view of the TEG 5000 User Manual (Ex. 1011). The TEG 5000 User Manual teaches using software for interrogation and data processing in viscoelastic methods. Most of the TEG 5000 User Manual is directed towards the TEG Analytical Software (TAS). A "minimum computer configuration" is required (Page, 173). Interrogation of the sample and automatically carried out using the computer (pages 128 and 149-150). Furthermore the software provides for "simultaneous analysis of up to eight samples, automatic calculation of a wide range

of coagulation parameters, and data management facilities" (page 2; see also page

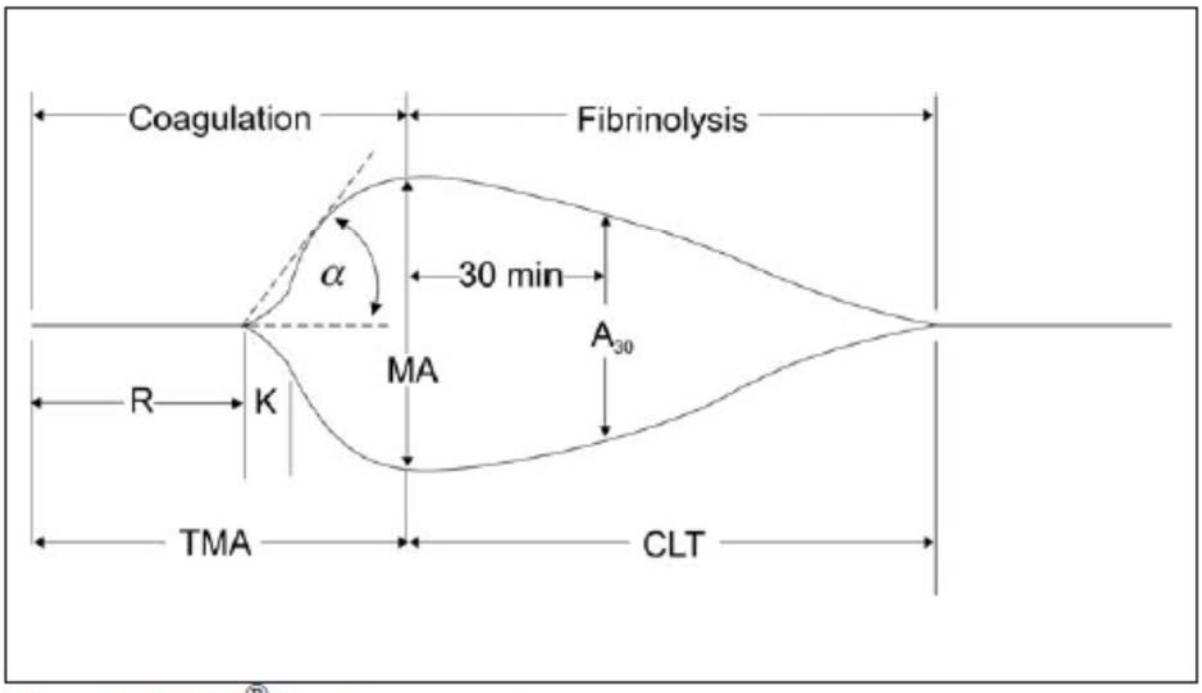

Figure 1.2. TEG® tracing parameters

22 on "differential diagnosis (simultaneous runs)). The resulting hemostasis profile is a measure of the time it takes for the first fibrin strand to be formed, the kinetics of clot formation, the strength of the clot (in shear elasticity units of dyn/cm2) and dissolution of clot (Figure 1.2)" (pages 3-4). The data is collected and displayed automatically. "While the sample is running, data is being collected and the various TEG® tracing parameters are calculated. As this happens, the sample data panel begins to fill with the numerical results at the same time that the tracing panel fills with the graphical results" (page 44). LaDuca Decl. ¶ 210.

While the TEG 5000 User Manual relates to a commercial implementation of TEG, a POSA would have found the teachings therein relating to interrogation and

data analysis equally applicable with respect to TEM. Indeed, Schubert itself expressly suggested adapting its device to the TEG approach. (Ex. 1005, ¶¶ 0007, 0084). Furthermore, TEG and TEM are very similar with respect to interrogation and data analysis – both use similar pin and cup mechanisms, both are viscoelastic methods which measure clot firmness as a function of changes in amplitude of the pin, and produce curves and extrapolate parameters[10] therefrom. TEM and TEG also can utilize similar non-contact methods of monitoring changes in rotational amplitude of the pin.[11] Thus, a POSA could reasonably apply teachings from the TEG 5000 User Manual relating to TEG (relating to interrogation and data

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[10] A POSA would have understood that corresponding parameters exist between TEG and TEM as corroborated by the March 23, 2010 FDA 510(K) clearance (No. K083842) for the ROTEM *delta* Thromboelastometry System ("ROTEM *delta*") (Ex. 1009 and 1010).

[11] Cohen (Ex. 1012) (which was cited in Schubert, Ex. 1005, ¶ 0010, as relating to TEG and is illustrative of the TEG 5000 design) illustrates (Ex. 1012, FIGS. 3 and 4) and describes (Ex. 1012, 3:54-4:4 and 4:35-45) the testing technique for TEG as including "an appropriate non-contacting rotation detector (*e.g.*,…laser/mirror/CCD arrangement, etc.)…to detect rotation of the transmission shaft."

processing) with respect to the implementation of TEM in Schubert, with a reasonable expectation of success. LaDuca Decl. ¶¶ 207-209.

B. GROUND 5: Obviousness over Schubert in view of the State of the Art on Acoustic-Echo Based Interrogation and Data Analysis:

It would have also been obvious, based on the pre-existing SoA, for a POSA to modify Schubert based on Viola 2009 (Ex. 1013) to implement acoustic-echo based interrogation and data analysis in the disclosed multi-chamber cartridge-based system (*i.e.*, replacing the interrogation and data analysis of TEM). LaDuca Decl. ¶ 211. Viola 2009 is but one example of a prior publication in which the '144 patent inventors teach an acoustic-echo technique for interrogation and data analysis. 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. LaDuca Decl. ¶ 212.

By substituting the acoustic-echo technique for interrogation and data analysis in Viola 2009 for TEM in Schubert, Viola 2009 addresses any deficiencies in Schubert with respect to each of Elements 1.3, 1.4, 1.8 of claim 1 and Elements 2.4, 2.5, 2.6 and 2.7 of independent claims 20, 42 and 61. In particular, the acoustic-echo technique for interrogating the cuvette in Viola 2009 (including interrogation and data analysis involving transducers and the use of a processor as well as configuration of the test chamber for acoustic-echo interrogation) would have been

obvious to implement with respect to each of the test chambers in Schubert. LaDuca Decl. ¶ 217.

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" and teaching that acoustic-echo interrogation 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). LaDuca Decl. ¶ 218.

The acoustic-echo instrumentation described in Section 2.3 of Viola 2009 includes a transducer for transmitting sound into cuvettes holding a blood sample (Section 2.3 teaching using a transducer to applying ultrasound pulses thereby inducing an acoustic radiation force). Viola further teaches how to configure the test chambers for acoustic interrogation (Section 2.3 teaching "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." LaDuca Decl. ¶ 219

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 (Section 4). LaDuca Decl. ¶ 220.

Viola 2009 further describes implementing acoustic-echo based interrogation and data analysis in a prototype bench-top instrument (Section 2.3). In the example bench-top prototype described in Viola 2009, the prototype includes a custom printed circuit board (PCB) controlled by an external laptop computer via USB 2.0 connection, where the PCB controls the transducers. Viola 2009 further teaches using a laptop to process the ultrasound data and calculate parameters (for example, clotting times TC1 and TC2, clotting formation rate CFR and clot stiffness S) (Table 1, and Sections 2.2 and 2.6). In particular, Viola 2009 teaches that the digitized data is transferred to the adjacent laptop computer for data analysis (Sections 2.3 and 2.6). The data is first processed to remove noise. Then, pulse-to-pulse time delays are estimated and used to generate a time-displacement curve which is then fitted (normalized) to form a relative compliance curve (stiffness as a function of time). The parameters are then derived by fitting a sigmoidal curve and evaluating the first derivative of the curve. (Section 2.6). Notably, this description of interrogation and data processing in Viola 2009 is nearly identical to the '144 patent. LaDuca Decl. ¶ 221.

While it is not explicitly disclosed, Viola 2009 contemplates implementation of testing for a plurality of test chambers. For example, Viola 2009 teaches that the instrument supports two transmit and 4 receive ultrasound channels. (Section 2.3). Moreover, Viola 2009 teaches running differential tests (which include intrinsic activation using kaolin (Section 2.4) and different concentrations of the platelet inhibitor abxicimab including a control amount of 0 (Figure 4, Section 3.2). Figure 4 compares maximum stiffness (S) (also referred to therein as baseline compliance) for samples with and without abciximab as part of the stated objective in Section 3.2 of "assessment of platelet function." Furthermore, Viola 2009 explicitly teaches "utilizing different activators, blocking agents, and other reagents" which evidences running multiple different tests. Thus, it would have been obvious to run INTEM, EXTEM and FIBTEM tests in parallel (as disclosed in Schubert) with the acoustic-echo technique disclosed in Viola 2009. LaDuca Decl. ¶ 222.

It would have been obvious for a POSA to combine the teachings of Viola 2009 relating to acoustic-echo interrogation and data analysis with the teachings of Schubert. In particular, Schubert teaches in 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" (Ex. 1005, ¶ 0077) thereby providing motivation for modifying the interrogation and data analysis techniques described in Schubert with a reasonable chance of success.

Moreover, Viola 2009 explicitly teaches that the acoustic-echo interrogation and data analysis techniques described therein are an improvement over mechanical methods (such as described in the Schubert), thereby providing motivation for person of ordinary skill in the art to replace mechanical interrogation in Schubert with the acoustic-echo technique with a reasonable expectation of success. Viola 2009, Section 1. LaDuca Decl. ¶¶ 213-215.

As reviewed in Section V.C.2.c, the acoustic-echo technique provides a similar response curve for clot stiffness over time which is comparable to the data provided by the TEM implementation in Schubert (as normalized to TEG). Thus, substituting acoustic-echo interrogation and analysis for TEM is tantamount to simple substitution of one known element for another to obtain predictable results. Viola 2009 is analogous art at least since it relates to implementation of a viscoelastic method of testing, same as Schubert. Furthermore, there is nothing in Viola 2009 or Schubert that would teach away from the combination. Because both Schubert and Viola 2009 both utilize a fixed "cup" or chamber, a modification of the Schubert chamber to eliminate the pin and substitute a sound-transparent or focusing surface is a relatively straightforward design change that saves space and complexity of the cartridge, providing further reason to combine. LaDuca Decl. ¶ 216.

XI. CONCLUSION

Petitioner submits that for the reasons set forth above, supported by the declaration of Dr. LaDuca and the Exhibits, it has been shown that more likely than not, Challenged Claims are invalid under all of 35 U.S.C. §§ 102, 103 and 112 and should reviewed by the Board and canceled.

Date: April 24, 2019

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 Post Grant Review of U.S. Patent No. (and accompanying exhibits), was served in its entirety on April 24, 2019, upon counsel for Patent Owner via overnight courier:

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Patent owner's correspondence
address of record for U.S. Patent No. 10,031,144

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

The undersigned hereby certifies that the attached Petition, including footnotes, but not the cover page, exhibit list, table of contents, table of authorities, mandatory notices, and certifications, contains 18,549 words, as measured by the Word Count function of Microsoft Word. This is less than the limit of 18,700 words as specified by 37 C.F.R. § 42.24(a)(ii).

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TABLE OF EXHIBITS

Ex. 1001	U.S. Patent No. 10,031,144 ("the '144 Patent")
Ex. 1002	Declaration of Dr. Frank LaDuca ("LaDuca Decl.")
Ex. 1003	Prosecution History for U.S. Patent Application No. 15/202,059 issued as the '144 Patent.
Ex. 1004	U.S. Provisional Application No. 61/443,088, earliest priority application for '144 Patent.
Ex. 1005	U.S. Patent Application Publication No. 2010/0154520 ("Schubert")
Ex. 1006	U.S. Patent No. 5,777,215 ("Calatzis")
Ex. 1007	Ganter, MT and Hofer, CK, Coagulation monitoring: current techniques and clinical use of viscoelastic point-of-care coagulation devices, Anesth Analg. 2008 May;106(5):1366-75 (PMID: 18420846) ("Ganter")
Ex. 1008	Hanecke, P and Klouche, M, Thrombelastography Today: Practicability and Analytical Power, Transfusion Medicine and Hemotherapy. 34. 421-428 (2007) ("Hanecke")
Ex. 1009	The 510(k) Summary for ROTEM delta, FDA clearance No. K083842 ("the 510(k) Summary for ROTEM *delta*")
Ex. 1010	The 510(k) Substantial Equivalence Determination Decision Summary for ROTEM delta, FDA clearance No. K083842 (the "Decision Summary for ROTEM *delta*")
Ex. 1011	User Manual (2007) for TEG 5000 Thrombelastograph Hemostasis System with TEG Analytical Software (TAS) Version 4.2.3 including an addendum (2008) for TEG Analytical Software (TAS) Version 4.3 (the "TEG 5000 User Manual")
Ex. 1012	U.S. Patent No. 6,537,819 ("Cohen")
Ex. 1013	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., published online 2009 Oct 25, PubMed Central P.M.C.I.D. PMC2791922 (“Viola 2009”)
Ex. 1014	U.S. Patent Application No. 2007/0259348 (“Phadke”)
Ex. 1015	U.S. Patent No. 6,221,672 (“Baugh”)
Ex. 1016	Lang T, Depka M; Possibilities and limitations of thrombelastometry/-graphy; Hamostaseologie 26:Suppl 1, S20-29, 2006 (“Lang 2006”)
Ex. 1017	Nielson V; A Comparison of the Thrombelastograph and ROTEM”, Blood Coagulation and Fibrinolysis 18:3, 247-252, 2007 (“Nielson 2007”)
Ex. 1018	U.S. Publication No. 2005/0148899 (“Walker”)
Ex. 1019	Viola F, Kramer MD, Lawrence MB, *et al.*, Sonorheometry: A Noncontact Method for the Dynamic Assessment of Thrombosis. Ann Biomed Eng. 2004;32(5):696-705 (“Viola 2004”)
Ex. 1020	Viola, *et al.*, "Sonorheometry: A new Method for Assessing Coagulation Potential," IEEE Ultrasonics Symposium, vol. 1, 2007, pp. 1001-1004 (“Viola 2007”)
Ex. 1021	U.S. Patent No. 5,534,226 (“Gavin”)
Ex. 1022	U.S. Patent No. 6,016,712 (“Warden”)
Ex. 1023	U.S. Patent No. 6,613,286 (“Braun ‘286”)
Ex. 1024	U.S. Patent No. 5,091,304 (“LaDuca”)
Ex. 1025	U.S. Patent No. 6,451,610 (“Gorman”)
Ex. 1026	Lang, T, *et al.*, “Multi-centre investigation on reference ranges for ROTEM thromboelastometry,” *Blood Coagul Fibrinolysis*, 16(4):301-10 (2005), PubMed P.M.I.D.: 15870552. (“Lang 2005”)
Ex. 1027	Rugeri, L, *et al.*, “Diagnosis of early coagulation abnormalities in trauma patients by rotation thrombelastography,” *J Thromb Haemost*, 5(2):289-95 (2007), PubMed P.M.I.D.: 17109736 (“Rugeri 2007”)

Ex. 1028	*Instrumentation Laboratory Co. v. HemoSonics LLP*, IPR2017-00852, Paper No. 47 (PTAB Feb. 13, 2019) ("'852 FWD")
Ex. 1029	*Instrumentation Laboratory Co. v. HemoSonics LLP*, IPR2017-00855, Paper No. 55 (PTAB Feb. 13, 2019) ("'971 FWD")