EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR
The Quantra QPlus System

DECISION MEMORANDUM

A. DEN Number:

DEN180017

B. Purpose for Submission:

De novo request for evaluation of automatic class III designation of the Quantra QPlus System

C. Measurand:

Clot Time (CT), Clot Time with Heparinase (CTH), Clot Time Ratio (CTR), Clot Stiffness (CS), Fibrinogen Contribution to Clot Stiffness (FCS), Platelet Contribution to Clot Stiffness (PCS)

D. Type of Test:

Sonic Estimation of Elasticity via Resonance (SEER) Sonorheometry to measure the shear modulus of whole blood during coagulation, semi-quantitative

E. Applicant:

HemoSonics, LLC

F. Proprietary and Established Names:

Quantra QPlus System

Quantra Hemostasis Analyzer (Model HS-002)

QPlus Cartridge

Quantra Controls Level 1 and Level 2

G. Regulatory Information:

1. Regulation section:

   21 CFR §864.5430

2. Classification:

   Class II (special controls)

3. Product code:

   QFR

4. Panel:

   Hematology (81)

H. Intended Use:

1. Intended use(s):

   See Indications for use below

2. Indication(s) for use:

   The Quantra QPlus System is composed of the Quantra Hemostasis Analyzer, QPlus Cartridge, and Quantra Quality Controls Level 1 and 2. The Quantra QPlus System is intended for in vitro diagnostic use.

   The Quantra Hemostasis Analyzer uses Sonic Estimation of Elasticity via Resonance (SEER) Sonorheometry, an ultrasound-based technology, to measure the shear modulus of whole blood during coagulation. The QPlus Cartridge is a multi-channel cartridge that provides semi-quantitative indications of the coagulation state of a 3.2% citrated venous whole blood sample. The QPlus Cartridge includes tests to assess coagulation characteristics via the intrinsic pathway, via the extrinsic pathway, and includes tests with a heparin neutralizer.

   The system is intended to be used by trained professionals at the point-of-care and in clinical laboratories to evaluate the viscoelastic properties of whole blood by means of the following functional parameters: Clot Time (CT), Clot Time with Heparinase (CTH), Clot Stiffness (CS), Fibrinogen Contribution to Clot Stiffness (FCS), Platelet Contribution to Clot Stiffness (PCS), and Clot Time Ratio (CTR).

   The Quantra QPlus System is indicated for the evaluation of blood coagulation in perioperative patients age 18 years and older to assess possible hypocoagulable and hypercoagulable conditions in cardiovascular or major orthopedic surgeries before, during, and following the procedure.

   Results obtained with the Quantra QPlus System should not be the sole basis for patient diagnosis.

For prescription use only.

3. Special conditions for use statement(s):

   For prescription use only

   Result(s) from the device are not intended to be used as the sole basis for a patient diagnosis

4. Special instrument requirements:

   Quantra Hemostasis Analyzer

I. Device Description:

The Quantra QPlus System is an in vitro diagnostic device designed to assess a patient's coagulation status by measuring the shear modulus of a blood sample during clot formation in perioperative settings in the point of care (POC) or clinical laboratory settings. The system consists of the Quantra Hemostasis Analyzer (instrument), QPlus Cartridge (single-use disposable cartridge), Quantra Controls Level 1 and Level 2 (external quality control materials), and the Quantra Cleaning Cartridge.

The Quantra Hemostasis Analyzer is a fully integrated and automated in vitro diagnostic device designed to assess a patient's coagulation status by measuring the viscoelastic properties of a blood sample during clot formation. The analyzer consists of a base instrument with a software component. The instrument and the software are a closed system, using only Quantra assay cartridges.

The QPlus Cartridge is a single-use four-channel plastic cartridge which has a sample port on one end to draw the blood sample into the cartridge without requiring any sample pipetting. Lyophilized reagents are embedded into the four channels within the cartridge. The four channels enable four independent reactions/tests to be run simultaneously.

The cartridge comes sealed in a foil pouch. After a QPlus Cartridge is removed from its primary packaging, it is inserted into the instrument dock. A venous whole blood sample, collected in a 3.2% sodium citrate anticoagulant blood collection tube (minimum volume 2.7 mL), is attached directly to the cartridge and the test is initiated using the touch screen interface on the Quantra Hemostasis Analyzer. The fluidic system within the instrument draws the sample into the cartridge where it is warmed to 37°C, aliquoted, introduced and mixed with the lyophilized reagents, and analyzed. When the test is complete, the cartridge is released from the dock to be disposed of in an appropriate biosafety sharps container.

The analyzer displays the test results in three different views: dial display screen, stiffness curves, and trend data. The dial display screen is the primary viewing screen and has a dial for each of the six output parameters. Each dial shows the reference range, assay measurement range, parameter abbreviation, and the numerical result for the corresponding

parameter. The stiffness curves are a graphical display of shear modulus measurements over time that enable the user to view the development of clot stiffness over time. The trend data display provides numeric results of tests run during the past 48 hours for a specific patient. In the trend data view, multiple samples from the same patient are displayed.

The device outputs four directly measured parameters (Clot Time, Clot Time with Heparinase, Clot Stiffness, and Fibrinogen Contribution to Clot Stiffness) as well as two calculated parameters (Clot Time Ratio and Platelet Contribution to Clot Stiffness).

Description of the QPlus Cartridge Channels/Reagents and Corresponding Parameters

Channel	Reagents	Parameter
1	Kaolin, buffers, calcium, stabilizers	Clot Time (CT in seconds)
2	Kaolin, heparinase I, buffers, calcium, stabilizers	Clot Time with Heparinase (CTH in seconds)
3	Thromboplastin, polybrene, buffers, calcium, stabilizers	Clot Stiffness (CS in hPa)
4	Thromboplastin, polybrene, abciximab, buffers, calcium, stabilizers	Fibrinogen Contribution to Clot Stiffness (FCS in hPa)

The Quantra Quality Controls (QQC) Level 1 and Level 2 are used to monitor the performance of the Quantra Hemostasis System with the QPlus Cartridges. The control materials are comprised of animal plasma (caprine and porcine) collected in 3.2% sodium citrate with human fixed red blood cells, buffers, and a preservative. Each vial contains a 3.4 mL solution. The vial is shipped with an extender that serves to guide the vial into the cartridge's evacuated sample tube attachment. The Quantra Quality Controls Level 1 and Level 2 test the following parameters: CT, CTH, CTR, CS, and FCS.

The Quantra Cleaning Cartridge is an accessory for the Quantra Hemostasis Analyzer and is intended to be used for simple, periodic cleaning.

J. Standard/Guidance Document Referenced:

1. CLSI EP05-A3, Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Third Edition

2. CLSI EP07-A2: Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition

3. CLSI EP25-A, Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline

4. CLSI C28-A3c: Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline – Third Edition

5. International Electrotechnical Commission. IEC 61010-1: Safety requirements for electrical equipment for measurement, control, and laboratory use, Part 1: General

requirements, 2010, 3rd Edition

6. International Electrotechnical Commission. IEC 61010-2-081: Safety requirements for electrical equipment for measurement, control and laboratory use - Part 2-010: Particular requirements for laboratory equipment for heating of materials, 2014, 3rd Edition

7. International Electrotechnical Commission. IEC 61010-2-101: Safety requirements for electrical equipment for measurement, control, and laboratory use, Part 2-101: Particular requirements for in vitro diagnostic (IVD) medical equipment, 2015, 2nd Edition

8. European Commission. EN 60601-1-2: Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance – Collateral Standard: Electromagnetic disturbances – Requirements and tests, 2015 (IEC 601601-2:2014)

9. European Commission. EN 61326-2-6:2013: Electrical equipment for measurement, control and laboratory use. EMC requirements. General requirements. February 2013.

10. International Electrotechnical Commission. IEC 62359 Ultrasonics – Field characterization - Test methods for the determination of thermal and mechanical indices related to medical diagnostic ultrasonic fields, 2010, 2nd Edition

11. National Electrical Manufacturers Association. NEMA UD 2-2004 (R2009) Acoustic Output Measurement Standard for Diagnostic Ultrasound Equipment, Revision 3

K. Test Principle:

The Quantra Hemostasis Analyzer uses Sonic Estimation of Elasticity via Resonance (SEER) Sonorheometry, an ultrasound-based technology, to measure the viscoelastic properties of citrated whole blood during clot formation in real time. SEER Sonorheometry applies a series of ultrasound pulses to a whole blood sample held in the cartridge and processes the returning echoes to measure the stiffness of the blood sample (the evolution of shear modulus, i.e., clot stiffness) during coagulation as a function of time.

Shear modulus is an objective parameter that describes the elastic properties of a solid material. The shear modulus of a blood clot evolves during its formation and is directly related to the blood clot structure and the function of the blood components. Clot time is determined by identifying when the shear modulus begins to increase (in seconds). This is calculated as the point at which the rate of change of shear modulus crosses a pre-defined threshold. Clot stiffness is determined by measuring the stiffness after the clot has formed. This is calculated by identifying the shear modulus value at a specific time after clot time (shear modulus value 7 minutes after clot time). Stiffness is reported in units of hectoPascals (hPa; same as shear modulus). The clot time and clot stiffness parameters, described below, provide information about the functional role of the coagulation factors, fibrinogen, and platelets.

1. <u>Clot Time (CT)</u>
   CT is measured in Channel 1 using calcium acetate to re-calcify the blood sample and

kaolin to provide contact surface activation of coagulation via the intrinsic pathway. Kaolin is an aluminum silicate mineral with a negatively charged surface. CT, reported in seconds, can indicate prolongation of the intrinsic pathway. CT, used in combination with CTH, may indicate the presence of heparin in a sample.

2. Clot Time with Heparinase (CTH)
   CTH is measured in Channel 2 using calcium acetate to re-calcify the blood sample, kaolin to activate the intrinsic pathway, and heparinase I to neutralize heparin. CTH, reported in seconds, provides an evaluation of coagulation without the effect of heparin anticoagulation.

3. Clot Stiffness (CS)
   CS is measured in Channel 3 using calcium acetate to re-calcify the blood sample, thromboplastin (tissue factor) to activate the extrinsic pathway of coagulation, and polybrene to neutralize heparin. CS, reported in hPa, provides an evaluation of coagulation without the effect of heparin anticoagulation.

4. Fibrinogen Contribution to Clot Stiffness (FCS)
   FCS is measured in Channel 4 using calcium acetate to re-calcify the blood sample, thromboplastin (tissue factor) to activate the extrinsic pathway of coagulation, polybrene to neutralize heparin, and abciximab to inhibit platelet aggregation and contraction. Abciximab is the Fab fragment of a monoclonal antibody that binds to the platelet surface receptor GPIIb/IIIa. FCS, reported in hPa, provides an evaluation of the contribution of functional fibrinogen to clot stiffness without the effect of heparin anticoagulation.

5. The Clot Time Ratio (CTR)
   CTR is defined as the ratio of CT and CTH (i.e. CT/CTH). The CTR parameter indicates prolongation of the intrinsic pathway which is likely due to the influence of unfractionated heparin. However, CTR values are not directly correlated with heparin concentration. If CTR is > 1.4, it is only implicative of the presence of heparin in a sample.

6. Platelet Contribution to Clot Stiffness (PCS)
   PCS is defined as the difference between CS and FCS. PCS, reported in hPa, provides an evaluation of the contribution of platelet function to clot stiffness.

L. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. Precision/Reproducibility:

   Single-site precision study: A single-site precision study was performed over the course of 20 days, with two runs per day, and two replicates per run using QQC Level 1 and Level 2. A single Quantra Hemostasis Analyzer and a single lot of QPlus Cartridges

were utilized in the study, which was performed by a single operator. The results of this study demonstrated within-laboratory precision (total) of 3.6–6.1% for QQC Level 1 and 3.6–9.8% for QQC Level 2. The QPlus Cartridges run on the Quantra Hemostasis Analyzer demonstrated acceptable precision when evaluated using control material.

Single-site precision study results summary:

QQC Level 1										
Parameter	**N**	**Mean**	**Repeatability**		**Between-Day**		**Between-Run**		**Total (Within-laboratory)**	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
CT (sec)	80	171.41	7.58	4.4	0.00	0.0	3.20	1.9	8.23	4.8
CTH (sec)	80	171.95	5.99	3.5	0.00	0.0	3.40	2.0	6.89	4.0
CTR	80	1.00	0.06	5.9	0.00	0.0	0.02	1.6	0.06	6.1
CS (hPa)	80	19.71	0.56	2.8	0.00	0.0	0.65	3.3	0.86	4.3
FCS (hPa)	80	19.87	0.54	2.7	0.00	0.0	0.48	2.4	0.72	3.6
PCS (hPa)	80	<0.2	N/A*		N/A*		N/A*		N/A*	
QQC Level 2										
Parameter	**N**	**Mean**	**Repeatability**		**Between-Day**		**Between-Run**		**Total (Within-laboratory)**	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
CT (sec)	80	309.50	26.28	8.5	0.00	0.0	10.18	3.3	28.18	9.1
CTH (sec)	80	179.89	6.20	3.4	0.00	0.0	2.01	1.1	6.51	3.6
CTR	80	1.72	0.15	8.5	0.00	0.0	0.08	4.8	0.17	9.8
CS (hPa)	80	13.24	0.50	3.8	0.15	1.1	0.10	0.7	0.53	4.0
FCS (hPa)	80	13.36	0.47	3.6	0.00	0.0	0.20	1.5	0.51	3.8
PCS (hPa)	80	<0.2	N/A*		N/A*		N/A*		N/A*	

**QQC materials do not contain platelets*

Multi-site precision study: The multi-site precision study was performed over the course of six days, with one run per day, and three replicates per run, evaluating a single lot of QQC Level 1 and Level 2. The sites selected for the study were an internal site, one clinical laboratory, and one near-patient test environment. For each site, two Quantra Hemostasis Analyzers with one operator per site were utilized in the study. Each site used the same lot of QQC Level 1 and Level 2, and three QPlus Cartridge lots were evaluated at each site. The multi-site precision study demonstrated within-laboratory % CVs ranging from 3.3–7.1% for QQC Level 1 and 2.8–11.6% for QQC Level 2 for each site evaluated individually. For pooled data from all sites, total precision (reproducibility) %CVs ranged from 3.9–5.3% for QQC Level 1 and 3.6–8.3% for QQC Level 2. Acceptable precision was demonstrated at multiple sites using control material.

Multisite precision study results summary:

All Sites - QQC Level 1																
Parameter	N	Mean	Repeatability		Between-Day		Between-Lot		Between-Analyzer		Within-Site		Between-Site		Total	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
CT (sec)	108	186.44	5.83	3.1	3.17	1.7	2.23	1.2	1.61	0.9	3.87	2.1	3.07	1.6	7.64	4.1
CTH (sec)	108	186.73	5.11	2.7	4.19	2.2	0.0	0.0	0.00	0.0	4.19	2.2	2.86	1.5	7.20	3.9
CTR	108	1.00	0.04	4.0	0.00	0.0	0.01	1.0	0.01	1.4	0.01	1.4	0.00	0.0	0.05	5.0
CS (hPa)	108	21.57	0.67	3.1	0.41	1.9	0.36	1.7	0.26	1.2	0.59	2.8	0.00	0.0	0.90	4.2
FCS (hPa)	108	22.45	0.76	3.4	0.39	1.7	0.38	1.7	0.78	3.5	0.91	3.5	0.00	0.0	1.19	5.3
PCS (hPa)	108	<2	N/A*		N/A*		N/A*		N/A*		N/A*		N/A*		N/A*	

All Sites - QQC Level 2																
Parameter	N	Mean	Repeatability		Between-Day		Between-Lot		Between-Analyzer		Within-Site		Between-Site		Total	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
CT (sec)	108	259.42	17.77	6.8	9.48	3.6	4.74	1.8	0.00	0.0	10.6	4.2	0.00	0.0	20.69	8.0
CTH (sec)	108	179.86	5.81	3.2	2.76	1.5	0.91	0.5	0.55	0.3	2.9	1.6	0.00	0.0	6.49	3.6
CTR	108	1.44	0.11	7.6	0.03	2.1	0.01	0.7	0.01	0.7	0.03	2.2	0.00	0.0	0.12	8.3
CS (hPa)	108	11.76	0.42	3.6	0.53	4.5	0.19	1.6	0.28	2.4	0.62	5.3	0.00	0.0	0.74	6.3
FCS (hPa)	108	12.25	0.40	3.3	0.47	3.8	0.27	2.2	0.39	3.2	0.65	5.3	0.26	3.1	0.81	6.6
PCS (hPa)	108	<2	N/A*		N/A*		N/A*		N/A*		N/A*		N/A*		N/A*	

**QQC materials do not contain platelets*

Whole blood repeatability study: The whole blood repeatability study was conducted at one internal site, by two operators, utilizing three lots of QPlus Cartridges and three Quantra Hemostasis Analyzers. The whole blood specimens evaluated included normal, abnormal, and contrived samples to cover the reportable ranges for each of the measured parameters (CT, CTH, CS and FCS).

Whole blood repeatability study results summary:

Parameter	Range†	n	Mean	Between-Replicate		Between-Lot		Between-Operator		Total	
				SD	%CV	SD	%CV	SD	%CV	SD	%CV
CT (sec)	60–104	3	71.8–95.2	3.4–7.4	4.1–10.4	0.0–2.0	0.0–2.8	0.0–0.0	0.0–0.0	3.5–8.3	4.1–10.8
	104–166	12	111.3–147.3	3.8–7.0	2.7–5.3	0.0–5.7	0.0–4.7	0.0–5.9	0.0–4.2	4.9–10.4	4.0–8.8
	166–480	12	169.5–409.1	6.2–36.0	2.6–10.7	0.0–13.4	0.0–4.0	0.0 - 21.5	0.0 - 5.3	6.6–38.4	3.7–11.5
CTH (sec)	60–103	4	66.1–97.5	3.3–6.6	3.5–7.8	0.0–5.7	0.0–5.9	0.0–2.3	0.0–2.3	3.8–8.2	4.0–8.4
	103–153	20	111.2–150.8	1.9–10.2	1.3–7.0	0.0–5.3	0.0–3.8	0.0–3.7	0.0–2.6	3.5–11.2	2.4–7.5
	153–480	3	163.2–373.4	6.8–34.3	3.4–9.2	0.0–26.8	0.0–7.2	0.0–8.3	0.0–2.8	8.4–44.0	5.2–11.8
CTR	≤ 1.4	22	0.98–1.41	0.03–0.14	2.0–12.3	0.00–0.08	0.0–7.6	0.00–0.06	0.0–5.4	0.05–0.17	4.2–14.5
	> 1.4	4	1.46–2.87	0.10–0.18	4.7–9.0	0.00–0.09	0.0–4.8	0.00–0.05	0.0–2.0	0.10–0.18	5.0–9.2
CS	2.0–13.0	6	2.03–12.13	0.11–0.64	3.0–5.6	0.00–0.22	0.0–2.9	0.00–0.12	0.0–1.0	0.12–0.84	3.4–7.5

Parameter	Range†	n	Mean	Between-Replicate		Between-Lot		Between-Operator		Total	
				SD	%CV	SD	%CV	SD	%CV	SD	%CV
(hPa)	13.0–33.2	16	15.81–31.06	0.33–1.53	2.0–7.2	0.00–0.69	0.0–4.0	0.00 - 1.17	0.0–3.8	0.41–2.03	2.4–9.1
	33.2–65.0	4	34.19–64.21	0.98–4.91	2.8 - 10.0	0.80–2.77	1.6–8.1	0.00–0.77	0.0–2.3	2.80–4.98	5.0–10.1
FCS (hPa)	0.2–1.0	2	0.53–0.79	0.09–0.10	13.1–17.1	0.03–0.05	5.4–6.3	0.00–0.08	0.0 –10.3	0.10–0.14*	17.9–18.0*
	1.0–3.7	16	1.28–3.56	0.03–0.23	2.2–10.3	0.00–0.20	0.0–9.0	0.00–0.19	0.0–8.7	0.06–0.30	3.9–13.6
	3.7–30.0	9	4.41–23.65	0.15–1.34	3.1–17.5	0.00–0.42	0.0–3.0	0.00–0.41	0.0–2.9	0.22–1.46	4.4–20.4**
PCS (hPa)	2.0–11.9	4	7.13–11.59	0.31–0.59	3.9–5.6	0.00–0.23	0.0–2.9	0.00–0.13	0.0–1.1	0.38–0.81	4.7–7.7
	11.9–29.8	17	14.46–26.62	0.39–2.22	2.3–9.1	0.00–1.39	0.0–5.7	0.00–1.29	0.0–5.3	0.42–2.71	2.9–11.1
	29.8–50.0	3	30.63–45.82	0.99–4.39	3.2–10.3	0.99–2.8	2.3–9.0	0.00–0.84	0.0–2.7	3.07–4.5	7.4–10.6

† For analysis, and presentation of results, samples for each QPlus parameter were grouped into two or three categories to include samples whose results were below, within, or above the reference range for that parameter (or above/below 1.4 CTR).
** For FCS below the reference range, results were compared to expected precision of CV%(total) ≤ 15% or SD(total) ≤ 0.2 hPa.*
***Included 1 sample with %CV (total) = 20.4%. The sample preparation steps required to achieve the high fibrinogen level of this sample likely contributed to the higher than expected precision. %CV (total) for the remaining 8 samples was 4.4–10.7%.*

Total imprecision (CV_{tot}) for CTH was determined to be below 12% for all samples. The total imprecision (CV_{tot}) for CT was below 12% for all samples within the reportable range. Total imprecision (CV_{tot}) for CS was determined to be below 12% for all samples. Total imprecision (CV_{tot} or SD_{tot}) for FCS was below 14% or 0.2 hPa for all but one sample tested. Acceptable precision was demonstrated using whole blood.

b. Linearity/assay reportable range:

Validation that the QPlus Cartridge parameters demonstrate functional performance across the claimed reportable ranges for each parameter was supported by validating the response of the QPlus Cartridge parameters to factors known to impact clotting time and clot stiffness (i.e. demonstration of a functional response). Data from these functional response studies, in addition to evaluation of precision (whole blood repeatability study) across the assay reportable ranges, and evaluation of clinical samples to cover the reportable ranges, supported the claimed reportable ranges.

Summary of studies supporting reportable ranges:

Parameter	Reportable Range	Clinical Study Sample Range (QPlus Cartridge Parameter)	Dose-Response Study Sample Range [test variable]	Whole Blood Repeatability Sample Range
CT (sec)	60–480	(b) (4)		
CTH	60–480			

Parameter	Reportable Range	Clinical Study Sample Range (QPlus Cartridge Parameter)	Dose-Response Study Sample Range [test variable]	Whole Blood Repeatability Sample Range
(sec)			(b) (4)	
CTR	0.8–4.0	(b) (4)		(b) (4)
CS (hPa)	2.0–65.0			
FCS (hPa)	0.2–30.0			
PCS (hPa)	2.0–50.0			

In order to validate the functional response of CT and CTH across the claimed reportable range, a heparin dose-response study and a dabigatran dose-response study were performed. In the heparin dose-response study, testing was performed on whole blood samples from five normal donors and spiked to generate samples containing five different levels of unfractionated heparin (final concentrations of 0–1.0 U/mL heparin evaluated). The results from this study demonstrated an approximate linear increase in CT for heparin concentrations from 0–0.5 U/mL. Above 0.5 U/mL heparin, the results generally exceeded the upper limit of the reportable range for CT.

In the dabigatran dose-response study, (b) (4)
(b) (4)

To validate the reportable ranges for the clot stiffness parameters (CS, FCS, PCS), samples containing varying levels of platelets and/or fibrinogen were prepared and analyzed.(b) (4)

To validate the response of clot stiffness parameters to varying platelet counts, whole blood specimens from (b) (4) donors were used to generate platelet-enriched, platelet-depleted and normal whole blood. Results indicated that PCS and CS increased in approximately linear relation to platelet count, tested over a range of (b) (4) platelets/µL.

To validate the response of clot stiffness parameters to different levels of platelet activity, whole blood specimens from one normal donor were treated with varying levels of the platelet inhibitor ReoPro (abciximab) to produce samples with varying levels of platelet activity. Whole blood was treated with ReoPro (b) (4) mg/mL (b) (4) µL) to produce samples containing (b) (4) µg/mL of the inhibitor. Results showed that CS and PCS decreased with progressively greater inhibition of platelet activity. Specifically, total clot stiffness (CS) decreased and approached a limiting value approximately equal to FCS, as expected for complete inhibition of PCS. PCS approached 0.0 hPa with increasing ReoPro, indicating complete platelet inhibition. FCS remained constant, regardless of ReoPro concentration.

To validate the response of clot stiffness parameters to different levels of fibrinogen, samples with reduced or elevated fibrinogen were generated. Fibrinogen levels in samples were confirmed using the Clauss fibrinogen assay. Samples with fibrinogen levels ranging from (b) (4) mg/dL to greater than (b) (4) mg/dL were evaluated. FCS showed a curvilinear relationship with fibrinogen for the range (b) (4) mg/dL. CS showed an approximate linear increase with fibrinogen for the range (b) (4) mg/dL.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

Calibrator and control material:

The Quantra Analyzer performs internal QC checks of all system components at regular intervals and during each phase of a test run on a cartridge to verify that the instrument hardware and all subsystems are functioning properly. There is no calibration material for the Quantra Hemostasis Analyzer, as user calibration is not required.

There are two levels of Quantra control material – Quantra Quality Control (QQC) Level 1 and Level 2. The QQC Level 1 and Level 2 contain materials to test the output parameters for the QPlus Cartridge: CT, CTH, CTR, CS and FCS. These QQC materials do not include platelets; therefore, values for the PCS parameter are expected to be at or below the reportable range (< 2 hPa). Value Assignment cards, supplied with each individual lot of QQC material, provide the lot-specific minimum and maximum values for the QPlus Cartridge output parameters.

QQC Level 1 and Level 2 vials are single-use only and should be stored frozen at -80°C. When stored frozen, QQC vials should be thawed completely at room temperature before use and vigorously resuspended before loading onto the QPlus Cartridge.

Quantra Quality Controls are recommended for use when changing QPlus Cartridge lots, changing control lots, or after significant changes are made to the Quantra instrument. End-users are recommended to run normal whole blood samples with QPlus Cartridges at times when QQC materials are recommended for use, in order to provide additional confirmation of QPlus Cartridge test performance. End-users may

also confirm the performance of the PCS arameter on QPlus Cartridges by running whole blood from a normal healthy donor with and without addition of the platelet inhibitor abciximab.

QPlus Cartridge Stability:

In order to establish initial shelf-life and expiration dating of QPlus Cartridges, three (b) (4) Each of the three cartridge lots were tested with the following sample types: Quantra Quality Control Level 1, Quantra Quality Control Level 2, whole blood without heparin, and whole blood with (b) (4) heparin/mL. One cartridge lot was also tested using (b) (4) heparin/mL. (b) (4)

Cartridges are intended to be used shortly after opening (the foil pouch package); however, a study was conducted to determine the stability of QPlus Cartridge parameter measurements after the cartridge was opened for 15 minutes (b) (4) The in-use cartridge stability study supports use of the QPlus Cartridge up to 15 minutes outside of the pouch/with opened pouch. Cartridges outside the pouch or with an open pouch should be discarded after 15 minutes.

d. Detection limit:

The lower limits of detection for all parameters (CT, CTH, CTR, CS, FCS, PCS) were supported by clinical data, precision with whole blood samples, and dose-response testing to validate functionality of the parameters across the claimed reportable ranges. Specifically, lower limits of the reportable ranges for all parameters were determined as values that: 1) reflect clinically relevant values as observed in clinical samples from the intended use population and supported by dose-response testing, 2) could be quantitated reliably with respect to pre-defined acceptance criteria for precision, and 3) were compatible with instrument considerations. The lowest reportable output for clot time parameters (CT and CTH) – 60 seconds – is based on instrument and test considerations (e.g. time needed for sample to be completely mixed and equilibrated prior to measurement). The lower limits of the reportable ranges for the clot stiffness parameters (CS and FCS) are based on the achievement of an accurate estimate of the signal to noise ratio for the lowest reported values.

Summary of studies supporting reportable ranges and lower limits of detection:

Parameter	Reportable Range	Clinical Test Sample Range	Dose-Response Study Sample Range [test variable]	Precision Study Sample Range
CT (sec)	60–480	(b) (4)	(b) (4)	(b) (4)
CTH (sec)	60–480			
CTR	0.8–4.0			
CS (hPa)	2.0–65.0			
FCS (hPa)	0.2–30.0			
PCS (hPa)	2.0–50.0			

e. Analytical specificity (interference):

The interference study evaluated the effect of the potential endogenous interferents lipid (Intralipid to achieve targeted triglyceride concentrations) and hemolysis. The interference study also evaluated the effect of the following potential exogenous interferents: clopidogrel, tranexamic acid, aspirin, dabigatran, rivaroxaban, heparin, and protamine sulfate. Whole blood samples were spiked to achieve the final concentrations of potential interferents. Normal whole blood and hypocoagulable blood were evaluated for potential interferences. Hypocoagulable blood types evaluated were: 1. heparin-treated whole blood (final concentration 0.20–0.25 U/mL unfractionated heparin), 2. abciximab-treated whole blood (final concentration 3–5µg/mL), and 3. fibrinogen-depleted plasma. The interference study also evaluated additional potential sources of variability for their effect on QPlus Cartridge parameter results, such as testing with a discard tube (70–95% normal volume), an under-filled tube (60–100% normal volume, 5–6 different levels tested), and hemodilution (0%, 10%, 30%, and 50% dilution of blood sample). Spiking studies were performed at one or two levels of potential interferent with the number of replicates at each level selected to provide a 95% confidence interval (two-sided), per the CLSI EP07-A2 guideline. Dose-response studies were performed at multiple levels in duplicate or triplicate to determine the relationship between concentration and effect on QPlus Cartridge parameter results. The table below describes the potential interferents for which no effect on each parameter was observed at the stated level/concentration for normal whole blood.

Agent or Variable [concentrations tested]	**Normal Whole Blood** Highest concentration tested where no effect observed (≤ 10% change compared to control)					
	CTH	**CT**	**CTR**	**CS**	**PCS**	**FCS**
(b) (4)						

Agent or Variable [concentrations tested]	Normal Whole Blood Highest concentration tested where no effect observed (≤ 10% change compared to control)					
	CTH	CT	CTR	CS	PCS	FCS
(b) (4)						

The table below describes the potential interferents for which no effect on QPlus Cartridge parameters was observed at the stated level/concentration for hypocoagulable whole blood.

Agent or Variable [concentrations tested]	Hypocoagulable Blood Heparin-treated (H); Abciximab-treated (X); Fibrinogen-depleted (F) Highest concentration tested where no effect observed (≤ 10% change compared to control)					
	CTH	CT	CTR	CS	PCS	FCS
(b) (4)						

The table below describes the potential interferents for which an effect was

demonstrated on QPlus Cartridge parameters at the stated level/concentration for normal and hypocoagulable whole blood.

Agent or Variable	Concentration(s) at which an effect was demonstrated (> 10% change compared to control)	Matrix	Effect
(b) (4)			

Agent or Variable	Concentration(s) at which an effect was demonstrated (> 10% change compared to control)	Matrix	Effect
(b) (4)			

For all parameters, the use of a discard tube or a tube filled at less than 80% of the specified volume may affect results or cause incomplete filling of the cartridge.

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

Not applicable

b. Matrix comparison:

Not applicable

3. Clinical studies:

a. Clinical Sensitivity:

Not applicable

b. Clinical specificity:

Not applicable

c. Other clinical supportive data (when a. and b. are not applicable):

The clinical performance study of the Quantra QPlus System was a multi-center, prospective observational study involving patients 18 years of age or older undergoing major cardiac and/or vascular procedures or major orthopedic surgery (primarily complex spine surgeries). The study was conducted at four clinical sites and was registered on ClinicalTrials.gov (NCT03152461). The study sites were the University of Virginia School of Medicine, Duke University Medical Center, Medical University of South Carolina, and University of Maryland School of Medicine. The aim of this study was to demonstrate the clinical performance of the Quantra QPlus System (Quantra Hemostasis Analyzer with the QPlus Cartridge) in patients undergoing major cardiac and/or vascular procedures or major orthopedic surgery (primarily complex spine surgeries) for its ability to aid in coagulation evaluations. Quantra Hemostasis Analyzers utilized in the clinical study were located near patient, directly outside of the operating rooms, in the operating room STAT Lab or in clinical research laboratories.

The enrolled patient set consisted of 302 consented subjects across the four sites. A total of 271 subjects >18 years of age were consented, of which 264 were patients scheduled for cardiac, vascular or orthopedic surgery, and 7 were patients who presented with acute bleeding or suspected hypercoagulation in a post-surgical unit following cardiac surgery. In addition, 13 patients with an abnormal coagulation profile were consented, as were 18 normal individuals whose blood was artificially manipulated (contrived) to mimic an abnormal coagulation profile. These abnormal contrived samples were used to supplement the clinical data collected from surgical subjects. Of the enrolled patient set, 25 did not complete the study. The final eligible patient set consisted of 277 subjects.

For subjects undergoing cardiac or vascular surgery involving cardiopulmonary bypass (CPB), the study protocol specified testing at four timepoints: 1) preoperatively after the induction of anesthesia before surgical incision (Baseline); 2) during surgery before the end of CPB (while the patient was still fully anticoagulated with heparin; Bypass); 3) after protamine reversal of heparin (Post-Bypass); and 4) postoperatively, within 1 to 24 hours after arrival in the Intensive Care Unit (ICU).

For subjects undergoing orthopedic surgery (e.g., complex spine surgery), cardiac or vascular surgery not involving CPB, the protocol specified testing to be performed at three time points selected from the following: 1) preoperatively before surgical incision (Baseline); 2) during surgery (1 or 2 timepoints; Intra-surgery); and 3) postoperatively, within 1 to 24 hours after arrival in the ICU.

From each subject, venous blood was collected at the three or four timepoints for analysis on the Quantra QPlus System, ROTEM delta Thromboelastometry System (Instrumentation Laboratory; K101533, K083842) and standard laboratory tests.

<u>Comparison of Quantra QPlus System performance to standard laboratory tests (SLTs):</u>

A clinical concordance analysis was conducted to determine the agreement of each

QPlus Cartridge test output to a corresponding Clinical Composite Index (CCI) comprised of data from FDA-cleared standard laboratory tests and the status of heparin use (for the patient). The CCIs were developed solely to serve as laboratory-based comparators to the Quantra and were designed based on in-depth review of the clinical literature, clinical guidelines and consideration from multiple physicians.

Summary table with CCI definitions

Parameter	Corresponding CCI	Standard Laboratory Tests Comprising each CCI
CT	CCI1	aPTT, ACT, INR, and presence of unfractionated heparin
CS	CCI2	Clauss fibrinogen, Platelet Count
FCS	CCI3	Clauss fibrinogen
PCS	CCI4	Clauss fibrinogen, Platelet Count
CTR	CCI5	aPTT, ACT, and presence of unfractionated heparin

Cardiac surgery and major orthopedic surgery patient samples were tested with the Quantra QPlus System and SLTs. Results from samples were categorized for the QPlus Cartridge test parameters as "Low," "Normal/Subclinical" and "High" based on the reference intervals established for each QPlus Cartridge parameter (with the exception of CTR, which has a threshold of 1.4). These Quantra QPlus System results were then compared to the results from the defined set of SLTs, which comprised the corresponding CCIs. For each CCI, specific criteria were defined to assign clinical samples as "High," "Low" or "Normal/Subclinical," representing increased, decreased or normal/subclinical coagulation function, respectively (i.e., hypercoagulable, hypocoagulable, normal coagulation). The concordance of the classification of the Quantra QPlus System results compared to the SLT results was then used to determine the overall agreement and agreement within coagulation state sub-categories between the Quantra and the CCIs.

Summary table of concordance analysis for QPlus Cartridge parameters vs. CCIs

Parameter vs CCI	Overall Agreement* (Lower bound 95% CI)	Low* (lower bound 95% CI)	Normal/subclinical* (lower bound 95% CI)	High* (lower bound 95% CI)
CT vs CCI1	0.72 (0.69)	0.98 (0.96)	0.62 (0.58)	0.92 (0.83)
CS vs CCI2	0.77 (0.73)	0.83 (0.66)	0.80 (0.77)	0.55 (0.42)
FCS vs CCI3	0.84 (0.81)	0.77 (0.50)	0.84 (0.80)	0.98 (0.93)
PCS vs CCI4	0.75 (0.72)	0.86 (0.71)	0.80 (0.76)	0.45 (0.35)
CTR** vs CCI5	0.98 (0.97)	0.94 (0.90)	0.99 (0.98)	N/A

**Point estimate*

***For CTR, clinical samples were categorized as Low if CTR > 1.4 or Not Low-Not High if CTR ≤ 1.4.*

Validation of the CTR threshold was demonstrated through the 94% agreement in the

Low category, 99% agreement in the Not Low category, and 98% for overall agreement.

Comparison to ROTEM delta assays (K083842, K101533):

The ROTEM delta is an FDA-cleared viscoelastic device that can perform up to four tests in parallel. The assays considered in this study included the INTEM (intrinsic activation), HEPTEM (intrinsic activation with heparin neutralization), EXTEM (extrinsic activation), and FIBTEM (extrinsic activation with platelet inhibition). The objective of this analysis was to demonstrate correlation between the QPlus Cartridge parameters and comparable assays on the ROTEM delta. In particular, the QPlus CT, CTH, CS, FCS parameters were compared to the ROTEM INTEM CT, HEPTEM CT, EXTEM A20, and FIBTEM A20, respectively. Deming regression analyses were conducted for all timepoints combined (overall) to define the relationship between parameters.

Best-Fit Deming regression analysis for Quantra vs. ROTEM

Comparison	N	Best fit equation	Intercept (95% CI)	Slope (95% CI)	R*
CT vs INTEM CT	681	CT=β0 + β1*INTEM CT	13.42 (-16.647, 43.493)	0.69 (0.496, 0.887)	0.84
CTH vs HEPTEM CT	846	CTH = β0 + β1* HEPTEM CT	18.01 (4.626, 31.389)	0.65 (0.568, 0.741)	0.84
CS vs EXTEM A20	835	CS = β0 + β1*EXTEM A20/(100-EXTEM A20)	-6.65 (-8.212, -5.089)	17.22 (16.145, 18.288)	0.89
FCS vs FIBTEM A20	830	FCS = β0 + β1*FIBTEM A20/(100-FIBTEM A20)	-0.89 (-1.240, -0.548)	17.04 (15.206, 18.884)	0.87

A clinical concordance analysis was also conducted to determine the agreement of each QPlus Cartridge parameter with the corresponding ROTEM delta parameter. Clinical samples were assigned as "High," "Low," or "Normal/Subclinical" based on the respective QPlus or ROTEM normal reference ranges.

Summary table of concordance analysis for QPlus Cartridge parameters vs. ROTEM

QPlus Parameter vs ROTEM parameter	Overall Agreement* (lower bound 95% CI)	Low* (lower bound 95% CI)	Normal/Subclinical* (lower bound 95% CI)	High* (lower bound 95% CI)
CT vs INTEM CT	0.85 (0.82)	0.90 (0.86)	0.82 (0.79)	0.87 (0.80)
CS vs EXTEM A20	0.87 (0.84)	0.89 (0.82)	0.87 (0.84)	0.76 (0.63)
FCS vs FIBTEM A20	0.87 (0.85)	0.50 (0.37)	0.91 (0.88)	0.88 (0.80)

**Point estimate*

Additional clinical concordance analyses were performed in which the "High" and "Normal/Subclinical" categories were combined (to create a new, "Not Low" category) and to demonstrate concordance in hypocoagulable samples.

Summary table of concordance analysis for QPlus Cartridge parameters vs. CCI or ROTEM, overall agreement and two sub-category analysis

Comparison	Overall Agreement* (lower bound 95% CI)	Low* (lower bound 95% CI)	Not Low* (lower bound 95% CI)
CT vs CCI1	0.98 (0.97)	0.97 (0.95)	0.98 (0.97)
CS vs CCI2	0.86 (0.83)	0.83 (0.66)	0.87 (0.83)
FCS vs CCI3	0.96 (0.94)	0.77 (0.50)	0.96 (0.95)
PCS vs CCI4	0.85 (0.81)	0.86 (0.71)	0.85 (0.81)
CTR** vs CCI5	0.98 (0.97)	0.94 (0.90)	0.99 (0.98)
CT vs INTEM CT	0.96 (0.95)	0.90 (0.86)	0.99 (0.97)
CS vs EXTEM A20	0.91 (0.89)	0.89 (0.82)	0.92 (0.89)
FCS vs FIBTEM A20	0.95 (0.93)	0.50 (0.37)	0.99 (0.98)

**Point estimate*

***For CTR, clinical samples were categorized as Low if CTR > 1.4 or Not Low-Not High if CTR ≤ 1.4.*

4. Clinical cut-off:

   Not applicable

5. Expected values/Reference range:

   The reference range study conducted was a multi-center, prospective, observational study aimed at establishing reference range intervals for a healthy population for the test parameters measured using the Quantra QPlus System, consisting of the Quantra Hemostasis Analyzer (Quantra) and the QPlus Cartridge (QPlus). The study population consisted of 158 healthy male and female volunteers (18 years of age or older) successfully enrolled across three external sites that are representative of the general population in the United States. Eligible data was obtained from 129 subjects.

   To summarize, 53.5% of subjects were female and 72% were white. The mean age across all participants was 40.5 years with subject ages ranging from 18 to 70 years. Approximately one third of subjects were in each of three age categories: 18–30 years, 31–50 years, and >50 years.

Adult reference ranges for QPlus Cartridge parameters

Parameter	Unit	Reference Range*
Clot Time (CT)	Seconds	104 – 166
Heparinase Clot Time (CTH)	Seconds	103 – 153
Clot Stiffness (CS)	hectoPascals	13.0 – 33.2
Fibrinogen Contribution to Clot Stiffness (FCS)	hectoPascals	1.0 – 3.7
Platelet Contribution to Clot Stiffness (PCS)	hectoPascals	11.9 – 29.8

**The reference ranges for each QPlus Cartridge parameter are expressed as the central 95% confidence interval of the mean.*

M. Instrument Name:

Quantra Hemostasis Analyzer

N. System Descriptions:

1. Modes of Operation:

   Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?

   Yes ___X_____ or No _____

   Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?

   Yes _____ or No __X_____

2. Software:

   FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:

   Yes __X___ or No _____

3. Specimen Identification:

   Bar code reader

4. Specimen Sampling and Handling:

   The QPlus requires a fresh sample of 3 mL or more of venous whole blood collected in an evacuated 3.2% sodium citrate anticoagulant collection tube. Becton-Dickinson 13x75 mm 2.7 mL BD Vacutainer Plus plastic citrate tubes were used in testing the

QPlus Cartridges. The blood collection tube must be filled to the minimum fill line. The entire blood sample is used for analysis on the Quantra.

Do not use a discard tube as it may affect results or cause incomplete filling of the cartridge. Gently invert the blood collection tube five times before attaching it to the cartridge. Store citrated blood at room temperature. Do not store at 2–8°C. Samples should be analyzed within 4 hours after collection.

5. Calibration:

   User calibration is not required, based on the design of the instrument.

6. Quality Control:

   The Quantra Quality Controls Level 1 and Level 2 are used to monitor performance of the Quantra Plus System with QPlus Cartridges. The Quantra Quality Controls Level 1 and Level 2 contain materials to test the output parameters for the QPlus Cartridge: CT, CTH, Clot Time Ratio (CTR), CS and FCS. Both QQC Level 1 and Level 2 are comprised of animal plasma (caprine and porcine) collected in 3.2% sodium citrate with human fixed red blood cells, buffers and a preservative added. Each vial of QQC material contains a 3.4 mL solution. The vial is shipped with an extender that serves to guide the vial into the cartridge's evacuated sample tube attachment.

O. Other Supportive Instrument Performance Characteristics Data Not Covered In The "Performance Characteristics" Section above:

Specimen stability study:

This study evaluated the stability of citrated whole blood specimens at (b) (4) temperature (b) (4) and at (b) (4) Both normal specimens and two types of hypocoagulable specimens were tested (b) (4) . Five normal specimens and one specimen of each hypocoagulable specimen were evaluated at baseline/time (b) (4) for each QPlus Cartridge parameter. Results from this study support a 4-hour claim at (b) (4) for citrated whole blood specimens.

Reader Study:

A Reader Study was conducted to assess the ability of potential Quantra users to correctly interpret results displayed on the Quantra Hemostasis Analyzers dial display screen. The study was prospectively conducted at three sites using a total of 14 readers who regularly assess the blood coagulation status of patients in the critical care setting (e.g. anesthesiologists). After training on use of the Quantra and how to interpret results generated from the QPlus Cartridge parameters, participants viewed 15 Quantra dial display screens, each containing results for six QPlus Cartridge parameters, and answered a total of

180 test questions. Participants correctly interpreted results for all QPlus Cartridge parameters >95% of the time.

P. Proposed Labeling:

The labeling supports the decision to grant the De Novo request for this device.

Q. Identified Risks to Health and Identified Mitigations

Identified Risks to Health	Identified Mitigations
Incorrect test results	Transparent device performance descriptions in labeling Transparent device limitations descriptions in labeling Certain precision, performance, interference, and specimen stability testing
Incorrect interpretation of test results	Transparent device performance descriptions in labeling Transparent device limitations descriptions in labeling Certain precision, performance, interference, specimen stability, and human factors testing
Cartridge malfunction	Transparent device performance descriptions in labeling Transparent device limitations descriptions in labeling Certain precision, performance, interference, and specimen stability testing

R. Benefit/Risk Analysis:

Summary of the Assessment of the Benefit
For the Proposed Indications for Use

The Quantra QPlus System ("System") is composed of the Quantra Hemostasis Analyzer ("Analyzer"), QPlus Cartridge ("Cartridge"), and Quantra Quality Controls Level 1 and 2. The Quantra QPlus System is intended for in vitro diagnostic use. The Analyzer evaluates the hemostatic state of a blood sample. The Analyzer uses Sonic Estimation of Elasticity via Resonance (SEER) Sonorheometry to measure the shear modulus of whole blood during coagulation. The Cartridge is a multi-channel cartridge that provides semi-quantitative indications of the coagulation state of a 3.2% citrated venous whole blood sample. The System is indicated for use with perioperative patients 18 years of age or older when an evaluation of

their blood coagulation properties is desired. Coagulation evaluations are commonly used to assess possible hypocoagulable and hypercoagulable conditions in cardiovascular or major orthopedic surgeries before, during, and following the procedure.

Based on published meta-analyses, the benefits of cleared viscoelastic devices (ROTEM and TEG) in cardiovascular surgeries include short turnaround time for early intervention of coagulation dysfunction and reduced risk for transfusion-transmitted infections associated with the reduction of blood products use, for those devices indicated for such use. The use of ROTEM and TEG to monitor perioperative hemostasis in major orthopedic surgeries (e.g. complex spine surgery) is recommended by professional society guidelines. In the current de novo submission, the clinical interpretation of patient coagulation status made from the System parameter results was compared to the interpretation of coagulation status from ROTEM and standard laboratory tests. The summary of the concordance analysis for the System parameter vs. standard laboratory tests (CCIs) or ROTEM is shown in the table below.

Comparison	Overall Agreement* (lower bound 95% CI)	Low* (lower bound 95% CI)	Not Low* (lower bound 95% CI)
CT vs CCI1	0.98 [821/840] (0.97)	0.97 [182/187] (0.95)	0.98 [639/653] (0.97)
CS vs CCI2	0.86 [719/832] (0.83)	0.83 [24/29] (0.66)	0.87 [695/803] (0.83)
FCS vs CCI3	0.96 [801/833] (0.94)	0.77 [10/13] (0.50)	0.96 [791/820] (0.95)
PCS vs CCI4	0.85 [698/823] (0.81)	0.86 [25/29] (0.71)	0.85 [673/794] (0.81)
CTR vs CCI5**	0.98 [821/838] (0.97)	0.94 [156/166] (0.90)	0.99 [665/672] (0.98)
CT vs INTEM CT	0.96 [811/842] (0.95)	0.90 [195/217] (0.86)	0.99 [616/625] (0.97)
CS vs EXTEM A20	0.91 [769/841] (0.89)	0.89 [75/84] (0.82)	0.92 [694/757] (0.89)
FCS vs FIBTEM A20	0.95 [793/834] (0.93)	0.50 [34/68] (0.37)	0.99 [759/766] (0.98)

**Point estimates (lower bounds of the 95% confidence intervals) [number of observations vs total number of occurrences in the specific category].*

***For CTR, clinical samples were categorized as Low if CTR > 1.4 or Not Low-Not High if CTR ≤ 1.4.*

The benefits of the System in the intended use setting are indirectly established using the above concordant analysis. Standard laboratory tests and ROTEM are often used to assess patients' coagulation status in such clinical settings. However, there is a lack of gold standard in the assessment of perioperative coagulation dysfunction. The use of the System in cardiovascular and major orthopedic surgeries is associated with probable benefit with a moderate degree of uncertainty.

Summary of the Assessment of Risk
For the Proposed Indications for Use

False positive results may lead to erroneous reporting of hypocoagulable state, unnecessary use of blood products for those devices indicated to guide blood product use, and additional confirmatory coagulation tests. False negative results could cause failure to detect hypocoagulability and withholding/delay of effective treatment. Incorrect interpretation of test results has a similar impact as erroneous test results. Test error associated with cartridge malfunction/leak may result in delay in turnaround time. The consequences of erroneous results and test error can be significant and there is moderate uncertainty about risk.

Summary of the Assessment of the Benefit-Risk
For the Proposed Indications for Use

The benefit-risk balance of this device is undetermined and requires additional mitigations.

Summary of the Assessment of the Benefit-Risk, considering general controls
For the Proposed Indications for Use

The benefit-risk balance of this device is undetermined and requires additional mitigations.

Summary of the Assessment of the Benefit-Risk, considering risk mitigation strategies
For the Proposed Indications for Use

The probable benefits of this device outweigh the probable risks when considering the labeling limitations below and special controls.

Labeling limitations: The IU/IFU states that results from Quantra QPlus System analysis should not be the sole basis for a patient diagnosis.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

S. Conclusion

The information provided in this de novo submission is sufficient to classify this device into class II under regulation 21 CFR 864.5430. FDA believes that the stated special controls, in combination with the applicable general controls, provide a reasonable assurance of the safety and effectiveness of the device type. The device is classified under the following:

Product Code: QFR
Device Type: Coagulation system for the measurement of whole blood viscoelastic properties in perioperative patients
Class: II (special controls)
Regulation: 21 CFR 864.5430

(a) Identification:

A coagulation system for the measurement of whole blood viscoelastic properties in perioperative patients is an in vitro diagnostic device used to evaluate blood coagulation, fibrinolysis, or both, in perioperative patients, as an aid in the assessment of coagulopathies when used in conjunction with clinical signs and symptoms and other clinical and laboratory findings.

(b) Classification: Class II (special controls). The special controls for this device are:

(1) Design verification and validation must include detailed documentation of, and results from, the following:

i. A study assessing precision using protocols determined to be acceptable by FDA, to cover the measurement range for each reported parameter (test output). Testing must include native specimens with coagulation profiles representative of the intended use population. In order to cover the measuring range, testing may include a limited number of contrived specimens, not to exceed 10–20%, or as otherwise deemed appropriate by FDA. The contrived specimens must be prepared to resemble clinical specimens. This testing must evaluate repeatability and reproducibility and provide assessments of within-run, within-day, between-run, between-day, between-reagent lot, between-instrument, between-site, and between-operator precision, as applicable to the system;

ii. Studies that demonstrate the performance of each parameter (test output) throughout the claimed measurement range, to include linearity studies or dose-response studies, as applicable to the parameter (test output);

iii. Potential interferent study that includes evaluation of hemolyzed and lipemic samples as potential interferents; exogenous and endogenous interferents associated with each patient population intended for use with the device, and which might be expected to affect assay performance, must be evaluated; and potential interferents that are specific for, or related to, the technology or methodology of the device. Evaluation of all potential interferents must be performed using a protocol determined to be acceptable to the FDA (e.g., an FDA-recognized standard) and include both normal and abnormal specimens covering coagulation profiles representative of the intended use population;

iv. A study that evaluates specimen stability under the intended conditions for specimen collection, handling, and storage, using samples that cover the coagulation profiles representative of the intended use population, and using protocols determined to be acceptable by FDA;

v. A multi-site clinical study, determined to be acceptable by FDA, demonstrating performance, relative to clinically relevant and clinically

validated laboratory test(s) for each parameter (test output). Further, the study must meet all of the following criteria:

A. The study must be performed in the intended use population and include representation from all patient populations for whom the device is intended to be used. Potential endogenous and exogenous interferents for each target patient population must be evaluated or known prior to the study;

B. The study must be conducted at a minimum of three external sites representative of the intended use setting by the intended operators;

C. Test samples must be collected at time intervals relevant to the device's use in the intended use population;

D. Clinical specimens, which cover coagulation profiles representative of the intended use population, must be evaluated at each of the three clinical sites in the study;

E. Analysis of the concordance of clinical interpretation of patient coagulation status made from individual test parameter (test output) results as compared to clinical interpretation of coagulation status from a clinically relevant laboratory test or tests (e.g., a comparative viscoelastic device or standard laboratory tests) must be conducted; and

F. Expected (reference) values for each parameter (test output) must be demonstrated by testing a statistically appropriate number of samples from apparently healthy normal individuals.

vi. For a device with a user interface that has information that needs to be interpreted by the user in correctly using the device to achieve the intended test results or a device that does not provide a final output that is a comprehensive interpretation of all parameter (test output) results, a study evaluating the ability of device users to correctly interpret results;

vii. For any device indicated to guide blood product use, a clinical outcome study determined to be acceptable by FDA that specifically validates the device's indicated use in guiding blood product use; and

viii. For any device indicated to guide use of medication, a clinical outcome study determined to be acceptable by FDA that specifically validates the device's indicated use in guiding use of medication.

(2) The labeling required under 21 CFR 809.10(b) must include the following:

i. A summary of results from the study required by paragraph (b)(1)(i), including repeatability, reproducibility, and assessments of within-run, within-day, between-run, between-day, between-reagent lot, between-instrument, between-site, and between-operator precision, as applicable to the system.

ii. The claimed measurement range of each parameter (test output), as supported by demonstrated performance of the parameter (test output) throughout the claimed measurement range, including, but not limited to, studies required by paragraphs (b)(1)(i), (b)(1)(ii), (b)(1)(iii), (b)(1)(v), and, if applicable, (b)(1)(vii) and (b)(1)(viii).

iii. Identification of known interferents, including all endogenous, exogenous, technology-specific, and patient population-specific interferents, specific to each parameter (test output). The information must include the concentration(s) or level(s) at which interference was found to occur and the concentration range or levels at which interference was not found to occur.

iv. Information regarding the multisite clinical study required by paragraph (b)(1)(v), including:

a. Each patient population evaluated;

b. Each intended use setting and the operators;

c. A summary of the results, including the concordance analysis to clinically relevant laboratory test(s); and

d. Demonstrated expected (reference) values for each parameter (test output).

(3) The labeling required under 21 CFR 809.10 must include:

i. A limiting statement that the result(s) from the device is(are) not intended to be used as the sole basis for a patient diagnosis.

ii. Unless appropriate clinical outcome studies are done in accordance with (b)(1)(vii) that specifically validate an indication for the device's use in guiding blood product use, a limiting statement that the device has not been evaluated to guide blood product use.

iii. Unless appropriate clinical outcome studies are done in accordance with (b)(1)(viii) that specifically validate an indication for the device's use in guiding use of medication, a limiting statement that the device has not been evaluated to guide use of medication.