June 23, 2023

Instrumentation Laboratory Co.
Carol Marble
Senior Regulatory Affairs Director
180 Hartwell Road
Bedford, Massachusetts 01730

Re: K223187
Trade/Device Name: HemosIL Liquid Anti-Xa
Regulation Number: 21 CFR 864.7295
Regulation Name: Heparin And Direct Oral Factor Xa Inhibitor Drug Test System
Regulatory Class: Class II
Product Code: QLU
Dated: May 23, 2023
Received: May 24, 2023

Dear Carol Marble:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's

requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Min Wu -S

Min Wu, Ph. D.
Branch Chief
Division of Immunology and Hematology Devices
OHT7: Office of In Vitro Diagnostics
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2023
See PRA Statement below.

510(k) Number *(if known)*
K223187

Device Name
HemosIL Liquid Anti-Xa

Indications for Use *(Describe)*
HemosIL Liquid Anti-Xa is an automated chromogenic assay for in vitro diagnostic use by laboratory professionals in clinical laboratories. The assay provides quantitative results on 3.2% citrated human plasma for the following analytes based on the calibrators used:

• When used with HemosIL Heparin Calibrators:
Quantitative determination of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) activity on the ACL TOP Family and ACL TOP Family 50 Series.

• When used with HemosIL Apixaban Calibrators:
Quantitative determination of apixaban on the ACL TOP Family and ACL TOP Family 50 Series through measurement of factor Xa activity, which is inversely proportional to the apixaban level. With HemosIL Apixaban Calibrators, the assay is intended to measure apixaban concentrations in patients on apixaban therapy in the following situations where measurement of apixaban levels could be useful to have as additional information:
- Patients at risk for major bleeding
- Patients experiencing a bleeding episode

• When used with HemosIL Rivaroxaban Calibrators:
Quantitative determination of rivaroxaban on the ACL TOP Family and ACL TOP Family 50 Series through measurement of factor Xa activity, which is inversely proportional to the rivaroxaban level. With HemosIL Rivaroxaban Calibrators, the assay is intended to measure rivaroxaban concentrations in patients on rivaroxaban therapy in the following situations where measurement of rivaroxaban levels could be useful to have as additional information:
- Patients at risk for major bleeding
- Patients experiencing a bleeding episode

The assay is not a stand-alone test and the results should be used in conjunction with other clinical and laboratory findings. For use in adult population. For prescription use only.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(k) Summary

This 510(k) Summary of Safety and Effectiveness is being submitted in accordance with the requirements of the Safe Medical Device Act of 1990 and 21 CFR 807.92.

<table>
<tr><td>Submitter's Information</td><td colspan="3">Instrumentation Laboratory (IL) Co.
180 Hartwell Road
Bedford, MA 01730, USA</td></tr>
<tr><td>Contact Person</td><td colspan="3">Carol Marble, Senior Regulatory Affairs Director
Phone: 781-861-4467
Fax: 781-861-4207
Email: cmarble@werfen.com</td></tr>
<tr><td>Preparation Date</td><td colspan="3">June 22, 2023</td></tr>
<tr><td>Device Trade Name</td><td colspan="3">HemosIL Liquid Anti-Xa</td></tr>
<tr><td rowspan="5">Regulatory Information</td><td>Regulation No.</td><td colspan="2">21 CFR 864.7295</td></tr>
<tr><td>Regulation Description</td><td colspan="2">Anti-Factor Xa Activity Test System</td></tr>
<tr><td>Classification</td><td colspan="2">Class II</td></tr>
<tr><td>Product Code</td><td colspan="2">QLU</td></tr>
<tr><td>Classification Panel</td><td colspan="2">Hematology (81)</td></tr>
<tr><td rowspan="2">Predicate Device Nos.</td><td>DEN190032</td><td rowspan="2">Predicate Device Name</td><td rowspan="2">HemosIL Liquid Anti-Xa</td></tr>
<tr><td>K213464</td></tr>
<tr><td>Device Description</td><td colspan="3">HemosIL Liquid Anti-Xa is a one stage chromogenic assay based on a synthetic chromogenic substrate and on Factor Xa inactivation. The assay provides quantitative rivaroxaban results on 3.2% citrated human plasma as follows:
Rivaroxaban levels in patient plasma are measured automatically on ACL TOP Family and ACL TOP Family 50 Series when this assay is calibrated with HemosIL Rivaroxaban Calibrators.
Rivaroxaban directly inhibits Factor Xa activity independent of the antithrombin present. The Factor Xa activity measured by the assay is exogenous. Factor Xa is neutralized directly by rivaroxaban.
Residual Factor Xa is quantified with a synthetic chromogenic substrate. The paranitroaniline released is monitored kinetically at 405 nm and is inversely proportional to the rivaroxaban level in the sample.</td></tr>
</table>

Intended Use / Indications for Use	HemosIL Liquid Anti-Xa is an automated chromogenic assay for in vitro diagnostic use by laboratory professionals in clinical laboratories. The assay provides quantitative results on 3.2% citrated human plasma for the following analytes based on the calibrators used: • When used with HemosIL Heparin Calibrators: Quantitative determination of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) activity on the ACL TOP Family and ACL TOP Family 50 Series. • When used with HemosIL Apixaban Calibrators: Quantitative determination of apixaban on the ACL TOP Family and ACL TOP Family 50 Series through measurement of factor Xa activity, which is inversely proportional to the apixaban level. With HemosIL Apixaban Calibrators, the assay is intended to measure apixaban concentrations in patients on apixaban therapy in the following situations where measurement of apixaban levels could be useful to have as additional information: - Patients at risk for major bleeding - Patients experiencing a bleeding episode • When used with HemosIL Rivaroxaban Calibrators: Quantitative determination of rivaroxaban on the ACL TOP Family and ACL TOP Family 50 Series through measurement of factor Xa activity, which is inversely proportional to the rivaroxaban level. With HemosIL Rivaroxaban Calibrators, the assay is intended to measure rivaroxaban concentrations in patients on rivaroxaban therapy in the following situations where measurement of rivaroxaban levels could be useful to have as additional information: - Patients at risk for major bleeding - Patients experiencing a bleeding episode The assay is not a stand-alone test and the results should be used in conjunction with other clinical and laboratory findings. For use in adult population. For prescription use only.

Substantial Equivalence Discussion

Following is a description of the similarities and differences between the predicate device, the currently marketed HemosIL Liquid Anti-Xa for apixaban measurement under DEN190032, with modified on-board instrument stability claims under K213464, compared to the subject device with the expanded intended use for rivaroxaban measurement.

Item	Predicate Device	Subject Device
Trade Name and Measurand	HemosIL Liquid Anti-Xa for apixaban measurement	HemosIL Liquid Anti-Xa for rivaroxaban measurement
Manufacturer	Instrumentation Laboratory Co.	Same
Intended Use / Indications for Use	See updated intended use / indications for use on previous page.	
Similarities		
Item	**Predicate Device**	**Subject Device**
Trade Name and Measurand	HemosIL Liquid Anti-Xa for apixaban measurement	HemosIL Liquid Anti-Xa for rivaroxaban measurement
Regulation No.	21 CFR 864.7295	Same
Regulation Description	Anti-Factor Xa Activity Test System	Same
Classification	Class II	Same
Product Code	QLU	Same
Review Panel	Hematology (81)	Same
Technical Method	The test detects residual factor Xa using a chromogenic substrate. The signal or optical density is compared to a drug-specific calibration curve and results are reported as nanograms per milliliter (ng/mL).	Same
Sample Type	3.2% citrated human plasma	Same
Measurement	Quantitative	Same
Testing Methodology	Chromogenic	Same
Reporting Unit	ng/mL	Same

Similarities (Cont.)		
Item	**Predicate Device**	**Subject Device**
Composition	The HemosIL Anti-Xa kit includes the following components: • Factor Xa reagent: Liquid preparation containing purified bovine Factor Xa (approximately 5.5 nkat/mL), Tris-Buffer, EDTA, dextran sulfate, sodium chloride and bovine serum albumin. • Chromogenic substrate: liquid chromogenic substrate S-2732 (approximately 1.2 mg/mL) and bulking agent.	Same
Instrumentation	ACL TOP Family (K160276) ACL TOP Family 50 Series (K150877)	Same
On-board Stability	4 days	Same
Open Reagent Stability	1 month	Same

Differences		
Item	**Predicate Device**	**Subject Device**
Measurand	apixaban	rivaroxaban
Limit of Detection	9 ng/mL for apixaban	8 ng/mL for rivaroxaban
Linearity	20 to 1000 ng/mL for apixaban	20 to 1000 ng/mL for rivaroxaban
Kit Size Configurations	**4 mL Kit Vial Size (Only 1 Size):** • Factor Xa reagent (Cat. No. 0020302612): 5 x 2.5 mL vial of a liquid preparation containing purified bovine Factor Xa (approximately 5.5 nkat/mL), Tris-Buffer, EDTA, dextran sulfate, sodium chloride and bovine serum albumin. • Chromogenic substrate (Cat. No. 0020302622): 5 x 3 mL vial of liquid chromogenic substrate S-2732 (approximately 1.2 mg/mL) and bulking agent.	**4 mL Kit Vial Size (Size 1):** • Factor Xa reagent (Cat. No. 0020302612): 5 x 2.5 mL vial of a liquid preparation containing purified bovine Factor Xa (approximately 5.5 nkat/mL), Tris-Buffer, EDTA, dextran sulfate, sodium chloride and bovine serum albumin. • Chromogenic substrate (Cat. No. 0020302622): 5 x 3 mL vial of liquid chromogenic substrate S-2732 (approximately 1.2 mg/mL) and bulking agent. **10 mL Kit Vial Size (Size 2):** • Factor Xa reagent (Cat. No. 0020303610): 5 x 5 mL vial of a liquid preparation containing purified bovine Factor Xa (approximately 5.5 nkat/mL), Tris-Buffer, EDTA, dextran sulfate, sodium chloride and bovine serum albumin. • Chromogenic substrate (Cat. No. 0020303620): 5 x 6 mL vial of liquid chromogenic substrate S-2732 (approximately 1.2 mg/mL) and bulking agent
Calibrators (Sold Separately)	HemosIL Apixaban Calibrators Target Levels: 0 and ~500 ng/mL	HemosIL Rivaroxaban Calibrators Target Levels: 0 and ~500 ng/mL
Controls (Sold Separately)	HemosIL Apixaban Controls Target Levels: ~75 and ~300 ng/mL	HemosIL Rivaroxaban Controls Target Levels: ~80 and ~300 ng/mL

Performance Summary

Precision

Within-run and total precision was assessed in accordance with CLSI EP05-A3 for 20 days, with 2 runs per day and 2 replicates per run for each sample level (n=80/instrument/lot), using 3 lots of HemosIL Liquid Anti-Xa on representative members of the ACL TOP Family and ACL TOP Family 50 Series. To span the assay range, 6 citrated plasma samples were tested, as well as HemosIL Rivaroxaban Controls.

The tables below include data for representative systems each with 1 reagent lot.

ACL TOP Family	Mean (ng/mL)	CV% (Within-run)	CV% (Total)
Rivaroxaban Low Control	77.2	3.3	4.1
Rivaroxaban High Control	284.0	1.4	2.4
Sample 1	49.3	3.9	5.5
Sample 2	762.1	1.4	2.5
Sample 3	904.0	1.3	2.8
Sample 4	125.0	1.3	1.6
Sample 5	32.0	4.1	5.2
Sample 6	428.0	0.9	1.0

ACL TOP Family 50 Series	Mean (ng/mL)	CV% (Within-run)	CV% (Total)
Rivaroxaban Low Control	80.9	2.5	4.9
Rivaroxaban High Control	283.9	1.4	2.4
Sample 1	51.0	2.7	3.2
Sample 2	798.7	1.6	1.6
Sample 3	943.7	1.1	1.2
Sample 4	130.4	1.0	1.5
Sample 5	33.0	3.4	4.5
Sample 6	445.0	1.2	1.2

Reproducibility

Reproducibility studies were conducted at 3 sites using different operators (1 operator per site) on 3 different ACL TOP Family systems (1 system per site), using 3 lots of HemosIL Liquid Anti-Xa and 1 lot of HemosIL Rivaroxaban Controls (Low and High). Five citrated plasma samples were also tested across the 3 sites. Each material was tested in triplicate, twice a day for 5 days, for a total of 30 replicates per level.

The pooled 3 site data is presented below.

Pooled 3 Site Data														
Level	Mean (ng/mL)	N	Repeatability (Within-Run)		Between-Run		Between-Day		Between-Site		Between-Lot		Reproducibility (Total)	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Rivaroxaban Low Control	72.6	270	2.28	3.1%	1.03	1.4%	0.00	0.0%	1.44	2.0%	0.80	1.1%	3.00	4.1%
Rivaroxaban High Control	281	270	4.58	1.6%	4.10	1.5%	0.00	0.0%	2.15	0.8%	0.17	0.1%	6.51	2.3%
Sample 1	45.0	270	2.55	5.7%	0.88	2.0%	0.56	1.3%	3.38	7.5%	0.66	1.5%	4.41	9.8%
Sample 2	750	270	19.68	2.6%	1.44	0.2%	6.30	0.8%	22.12	3.0%	5.26	0.7%	30.76	4.1%
Sample 3	939	270	25.49	2.7%	3.43	0.4%	7.41	0.8%	22.98	2.4%	8.83	0.9%	36.36	3.9%
Sample 4	51.8	270	2.46	4.7%	1.30	2.5%	0.84	1.6%	1.55	3.0%	0.83	1.6%	3.39	6.5%
Sample 5	118	270	3.71	3.1%	4.29	3.6%	2.76	2.3%	5.71	4.8%	1.64	1.4%	8.67	7.3%

Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantitation (LoQ)

LoB, LoD and LoQ studies for rivaroxaban were performed in accordance with CLSI EP17-A2, using 3 lots of HemosIL Liquid Anti-Xa on a representative ACL TOP Family model and a representative ACL TOP Family 50 Series model. The following maximum limits were determined:

Limit of Blank (LoB)	Limit of Detection (LoD)	Limit of Quantitation (LoQ)
2.4 ng/mL	8 ng/mL	20 ng/mL*

***Note:** The reportable value for the LoQ will be 20 ng/mL as the lower limit of the linear range.

Linearity

Linearity studies for rivaroxaban were performed in accordance with CLSI EP06, 2nd Edition, using 3 lots of HemosIL Liquid Anti-Xa on a representative ACL TOP Family model and a representative ACL TOP Family 50 Series model.

- Analytical Measuring Interval (AMI): The AMI was performed over the range of 18-550 ng/mL for 13 rivaroxaban concentrations. Each rivaroxaban level was tested in quadruplicate on both instrument models with each reagent lot.
- Extended Measuring Interval (EMI): The EMI was performed over the range of 425-1100 ng/mL for 9 rivaroxaban concentrations. Each rivaroxaban level was tested in quadruplicate on both instrument models with each reagent lot.

The studies support a reportable linear range for rivaroxaban on the ACL TOP Family and ACL TOP Family 50 Series of 20 to 1000 ng/mL.

Interferences and Limitations

Interference studies for rivaroxaban were performed in accordance with CLSI EP07, 3rd Edition, using 1 lot of HemosIL Liquid Anti-Xa on a representative ACL TOP Family model. The studies support that rivaroxaban results on the ACL TOP Family and ACL TOP Family 50 Series are not affected by the following interferents up to:

Hemoglobin	600 mg/dL
Bilirubin (unconjugated)	40 mg/dL
Bilirubin (conjugated)	40 mg/dL
Triglycerides	921 mg/dL
Acetylsalicylic acid	3.00 mg/dL
Atorvastatin	0.075 mg/dL
Isosorbide dinitrate	0.600 mg/dL
Ticagrelor	0.188 mg/dL
Warfarin	7.50 mg/dL
Lupus anticoagulant	dRVVT Screen/Confirm Ratio 2.47

Rivaroxaban results may be falsely elevated in samples tested post-andexanet alfa administration.

The assay is not intended for the monitoring and dosage adjustment of rivaroxaban.

Administer a reversal agent based on current clinical guidance, and take into consideration other clinical and laboratory findings including the Factor Xa inhibitor dose and time since last dose. For additional information, refer to current clinical guidance and reversal agent prescribing information.

In-Use Stability and Shelf-life

In-use stability and shelf-life studies for rivaroxaban were performed in accordance with CLSI EP25-A, using multiple lots of HemosIL Liquid Anti-Xa on a representative ACL TOP Family model. The studies support the following rivaroxaban claims on the ACL TOP Family and ACL TOP Family 50 Series:

Study Type	Storage Condition	Claim
Open Vial	2-8°C	1 Month
On-Board Instrument	15-25°C	4 Days
Shelf-life	2-8°C	30 Months

Method Comparison

A multicenter study was performed in accordance with CLSI EP09c, 3rd Edition, at 3 laboratory sites comparing HemosIL Liquid Anti-Xa for the measurement of rivaroxaban on the ACL TOP Family to LC-MS/MS. Samples were from patients treated with rivaroxaban, including 12 samples from bleeding patients and 261 samples from patients at risk of major bleeding. A summary of the individual site and pooled 3-site results on 337 samples is shown below.

	N	r	Slope			Intercept			Mean Bias
			Value	95% CI		Value	95% CI		
Site 1	111	0.995	0.947	0.927	0.966	-3.872	-5.922	-1.822	-8.7%
Site 2	107	0.995	0.981	0.944	1.019	2.374	-2.750	7.497	2.0%
Site 3	119	0.995	0.994	0.962	1.025	-1.376	-5.114	2.362	-1.6%
Pooled	337	0.995	0.971	0.953	0.990	-0.697	-3.087	1.692	-2.8%

An internal method comparison study was performed comparing the performance of the ACL TOP Family 50 Series to the ACL TOP Family using representative systems from both families. Representative results are shown below.

System	Analyte	Slope	Intercept	r	Comparator method
ACL TOP Family 50 Series	Rivaroxaban	0.972	0.810	0.999	ACL TOP Family

Conclusion

HemosIL Liquid Anti-Xa for rivaroxaban measurement is substantially equivalent to the legally marketed predicate device, HemosIL Liquid Anti-Xa, FDA marketing authorized under DEN190032 for apixaban measurement and FDA cleared under K213464 with modified on-board instrument stability claims.