December 13, 2023

Instrumentation Laboratory Company
Carol Marble
Senior Director of Regulatory Affairs
180 Hartwell Road
Bedford, Massachusetts 01730

Re: K230852
Trade/Device Name: HemosIL Chromogenic Factor IX
Regulation Number: 21 CFR 864.7290
Regulation Name: Factor deficiency test
Regulatory Class: Class II
Product Code: GGP
Dated: March 27, 2023
Received: March 28, 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 (the 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 available 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.

Additional information about changes that may require a new premarket notification are provided in the FDA guidance documents entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device" (https://www.fda.gov/media/99812/download) and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" (https://www.fda.gov/media/99785/download).

Your device is also subject to, among other requirements, the Quality System (QS) regulation (21 CFR Part 820), which includes, but is not limited to, 21 CFR 820.30, Design controls; 21 CFR 820.90, Nonconforming product; and 21 CFR 820.100, Corrective and preventive action. Please note that regardless of whether a change requires premarket review, the QS regulation requires device manufacturers to review and approve changes to device design and production (21 CFR 820.30 and 21 CFR 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

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 Part 803) for devices or postmarketing safety reporting (21 CFR Part 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 Part 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR Parts 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 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: 07/31/2026
See PRA Statement below.

510(k) Number *(if known)*
K230852

Device Name
HemosIL Chromogenic Factor IX

Indications for Use *(Describe)*
HemosIL Chromogenic Factor IX is an automated assay for the photometric, quantitative determination of factor IX activity in 3.2% citrated plasma on the ACL TOP® Family and ACL TOP Family 50 Series in the laboratory setting by a healthcare professional. HemosIL Chromogenic Factor IX is indicated for use on patients when identifying factor IX deficiency or measuring factor IX activity from patients on replacement therapy.
For adult population only. 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.

Submitter's Information	Instrumentation Laboratory (IL) Company 180 Hartwell Road Bedford, MA 01730, USA	
Contact Person	Carol Marble, Senior Director of Regulatory Affairs Phone: 781-861-4467 Fax: 781-861-4207 Email: cmarble@werfen.com	
Preparation Date	December 12, 2023	
Device Trade Name	HemosIL Chromogenic Factor IX	
Regulatory Information	Regulation No.	21 CFR 864.7290
	Regulation Description	Factor deficiency test
	Classification	Class II
	Product Code	GGP
	Classification Panel	Hematology (81)
Predicate Device	K031829	HemosIL Factor IX deficient plasma
Device Description	Factor IX activity in a patient's plasma is determined using a chromogenic method, in which human factor IX is activated by human factor XIa, and, when formed, factor IXa activates human factor X in the presence of human factor VIII, calcium and phospholipid. The amount of factor Xa generated is proportionate to the factor IX activity and is determined from the hydrolysis of a chromogenic factor Xa substrate. Results are determined by comparing a chromogenic signal to a calibration curve.	
Intended Use / Indications for Use	HemosIL Chromogenic Factor IX is an automated assay for the photometric, quantitative determination of factor IX activity in 3.2% citrated plasma on the ACL TOP Family and ACL TOP Family 50 Series in the laboratory setting by a healthcare professional. HemosIL Chromogenic Factor IX is indicated for use on patients when identifying factor IX deficiency or measuring factor IX activity from patients on replacement therapy. For adult population only. For prescription use only.	

Comparison to Predicate Device		
Item	**Predicate Device (K031829)**	**Subject Device**
Proprietary and Established Name	HemosIL Factor IX deficient plasma	HemosIL Chromogenic Factor IX
Legal Manufacturer	Instrumentation Laboratory Co.	Same
Similarities		
Measurand	Factor IX activity	Same
Measurement	Quantitative	Same
Regulation No.	21 CFR 864.7290	Same
Regulation Description	Factor deficiency test	Same
Classification	Class II	Same
Product Code	Classification Product Code: GJT Subsequent Product Code: GGP	GGP
Review Panel	Hematology (81)	Same
Intended Use / Indications for Use	HemosIL Factor IX deficient plasma is human plasma immunodepleted of factor IX for the quantitative determination of factor IX activity in citrated plasma, based on activated partial thromboplastin time (APTT) assay, on IL Coagulation Systems.	HemosIL Chromogenic Factor IX is an automated assay for the photometric, quantitative determination of factor IX activity in 3.2% citrated plasma on the ACL TOP Family and ACL TOP Family 50 Series in the laboratory setting by a healthcare professional. HemosIL Chromogenic Factor IX is indicated for use on patients when identifying factor IX deficiency or measuring factor IX activity from patients on replacement therapy. For adult population only. For prescription use only.
Sample Type	Citrated plasma	Same
Type of Test	Quantitative	Same
Reporting Units	% Activity, U/mL and/or sec	% Activity and/or IU/mL
Instruments	ACL Elite/Elite Pro ACL TOP Family ACL TOP Family 50 Series	ACL TOP Family ACL TOP Family 50 Series
Controls (Sold Separately)	HemosIL Normal Control Assayed HemosIL Special Test Control Level 2	Same
Calibrator (Sold Separately)	HemosIL Calibration Plasma	Same
Linear Range	1.0-150%	Same

Differences		
Item	**Predicate Device (K031829)**	**Subject Device**
Test Principle	Factor IX activity in a patient's plasma is determined by performing a modified activated partial thromboplastin time test (APTT). Patient plasma is diluted and added to a plasma deficient in factor IX. Correction of the clotting time of the deficient plasma is proportional to the concentration (% activity) of that factor in the patient plasma, interpolated from a calibration curve.	Factor IX activity in a patient's plasma is determined using a chromogenic method, in which human factor IX is activated by human factor XIa, and, when formed, factor IXa activates human factor X in the presence of human factor VIII, calcium and phospholipid. The amount of factor Xa generated is proportionate to the factor IX activity and is determined from the hydrolysis of a chromogenic factor Xa substrate. Results are determined by comparing a chromogenic signal to a calibration curve.
Methodology	Functional clotting assay	Chromogenic assay
Kit Components	Factor IX deficient plasma: Lyophilized human plasma that has been artificially depleted of factor IX containing buffer and stabilizers. The residual factor IX activity is less than or equal to 1% whereas all other coagulation factors have normal levels.	• Reagent A: Lyophilized preparation containing human factor VIII, human factor X, bovine factor V, bovine serum albumin and a fibrin polymerization inhibitor. • Reagent B: Lyophilized preparation containing human factor XIa, human factor II, bovine serum albumin, calcium chloride and phospholipids. • Substrate: Solution containing 2.5 mmol/L chromogenic factor Xa substrate (Z-D-Arg-Gly-Arg-pNA), a thrombin inhibitor and preservative. • Buffer: Stock solution of buffer containing a heparin antagonist, bovine serum albumin and preservative. • Diluted Buffer Barcode Labeled Vials: Empty vials with linear barcode labels for Diluted Buffer (to be prepared).

Performance Summary

Precision

Within-run (repeatability) and total (within-device) precision were assessed in accordance with EP05-A3 for 20 days, with two runs per day and two replicates per run for each sample level (n=80) for three reagent lots on representative members of the ACL TOP Family. To span the assay range, three patient sample pools were tested, as well as two control levels. The tables below show data for one representative reagent lot on one instrument and also aggregated data for the three reagent lots on one instrument.

Representative Reagent Lot on ACL TOP Family Instrument					
Material	**Mean (%)**	**Within-run**		**Total**	
		SD	**%CV**	**SD**	**%CV**
Normal Control Assayed	111.7	3.9	3.5	6.3	5.6
Special Test Control Level 2	33.3	1.1	3.3	1.7	5.1
Sample 1 (Pool)	4.3	0.2	5.4	0.3	7.3
Sample 2 (Pool)	65.7	2.5	3.7	3.4	5.1
Sample 3 (Pool)	102.7	3.4	3.3	5.3	5.2

Aggregated Data (Reagent Lots 1, 2 and 3)			
Material	**Mean (%)**	**Total (Within-Laboratory)**	
		SD	**%CV**
Normal Control Assayed	110.6	6.4	5.8
Special Test Control Level 2	33.0	1.8	5.3
Sample 1 (Pool)	4.2	0.4	8.4
Sample 2 (Pool)	65.3	3.5	5.4
Sample 3 (Pool)	101.8	5.9	5.8

Further, within-run (repeatability) and total (within-device) precision were assessed in accordance with EP05-A3 for 20 days, with two runs per day and two replicates per run for each sample level (n=80) for one reagent lot on representative members of the ACL TOP Family 50 Series. To span the assay range, three patient sample pools were tested, as well as two control levels. The table below shows data for one instrument.

Representative Reagent Lot on ACL TOP Family 50 Series Instrument					
Material	**Mean (%)**	**Within-run**		**Total**	
		SD	**%CV**	**SD**	**%CV**
Normal Control Assayed	111.9	3.0	2.7	5.0	4.5
Special Test Control Level 2	33.5	0.8	2.5	1.3	3.9
Sample 1 (Pool)	4.1	0.1	3.3	0.2	5.3
Sample 2 (Pool)	66.4	2.1	3.1	2.5	3.8
Sample 3 (Pool)	103.5	3.5	3.4	4.6	4.5

Reproducibility

Reproducibility studies were conducted in accordance with EP05-A3 at two external clinical sites and one internal site using different operators (one operator per site) on three different ACL TOP Family and ACL TOP Family 50 Series members (one instrument per site), using three reagent lots of HemosIL Chromogenic Factor IX with each site testing a different reagent lot. The same five patient pools and control lot were tested across the three sites, as well as three patient sample pools spiked with a factor IX concentrate. Each material was tested in triplicate, twice a day for five days, for a total of 30 replicates per level. The table below shows the pooled three-site data for all reagent lots.

Pooled Three-Site Data												
Level	**Mean (%)**	**N**	**Repeatability (Within-Run)**		**Between-Run**		**Between-Day**		**Between-Site**		**Reproducibility (Total)**	
			SD	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
Normal Control Assayed	108.9	90	5.5	5.0	4.4	4.0	3.7	3.4	4.3	3.9	9.0	8.3
Special Test Control Level 2	30.7	90	1.2	3.9	0.5	1.6	1.0	3.3	0.5	1.5	1.7	5.6
Sample 1 (Pool)	1.3	90	0.2	15.2	0.0	0.0	0.2	12.7	0.1	7.1	0.3	21.1
Sample 2 (Pool)	4.0	90	0.2	5.3	0.0	0.0	0.1	3.3	0.1	3.3	0.3	7.1
Sample 3 (Pool)	33.6	90	1.2	3.6	0.9	2.7	0.7	2.1	0.4	1.2	1.7	5.1
Sample 4 (Pool)	73.9	90	3.0	4.1	1.4	1.9	3.1	4.2	0.0	0.0	4.5	6.1
Sample 5 (Pool)	109.7	90	4.9	4.5	1.7	1.5	5.4	4.9	0.0	0.0	7.5	6.8
Concentrate Sample 1 (Pool)	3.7	90	0.2	6.2	0.0	0.0	0.1	1.7	0.1	3.4	0.3	7.3
Concentrate Sample 2 (Pool)	30.1	90	1.1	3.6	0.1	0.3	0.9	3.1	0.4	1.3	1.5	4.9
Concentrate Sample 3 (Pool)	98.8	90	3.8	3.8	1.5	1.5	4.1	4.1	0.3	0.3	5.8	5.8

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

LoB, LoD and LoQ studies were performed in accordance with CLSI EP17-A2, using three reagent lots of HemosIL Chromogenic Factor IX on representative members of the ACL TOP Family and ACL TOP Family 50 Series.

The following maximum limits were determined:

Limit of Blank (LoB)	Limit of Detection (LoD)	Limit of Quantitation (LoQ)
0.1%	0.3%	0.6%

Linearity

Linearity studies were performed in accordance with CLSI EP06, 2nd Edition, using three reagent lots of HemosIL Chromogenic Factor IX on a representative member of the ACL TOP Family and one reagent lot on a representative member of the ACL TOP Family 50 Series. The studies support a reportable linear range on the ACL TOP Family and ACL TOP Family 50 Series of 1.0 to 150%.

Interferences and Limitations

Interference studies were performed in accordance with CLSI EP07, 3rd Edition, and CLSI EP37, 1st Edition (where applicable), using a minimum of one reagent lot of HemosIL Chromogenic Factor IX on a representative member of the ACL TOP Family or ACL TOP Family 50 Series model. The studies support that results on the ACL TOP Family and ACL TOP Family 50 Series are not affected by the following interferents up to:

Hemoglobin	1000 mg/dL
Bilirubin (unconjugated)	40 mg/dL
Bilirubin (conjugated)	40 mg/dL
Triglycerides	1500 mg/dL
Unfractionated heparin	2.0 IU/mL
Low molecular weight heparin	2.0 IU/mL
Dabigatran	5.0 mg/L
Rivaroxaban	0.05 mg/L
Fondaparinux	1.02 mg/L
Lupus anticoagulant	dRVVT Screen/Confirm Ratio 1.8

Note: Warfarin inhibits vitamin K dependent coagulation factors and interferes with the quantification of factor IX activity.

Due to different methodologies used to assign potency for factor IX replacement therapies, differences between factor IX recovery may exist. For recommendations on monitoring factor IX replacement therapy, refer to current guidance and factor IX replacement therapy prescribing information.

To avoid discrepancies that have been reported, consider performing both a chromogenic and one stage factor IX clotting assay for the laboratory investigation of patients being assessed due to the clinical suspicion of hemophilia B. Results of this test should always be interpreted in conjunction with the patient's medical history, clinical presentation and other findings.

Normal Reference Interval

A normal reference interval study was performed in accordance with CLSI EP28-A3c on one reagent lot of HemosIL Chromogenic Factor IX with a representative ACL TOP Family instrument. A population of 120 plasma samples from apparently healthy individuals were tested. The nonparametric 95% reference interval with two-sided 90% confidence intervals was calculated as 71.1 to 134.1% (0.7-1.3 IU/mL).

Due to many variables which may affect the results (including the population age), each laboratory should determine its own normal range.

Recovery of Factor IX Replacement Therapies

A recovery study was performed using one reagent lot of HemosIL Chromogenic Factor IX on a representative member of the ACL TOP Family. Immunodepleted FIX deficient plasma was spiked with four factor IX replacement therapies at seven to fourteen concentrations, ranging from 0.5 to 200% and percent recovery was determined. HemosIL Chromogenic Factor IX accurately evaluated the potency of factor IX concentrates including AlphaNine SD, BeneFIX, and Rebinyn.

Product	Mean Percent Recovery (%)
AlphaNine SD	90
BeneFIX	93
Rebinyn	112
Idelvion*	159

* Per the manufacturer's recommendations, a one stage clotting assay is recommended for measurement of Idelvion and results may vary based on the APTT reagent in use.

In-Use Stability and Shelf-life

In-use stability and shelf-life studies were performed in accordance with CLSI EP25-A, using three reagent lots of HemosIL Chromogenic Factor IX on a representative ACL TOP Family model. The studies support the following labeled claims on the ACL TOP Family and ACL TOP Family 50 Series:

- **Reagent A:** Stability after reconstitution: 72 hours at 2-8°C in the closed original vial or 4 months at ≤ -65°C or 8 hours at 15°C on the ACL TOP Family and ACL TOP Family 50 Series. Frozen reagent may be thawed once and gently mixed before use. **Do not refreeze.**
- **Reagent B:** Stability after reconstitution: 72 hours at 2-8°C in the closed original vial or 4 months at ≤ -65°C or 8 hours at 15°C on the ACL TOP Family and ACL TOP Family 50 Series. Frozen reagent may be thawed once and gently mixed before use. **Do not refreeze.**
- **Substrate:** Opened reagent is stable 1 month at 2-8°C in the closed original vial or 12 months at ≤ -65°C or 24 hours at 15°C on the ACL TOP Family and ACL TOP Family 50 Series. Frozen reagent may be thawed once and gently mixed before use. **Do not refreeze.**
- **Buffer:** Opened reagent is stable 12 months at 2-8°C.
- **Diluted Buffer:** Stability after dilution: 24 hours on the ACL TOP Family and ACL TOP Family 50 Series.
- **Shelf-life:** 28 Months at 2-8°C

Sample Stability

A sample stability study was performed using one reagent lot of HemosIL Chromogenic Factor IX on a representative ACL TOP Family model or ACL TOP Family 50 Series model. The study supports the following labeled claims on the ACL TOP Family and ACL TOP Family 50 Series:

- Specimens are stable up to 8 hours at 15-25°C and up to 8 hours at 2-8°C.

Multicenter Method Comparison

A multicenter method comparison study was conducted at four sites (three external and one internal) in accordance with CLSI EP09c to compare the accuracy of the HemosIL Chromogenic Factor IX assay relative to the predicate device, HemosIL Factor deficient plasma, on representative members of the ACL TOP Family and ACL TOP Family 50 Series, using samples from patients with von Willebrand disease, patients with hemophilia A and B and patients on factor IX replacement therapy.

The following results were obtained:

	N	r	Slope			Intercept		
			Value	95% CI		Value	95% CI	
Site 1	105	0.927	1.023	0.977	1.101	-0.411	-2.867	1.049
Site 2	105	0.978	0.960	0.922	0.995	-1.977	-3.298	-0.490
Site 3	104	0.984	1.072	1.041	1.105	-3.161	-4.713	-1.629
Site 4	30	0.984	1.024	0.952	1.110	0.592	-0.818	8.478
Overall	344	0.972	1.015	0.994	1.037	-0.920	-2.064	-0.185

Factor IX (%)	Predicted Bias	Lower CI	Upper CI
1	-0.90	-2.03	-0.19
5	-0.84	-1.89	-0.17
50	-0.3%	-2.5%	0.8%
100	0.6%	-1.4%	2.2%

Note: In the table above, the 1 and 5% results are presented in absolute measured units and the 50 and 100% results are presented in relative units.

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.

System	N	Slope	Intercept	r	Reference Method
ACL TOP Family 50 Series	126	0.980	1.731	0.998	ACL TOP Family

Conclusion

The performance testing results demonstrate that HemosIL Chromogenic Factor IX is substantially equivalent to the predicate device, HemosIL Factor IX deficient plasma (K031829), and that the assay is safe and effective for its labeled intended use.