December 23, 2022

Precision BioLogic Inc.
Karen Black
VP of Compliance and Product Development
140 Eileen Stubbs Avenue
Dartmouth, Nova Scotia B3B 0A9
Canada

Re: K214002
Trade/Device Name: Cyrocheck Chromogenic Factor IX
Regulation Number: 21 CFR 864.7290
Regulation Name: Factor Deficiency Test
Regulatory Class: Class II
Product Code: GGP
Dated: December 20, 2021
Received: December 21, 2021

Dear Karen Black:

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
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)*
K214002

Device Name
CRYOcheck™ Chromogenic Factor IX

Indications for Use *(Describe)*
CRYOcheck Chromogenic Factor IX is for clinical laboratory use in the quantitative determination of factor IX activity in 3.2% citrated human plasma. It is intended to be used in identifying factor IX deficiency and as an aid in the management of hemophilia B in individuals aged 2 years and older. For in vitro diagnostic use.

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
CRYO*check*™ Chromogenic Factor IX

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

The assigned 510(k) number is K214002

Submitter's Information	Precision BioLogic Inc.140 Eileen Stubbs Ave. Dartmouth, Nova Scotia B3B 0A9Canada	
Contact Person	Karen M. Black, VP of Compliance & Product Development Phone: 902-468-6422, ext. 226, or 902-706-3125 E-mail: kblack@precisionbiologic.com	
Preparation Date	20 December 2022	
Device Trade Name	CRYO*check*™ Chromogenic Factor IX	
RegulatoryInformation	Regulation Number and Description	21 CFR 864.7290 Factor Deficiency Test
	Classification	Class II
	Product Code	GGP; Test, Qualitative and Quantitative Factor Deficiency; 21 CFR 864.7290
	Classification Panel	Hematology
Predicate Device	HemosIL Factor IX Deficient Plasma (K031829)	
Indication for Use/Intend Use	CRYO*check* Chromogenic Factor IX is for clinical laboratory use in the quantitative determination of factor IX activity in 3.2% citrated human plasma. It is intended to be used in identifying factor IX deficiency and as an aid in the management of hemophilia B in individuals aged 2 years and older. For in vitro diagnostic use.	
Device Description	CRYO*check* Chromogenic Factor IX is used for determination of FIX activity and contains the following four components, packaged in vials, and provided frozen to preserve the integrity of the components: **Reagent 1:** Human FVIII, human FX, bovine FV and a fibrin polymerization inhibitor. **Reagent 2:** Human FXIa, human FII, calcium chloride and phospholipids. **Reagent 3:** FXa Substrate containing EDTA and a thrombin inhibitor. **Diluent Buffer:** Tris buffer solution containing 1% BSA and a heparin antagonist.	

Comparison to Predicate		
Item	**Predicate**	**New Device**
Proprietary and Established Names	HemosIL Factor IX Deficient Plasma	CRYO*check* Chromogenic Factor IX
Manufacturer	Instrumentation Laboratory	Precision BioLogic
Similarities		
Measurand	Human Factor IX	Human Factor IX
Product Code	Classification Product Code: GJT; Factor deficiency test Subsequent Product Code: GGP Test, Qualitative and Quantitative Factor Deficiency	GGP Test, Qualitative and Quantitative Factor Deficiency

Item	Predicate	New Device
Regulation Section	21 CFR 864.7290 Factor Deficiency Test	21 CFR 864.7290 Factor Deficiency Test
Classification	Class II	Class II
Panel	81 (Haematology)	81 (Haematology)
Intended Use	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.	CRYO*check* Chromogenic Factor IX is for clinical laboratory use in the quantitative determination of factor IX activity in 3.2% citrated human plasma. It is intended to be used in identifying factor IX deficiency and as an aid in the management of hemophilia B in individuals aged 2 years and older. For in vitro diagnostic use.
Assay Type	Quantitative (clot-based measurement of FIX)	Quantitative (chromogenic measurement of FIX)
Expression of results	Quantitative; results are expressed as percent activity interpreted relative to acalibration curve.	Quantitative; results are expressed as percent activity interpreted relativeto a calibration curve.
Instrument(s)	IL Coagulation Systems	ACL TOP Family/ ACL TOP Family 50 Series
Differences		
Device Description	The Factor IX deficient plasma kit consists of: Factor IX deficient plasma (Cat. No. 0020011910): 10 x 1 mL vials of lyophilized human plasma that has been artificially depletedof factor IX containing buffer and stabilizers. Theresidual factor IX activity is less than or equal to 1% whereas all other coagulation factors have normal levels.	CRYO*check* Chromogenic Factor IX is used for determination of FIX activity and contains the following four components, packaged in vials and provided frozen to preservethe integrity of the components: **Reagent 1:** Human FVIII, human FX, bovine FV and a fibrin polymerization inhibitor. **Reagent 2:** Human FXIa, human FII, calcium chloride and phospholipids. **Reagent 3:** FXa Substrate containing EDTA and a thrombin inhibitor. **Diluent Buffer:** Tris buffer solution containing 1% BSA and a heparin antagonist
Methodology	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.	FIX activity is determined in a chromogenic method, in which human FIX is activated by human FXIa and where formed FIXa activates human FX in the presence of human FVIII, calcium ions and phospholipid. Similar to in vivo conditions, FVIII is activated by thrombin which is generated during the incubation. The amountof FXa formed is related to the FIX activity and isdetermined from the hydrolysis of a chromogenic FXa substrate. The color producedby the release of pNA is measured spectrophotometrically at 405 nm and is proportional to the factor IX in the sample.

Performance Summary:

All studies were performed using CRYO*check* Chromogenic Factor IX on Instrumentation Laboratories' ACL TOP Series or TOP 50 Series Instruments; the specific instrument(s) used for each study are indicated in the summary reports below.

Multi-Reagent Lot Precision

An internal precision study was performed using three (3) lots of CRYO*check* Chromogenic Factor IX by two operators on an IL ACL TOP 700 CTS analyzer (K160276) in accordance with CLSI EP05-A3. The study quantified one normal and two abnormal reference controls and three patient plasma samples representing very low, low and high levels of FIX activity. Each sample was measured with each product lot in duplicate, twice a day for 20 days for a total of 80 replicates per sample per lot.

Aggregated Data (Lots 1, 2 and 3)			
Sample	**Mean FIX (%)**	**Within-Laboratory**	
		SD	**%CV**
CRYO*check* Reference Control Normal	114.9	4.2	3.7
CRYO*check* Abnormal 1 Reference Control	39.3	1.8	4.5
CRYO*check* Abnormal 2 Reference Control	10.4	0.8	7.3
Very Low FIX Plasma Sample	1.2	0.2	14.5
Low FIX Plasma Sample	6.1	0.6	10.1
High FIX Plasma Sample	174.0	6.4	3.7

Multi-Reagent Lot Site to Site Reproducibility

Reproducibility studies were conducted at three sites (one internal and two external) by two operators per site on IL ACL TOP 700 CTS (K160276), IL ACL TOP 700 (K160276) and IL ACL TOP 750 CTS (K150877) analyzers using three lots of CRYO*check* Chromogenic Factor IX in accordance with CLSI EP05-A3. The study quantified one normal and two abnormal reference controls and three patient plasma samples representing very low, low and high levels of FIX activity. Each sample was measured in triplicate, twice a day for 5 days at each site.

Pooled 3-Site Data											
Sample	**Mean (%)**	**Within-Run**		**Between- Run**		**Between-Day**		**Between-Site**		**Across-Site**	
		SD	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
Reference Control Normal	113.1	5.0	4.5	0.9	0.8	1.1	1.0	1.9	1.7	6.3	5.6
Abnormal 1 Reference Control	38.4	1.8	4.8	0.2	0.6	0.1	0.3	1.3	3.4	2.5	6.6
Abnormal 2 Reference Control	10.8	0.8	7.5	0.2	1.7	0.0	0.0	0.2	2.0	0.9	8.6
Very Low FIX Plasma Sample	1.2	0.1	6.9	0.0	1.7	0.0	0.0	0.0	0.0	0.2	15.7
Low FIX Plasma Sample	6.3	0.5	7.9	0.1	1.2	0.1	2.1	0.2	2.4	0.8	13.0
High FIX Plasma Sample	168.5	7.6	4.5	0.0	0.0	1.3	0.8	4.4	2.6	10.0	6.0

Linearity/Assay Reportable Range

A linearity study was conducted in accordance with CLSI EP06-2nd Ed using three lots of CRYO*check* Chromogenic Factor IX on an IL ACL TOP 700 CTS instrument (K160276). A high FIX (230%) plasma was combined with congenital FIX deficient plasma (0%) to create fourteen sample dilutions with estimated FIX activities in the range of 0 to 230% FIX. Each level was tested in quadruplicate. The results support the linearity claim described below.

Linearity Range: 0 to 200% FIX activity

Reference Interval

A reference interval study was conducted by two operators on IL ACL TOP 700 CTS and IL ACL TOP CTS instruments (K160276) in accordance with CLSI EP28-A3c using three lots of CRYO*check* Chromogenic Factor IX and citrated plasma samples from 128 normal, ostensibly healthy individuals. The reference interval was established by calculating the non-parametric 95% confidence interval (2.5th to 97.5th percentiles).

Reference Interval: 79 to 155% FIX activity

Stability

Shelf-Life Stability

A shelf-life stability study was conducted in accordance with CLSI EP25-A using an IL ACL TOP 700 CTS instrument (K160276). At each timepoint, five replicates of one normal and two abnormal reference controls and two patient plasma samples representing very low and high levels of FIX activity levels were quantified. The study has been completed up to 19 months and supports a shelf-life stability claim of at least 18 months when the product is stored at ≤-70 °C.

In-Use Stability

An in-use stability study was conducted in accordance with CLSI EP25-A using an IL ACL TOP 700 CTS instrument (K160276). Each lot was used to quantify five replicates of one normal and two abnormal reference controls and two patient plasma samples representing very low and low levels of FIX activity levels from each storage condition at defined timepoints. The data support a stability claim of 24 hours on board the instrument and 48 hours at 2-8 °C.

Three lots of CRYO*check* Chromogenic Factor IX were maintained on board an analyzer for 4 hours, then subsequently refrozen at ≤-70 °C for up to 3 months. Each lot was used to quantify five replicates of one normal and two abnormal reference controls and two patient plasma samples representing very low and low levels of FIX activity levels at defined timepoints. The data support a stability claim of one month refrozen storage at ≤-70 °C if the product is stored on-board and refrozen within 4 hours of the initial thaw. The refrozen product must be used within eight hours of next thawing while kept on-board the analyzer.

Detection Limit

The limit of blank (LoB) was determined in accordance with CLSI EP17-A2 by measuring four blank plasma samples obtained from individuals with severe congenital hemophilia B. Samples were measured in triplicate on an IL ACL TOP 700 CTS instrument (K160276) using three lots of CRYO*check* Chromogenic Factor IX over five days. The LoB was determined to be 0.4% FIX activity.

The limit of detection (LoD) was determined in accordance with CLSI EP17-A2 by measuring four plasma samples with low FIX activity obtained from congenital hemophilia B donors. Samples were measured in triplicate on an IL ACL TOP CTS instrument (K160276) using three lots of CRYO*check* Chromogenic Factor IX over five days. The LoD was determined to be 0.5%FIX activity.

The limit of quantitation (LoQ) was determined in accordance with CLSI EP17-A2. Aliquots of four plasma samples with low FIX activity obtained from congenital hemophilia B donors were sent to an external laboratory for testing in three replicates on five different days on an IL ACL TOP 700 instrument (K160276) to determine assigned values using a validated laboratory developed chromogenic factor IX assay. The LoQ was determined to be 0.5% FIX activity.

Interferences

Interference studies were conducted according to CLSI EP07-A3 using a single lot of CRYO*check* Chromogenic Factor IX on an IL ACL TOP 700 CTS instrument (K160276). Plasma samples were spiked with possible interferents, and 10 replicates were tested alongside 10 replicates of the corresponding blank matrix control. The following substances showed no interference up to the concentrations indicated:

Possible Interferent	Concentration
Hemoglobin	≤ 1000 mg/dL
Intraplipid	≤ 2000 mg/dL
Bilirubin (unconjugated)	≤ 40 mg/dL
Bilirubin (conjugated)	≤ 23 mg/dL
Unfractionated heparin	≤ 1.2 IU/mL
Low molecular weight heparin	≤ 1.5 IU/mL
Dabigatran	≤ 0.04 mg/L
Fondaparinux	≤ 0.26 mg/L
Lupus Anticoagulant	≤ 1.8 dRVVT ratio

Rivaroxaban and warfarin interfered with the quantification of FIX activity.

Recovery of FIX Replacements

A recovery study was conducted using a single lot of CRYO*check* Chromogenic Factor IX on an IL ACL TOP 700 CTS instrument (K160276). Congenital FIX deficient plasma was spiked with seven FIX replacement therapies at seven concentrations and percent recovery was determined. CRYO*check* Chromogenic Factor IX accurately evaluated the potency of FIX concentrates including AlphaNine® SD, Alprolix®, BeneFIX®, Ixinity, Rebinyn® and Rixubis at concentrations ranging from 0.05 to 1.0 IU/mL. There was an overestimation of Idelvion*.

Product	Mean Percent Recovery (%)
AlphaNine SD	96
Alprolix	116
BeneFIX	93
Ixinity	82
Rebinyn	117
Rixubis	102
Idelvion*	153

** 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.*

Method Comparison Studies

A method comparison study was conducted at four sites (one internal and three external) according to CLSI EP09c to compare the accuracy of CRYO*check* Chromogenic Factor IX relative to a comparator device. Three hundred and sixty eight human plasma samples from normal ostensibly healthy individuals, from patients with von Willebrand disease, from patients with congenital and acquired hemophilia A and B and patients on recombinant factor IX treatments were distributed across four sites and tested for FIX activity using a single lot of CRYO*check* Chromogenic Factor IX on IL ACL TOP 700 CTS (K160276), IL ACL TOP 700 (K160276) and IL ACL TOP 750 (K150877) analyzers. A second aliquot of each sample was tested at two central reference laboratories using a validated laboratory developed chromogenic factor IX assay on an IL ACL TOP 700 instrument (K160276).

Results were compared by Passing-Bablok regression analysis. Regression statistics show that CRYO*check* Chromogenic Factor IX performed equivalently to the comparator method.

	N	Slope		Intercept		Pearson Correlation Coefficient
		Value	95% CI	Value	95% CI	
Site 1	108	1.11	1.08, 1.13	-0.01	-0.12, 0.17	0.996 (r^2=0.991)
Site 2	112	1.17	1.13, 1.20	1.72	1.16, 2.38	0.995 (r^2=0.990)
Site 3	112	1.21	1.15, 1.27	-11.76	-17.85, -7.26	0.979 (r^2=0.959)
Site 4	36	1.05	1.02, 1.12	2.44	0.63, 3.61	0.993 (r^2=0.987)
Overall	368	1.10	1.08, 1.12	0.64	0.20, 1.34	0.992 (r^2=0.983)

Absolute predicted biases at medical decision levels are reported below.

FIX activity (%)	Predicted Bias (%)	Lower CI (%)	Upper CI (%)
1	0.74	0.32	1.40
5	1.14	0.75	1.76
50	5.66	5.09	6.40
100	10.68	9.38	12.07

Sample Integrity

A sample integrity study was conducted at two external sites to assess the stability of fresh plasma samples at room temperature, when stored frozen at ≤-70 °C and after up to two freeze thaw cycles. The FIX activity of sixty-five plasma samples was measured using two lots of CRYO*check* Chromogenic Factor IX on IL ACL TOP 300 and IL ACL TOP 700 (K160276) analyzers. Results were compared using Passing Bablok regression analysis and support a fresh sample stability claim of 4 hours at room temperature and a frozen storage claim of 3 months at ≤-70 °C, including up to two freeze thaw cycles.

Conclusion

The performance testing results demonstrate that CRYO*check* Chromogenic FIX is substantially equivalent to the predicate device, HemosIL Factor IX Deficient Plasma (K031829) and the comparator assay (validated laboratory developed chromogenic FIX assay), and that the assay is effective for its labeled intended use.