July 17, 2020

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

Re: K193204
Trade/Device Name: CRYOcheck Chromogenic Factor VIII
Regulation Number: 21 CFR 864.7290
Regulation Name: Factor deficiency test
Regulatory Class: Class II
Product Code: GGP
Dated: November 19, 2019
Received: November 20, 2019

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,

for

Takeesha Taylor-Bell
Chief
Division of Immunology
and Hematology Devices
OHT7: Office of In Vitro Diagnostics
and Radiological Health
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: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
K193204

Device Name
CRYOcheck Chromogenic Factor VIII

Indications for Use *(Describe)*
CRYOcheck Chromogenic Factor VIII is for clinical laboratory use in the quantitative determination of factor VIII activity in 3.2% citrated human plasma. It is intended to be used in identifying factor VIII deficiency and as an aid in the management of hemophilia A 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 VIII

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 K193204

Submitter's Information	Precision BioLogic Inc. 140 Eileen Stubbs Ave. Dartmouth, Nova Scotia B3B 0A9 Canada	
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	9 July 2020	
Device Trade Name	CRYO*check*™ Chromogenic Factor VIII	
Regulatory Information	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	Coatest SP FVIII (K042576)	
Indication for Use/ Intended Use	CRYO*check* Chromogenic Factor VIII is for clinical laboratory use in the quantitative determination of factor VIII activity in 3.2% citrated human plasma. It is intended to be used in identifying factor VIII deficiency and as an aid in the management of hemophilia A in individuals aged 2 years and older. For in vitro diagnostic use.	
Device Description	CRYO*check* Chromogenic Factor VIII is used for determination of FVIII activity and contains the following four components, packaged in glass vials and provided frozen to preserve the integrity of the components: **Reagent 1:** Bovine FX and a fibrin polymerization inhibitor, with activators and stabilizers. **Reagent 2:** Human FIIa, human FIXa, 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	Coatest SP FVIII	CRYO*check* Chromogenic Factor VIII
Manufacturer	Instrumentation Laboratory	Precision BioLogic
Similarities		
Measurand	Human Factor VIII	Human Factor VIII
Product Code	GGP Test, Qualitative and Quantitative Factor Deficiency	GGP Test, Qualitative and Quantitative Factor Deficiency
Regulation Section	21 CFR 864.7290	21 CFR 864.7290

	Factor Deficiency Test	Factor Deficiency Test
Classification	Class II	Class II
Panel	81 (Haematology)	81 (Haematology)
Intended Use	Coatest SP FVIII is intended for the photometric determination of factor VIII activity in citrated plasma.	CRYO*check* Chromogenic Factor VIII is for clinical laboratory use in the quantitative determination of factor VIII activity in 3.2% citrated human plasma. It is intended to be used in identifying factor VIII deficiency and as an aid in the management of hemophilia A in individuals aged 2 years and older. For in vitro diagnostic use.
Assay Type	Quantitative (chromogenic measurement of FVIII)	Quantitative (chromogenic measurement of FVIII)
Device Description	Coatest SP FVIII is a modified version of Coatest Factor VIII (K833892) reformulated to European Pharmacopoeia Standards. Coatest SP FVIII is a photometric assay containing a chromogenic substrate, S-2765, with EDTA added as a preservative, lyophilized bovine factors IXa and X with bovine albumin added as a stabilizing agent. The device also contains calcium chloride, Tris buffer stock solution containing sodium chloride, bovine serum albumin with added antimicrobial in addition to a mixture of highly purified synthetic phospholipids.	CRYO*check* Chromogenic Factor VIII is used for determination of FVIII activity and contains the following four components, packaged in glass vials and provided frozen to preserve the integrity of the components: **Reagent 1:** Bovine FX and a fibrin polymerization inhibitor, with activators and stabilizers. **Reagent 2:** Human FIIa, human FIXa, 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	In the presence of calcium and phospholipids, factor X is activated to factor Xa by factor IXa. This generation is greatly stimulated by factor VIII, which may be considered as a cofactor in this reaction. By using optimal amounts of Ca2+ and phospholipids and an excess of factors IXa and X, the rate of activation of factor X is solely dependent on the amount of factor VIII. Factor Xa hydrolyses the chromogenic substrate S-2765 thus liberating the chromophoric group, pNA. The color is then read photometrically at 405 nm. The generated factor Xa and thus the intensity of color are	In the first stage of the chromogenic assay, test plasma (containing an unknown amount of functional FVIII) is added to a reaction mixture comprised of calcium, phospholipids, purified human thrombin and FIXa, and purified bovine FX (Reagent 1 and Reagent 2). This mixture swiftly activates FVIII to FVIIIa, which works in concert with FIXa to activate FX. When the reaction is stopped, FXa production is assumed to be proportional to the amount of functional FVIII present in the sample. The second stage of the assay is to measure FXa through cleavage of an FXa-specific peptide nitroanilide substrate (FXa Substrate). P-nitroaniline is produced, giving a color that can be

	proportional to the factor VIII activity in the sample. Hydrolysis of S-2765 by thrombin formed is prevented by the addition of the synthetic thrombin inhibitor, I-2581, together with the substrate.	measured spectrophotometrically by absorbance at 405 nm.
Expression of results	Quantitative; results are expressed as percent activity interpreted relative to a calibration curve.	Quantitative; results are expressed as percent activity interpreted relative to a calibration curve.
Differences		
Instrument(s)	Manual method, IL ACL 9000	IL ACL TOP CTS Series and IL ACL TOP 50 CTS Series
Storage	2-8 ºC until expiration	≤-70°C until expiration
Linearity Range	0-150% FVIII activity	0-200% FVIII activity
Reference Range	48.6- 126% (manual method) 55.4-148.9% (instrument application)	43.2-159.3% FVIII activity
Limit of Detection	1% FVIII activity	0.5% FVIII activity
In Use Stability	Working Factor Reagent Stability (phospholipids + factor IXa + factor X reagent): 12 hours on ice. S-2765 + I-2581: Reconstituted substrate is stable 3 months at 2-8ºC $CaCl_2$: Opened vial is stable 3 months at 2-8ºC Buffer, stock solution: Opened vial is stable 3 months at 2-8ºC Phospholipid: Opened vial is stable for 3 months at 2-8ºC Factor Reagent (IXa + X): Aliquoted for -20ºC for 3 months.	8 hours on-board instrument 5 days at 2-8ºC 1 month refrozen storage at ≤-70 °C if refrozen within 4 hours of the initial thaw. Previously refrozen reagents can be thawed and used once for up to four hours on board the instrument.
Interferences	Manual method: Triglycerides up to 700 mg/dL Bilirubin up to 20 mg/dL Hemoglobin up to 100 mg/dL Unfractionated Heparin up to 1.0 IU/mL Automated Method: Triglycerides up to 900 mg/dL Bilirubin up to 20 mg/dL Hemoglobin up to 50 mg/dL	Hemoglobin: ≤ 500 mg/dL Intralipid: ≤ 500 mg/dL Bilirubin (unconjugated): ≤ 29 mg/dL vWF: ≤ 20 µg/mL Unfractionated heparin: ≤ 2 IU/mL Low molecular weight heparin: ≤ 2 IU/mL Fondaparinux: ≤ 1.25 mg/L Lupus Anticoagulant: ≤ 1.8 dRVVT ratio Rivaroxaban and dabigatran interfered with the quantification of FVIII activity.

	Unfractionated Heparin up to 1.0 IU/mL Due to the high dilutions used there is no underestimation of FVIII activity in samples containing lupus anticoagulant	The potential interference effects of conjugated bilirubin on this device have not been evaluated. The performance of this device has not been established in individuals with von Willebrand disease Type 2M. The performance of this device has not been established in evaluating the potency of FVIII concentrates.
Sample Stability	None specified. Package insert indicates "Refer to NCCLS document H21-A4 for further instructions on specimen collection, handling and storage."	2 hours at room temperature and 3 months at ≤-70 °C, including up to two freeze thaw cycles

Performance Summary:

All studies were performed using CRYO*check* Chromogenic Factor VIII 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 VIII by one operator on an IL ACL TOP CTS analyzer (K160276) in accordance with CLSI EP05-A3. The study quantified one normal and two abnormal reference controls and five patient plasma samples representing very low, low, mid, normal and high levels of FVIII 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. The results demonstrated a pooled precision of <10% CV and ≤0.1% SD for the Very Low FVIII plasma sample.

Aggregated Data (Lots 1, 2 and 3)			
Sample	**Mean FVIII (%)**	**Within-Laboratory**	
		SD	**%CV**
CRYO*check* Reference Control Normal	80.8	4.0	5.0
CRYO*check* Abnormal 1 Reference Control	26.1	1.9	7.1
CRYO*check* Abnormal 2 Reference Control	7.8	0.8	9.9
Very Low FVIII Plasma Sample	1.0	0.1	NA
Low FVIII Plasma Sample	5.4	0.4	7.4
Mid FVIII Plasma Sample	26.0	1.7	6.7
Normal FVIII Plasma Sample	85.3	4.3	5.1
High FVIII Plasma Sample	152.1	5.7	3.8

Multi-Reagent Lot Site to Site Reproducibility

Reproducibility studies were conducted at three sites (one internal and two external) by different operators on an IL ACL TOP CTS (K160276) and two different IL ACL TOP 750 (K150877) analyzers using three lots of CRYO*check* Chromogenic Factor VIII in accordance with CLSI EP05-A3. The study quantified one normal and two abnormal reference controls and three patient plasma samples representing very low, normal and high levels of FVIII activity. Each sample was measured in triplicate, twice a day for 5 days at each site. The data across three sites demonstrated a pooled reproducibility of <10% CV for the controls and plasma samples >1% FVIII; and ≤0.1% SD for the Very Low FVIII plasma sample.

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
CRYO*check* Reference Control Normal	80.3	3.6	4.5	0.2	0.2	0.5	0.7	0.0	0.0	4.1	5.1
CRYO*check* Abnormal 1 Reference Control	25.4	1.3	5.2	0.2	0.6	0.3	1.2	1.5	5.7	2.1	8.2
CRYO*check* Abnormal 2 Reference Control	7.7	0.5	7.0	0.0	0.4	0.1	1.6	0.4	4.9	0.7	9.6
Very Low FVIII Plasma Sample	1.1	0.1	NA	0.0	NA	0.0	NA	0.0	NA	0.2	NA
Normal FVIII Plasma Sample	85.4	4.3	5.1	1.1	1.3	0.0	0.0	0.0	0.0	5.0	5.8
High FVIII Plasma Sample	156.9	7.8	5.0	0.9	0.5	0.0	0.0	6.1	3.9	11.4	7.3

Linearity/Assay Reportable Range

A linearity study was conducted in accordance with CLSI EP6-A using three lots of CRYO*check* Chromogenic Factor VIII on an IL ACL TOP CTS instrument (K160276). A high FVIII (260%) plasma was combined with congenital FVIII deficient plasma (0%) to create fifteen sample dilutions with estimated FVIII activities in the range of 0 to 260% FVIII. Each level was tested in quadruplicate. The results support the linearity claim described below.

Linearity Range: 0 to 200% FVIII activity

Reference Interval

A reference interval study was conducted by multiple operators in accordance with CLSI EP28-A3c using three lots of CRYO*check* Chromogenic Factor VIII on an IL ACL TOP CTS instrument (K160276). Citrated plasma samples were collected from one hundred and twenty ostensibly healthy individuals ≥ 18 years. The reference interval was established by calculating the non-parametric 95% confidence interval (2.5^{th} to 97.5^{th} percentiles).

Reference Interval: 43.2-159.3% FVIII activity

Stability

Shelf Life Stability

A shelf life stability study was conducted in accordance with CLSI EP25-A using an IL ACL TOP CTS instrument (K160276). Three lots of CRYO*check* Chromogenic Factor VIII were stored at and at ≤-70°C (monitored condition -76 to -82°C) and tested at t=0 and regular intervals defined by the lot-specific pull schedule up to 37 months. At each timepoint, five replicates of six plasma samples representing low to normal FVIII activity levels were quantified. The study has been

completed up to 13 months and supports a shelf-life stability claim of at least 12 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 CTS instrument (K160276). Three lots of CRYO*check* Chromogenic Factor VIII were maintained on board the analyzer (12–18 °C) for up to 9 hours and in a refrigerator (2–8 °C) for up to 121 hours. Each lot was used to quantify five replicates of six plasma samples representing low to normal FVIII activity levels at each storage condition at defined timepoints. The data support a stability claim of 8 hours on board the instrument and 120 hours (5 days) at 2-8 °C.

Three lots of CRYO*check* Chromogenic Factor VIII were maintained on board an analyzer for 4 hours, then subsequently refrozen at ≤-70 °C for up to 2 months. Each lot was used to quantify five replicates of six plasma samples representing low to normal FVIII activity levels at defined timepoints. The data support a stability claim of 1 month refrozen storage at ≤-70 °C if refrozen within 4 hours of the initial thaw. Previously refrozen reagents can be thawed and used once for up to four hours on board the instrument.

Detection Limit

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

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

The limit of quantitation (LoQ) was determined according to the CLSI EP17-A2 guideline. Aliquots of four plasma samples with low FVIII activity obtained from congenital hemophilia A 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 Coatest SP FVIII. The LoQ was determined to be 0.5% FVIII activity.

Interferences

Interference studies were conducted according to CLSI EP7-A3 using a single lot of CRYO*check* Chromogenic Factor VIII on an IL ACL TOP 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	≤ 500 mg/dL
Intralipid	≤ 500 mg/dL
Bilirubin (unconjugated)	≤ 29 mg/dL
vWF	≤ 20 µg/mL
Unfractionated heparin	≤ 2 IU/mL
Low molecular weight heparin	≤ 2 IU/mL
Fondaparinux	≤ 1.25 mg/L
Lupus Anticoagulant	≤ 1.8 dRVVT ratio

Rivaroxaban and dabigatran interfered with the quantification of FVIII activity.

The potential interference effects of conjugated bilirubin on this device have not been evaluated.

The performance of this device has not been established in individuals with von Willebrand disease Type 2M.

The performance of this device has not been established in evaluating the potency of FVIII concentrates.

Method Comparison Studies

A method comparison study was conducted at three sites (one internal and two external) according to CLSI EP09c to compare the accuracy of CRYO*check* Chromogenic Factor VIII relative to a comparator device. Three hundred and eighteen human plasma samples from normal ostensibly healthy individuals and from patients with congenital or acquired hemophilia A and Type 1, Type 2A, Type 2B and Type 2N von Willebrand disease were distributed across three sites and tested for FVIII activity using a single lot of CRYO*check* Chromogenic Factor VIII on an IL ACL TOP CTS (K160276) and two different IL ACL TOP 750 (K150877) analyzers. A second aliquot of each sample was tested at a central reference laboratory using Coatest SP FVIII on an IL ACL TOP 700 instrument (K160276).

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

	N	Slope		Intercept		Pearson Correlation Coefficient
		Value	95% CI	Value	95% CI	
Site 1	133	1.041	1.027, 1.058	0.720	0.252, 1.205	0.997 (r^2=0.993)
Site 2	53	1.138	1.109, 1.168	0.252	0.001, 0.409	0.998 (r^2=0.996)
Site 3	132	1.012	0.989, 1.045	-0.140	-1.768, 0.404	0.991 (r^2=0.982)
Overall	318	1.038	1.022, 1.051	0.473	0.265, 0.594	0.994 (r^2=0.987)

Absolute predicted biases are reported below.

FVIII activity (%)	Predicted Bias (%)	Lower CI (%)	Upper CI (%)
1	-1.11	-1.87	-0.35
5	-0.81	-1.53	-0.08
45	2.20	1.71	2.69
50	2.57	2.09	3.06
100	6.33	5.51	7.15
150	10.09	8.71	11.47

Sample Integrity

A sample integrity study was conducted at two external sites to assess sample stability of fresh samples at room temperature, when stored frozen at ≤-70 °C and after up to two freeze thaw cycles. The FVIII activity of forty-six plasma samples was measured using a single lot of CRYO*check* Chromogenic Factor VIII on an IL ACL TOP 300 and IL ACL TOP 700 (K160276) analyzer. Results were compared using Passing Bablok regression analysis and support a fresh sample stability claim of 2 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 Factor VIII is substantially equivalent to the predicate device, Coatest SP FVIII (K042576), and that the assay is effective for its labeled intended use.