September 13, 2023

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

Re: K222831
Trade/Device Name: CRYOcheck Factor VIII Deficient Plasma with VWF
Regulation Number: 21 CFR 864.7290
Regulation Name: Factor Deficiency Test
Regulatory Class: Class II
Product Code: GJT
Dated: May 19, 2023
Received: May 19, 2023

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, 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)*
K222831

Device Name
CRYOcheck Factor VIII Deficient Plasma with VWF

Indications for Use *(Describe)*
CRYOcheck Factor VIII Deficient Plasma with VWF is for clinical laboratory use as a deficient substrate in the quantitative determination of Factor VIII activity in 3.2% citrated human plasma based on the activated partial thromboplastin time (APTT) assay. 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*™ Factor VIII Deficient Plasma with VWF

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: K222831

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	25 August 2023	
Device Trade Name	CRYO*check*™ Factor VIII Deficient Plasma with VWF	
Regulatory Information	Regulation Number and Description	21 CFR 864.7290 Factor Deficiency Test
	Classification	Class II
	Product Code	GJT, Plasma, Coagulation Factor Deficient; 21 CFR 864.7290
	Classification Panel	Hematology
Predicate Device	HemosIL Factor VIII Deficient Plasma (K110237)	
Indication for Use/ Intended Use	CRYO*check* Factor VIII Deficient Plasma with VWF is for clinical laboratory use as a deficient substrate in the quantitative determination of Factor VIII activity in 3.2% citrated human plasma based on the activated partial thromboplastin time (APTT) assay. 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* Factor VIII Deficient Plasma with VWF is normal human citrated plasma which has been immunodepleted of factor VIII and to which an exogenous source of human von Willebrand Factor (vWF) has been added and buffered with HEPES. Factor VIII has been assayed at less than 1% of normal activity levels and vWF antigen and activity are >50%. It will be provided to users frozen in small-volume aliquots (25 vials of 1.0 mL, and 25 vials of 1.5 mL). Vials will be packaged into boxes; these will be frozen during the manufacturing process and will be shipped and stored frozen until use to preserve the integrity of the components.	

Comparison to Predicate		
Item	**Predicate**	**New Device**
Proprietary and Established Names	HemosIL Factor VIII Deficient Plasma	CRYO*check* Factor VIII Deficient plasma with VWF
Manufacturer	Instrumentation Laboratory	Precision BioLogic
Similarities		
Measurand	Human Factor VIII	Same
Classification Product Code	GJT, Plasma, Coagulation Factor Deficient	Same
Regulation Section	21 CFR 864.7290 Factor Deficiency Test	21 CFR 864.7290 Factor Deficiency Test

Comparison to Predicate		
Item	**Predicate**	**New Device**
Classification	Class II	Class II
Panel	81 (Haematology)	81 (Haematology)
Intended Use	HemosIL Factor VIII deficient plasma is human plasma depleted for Factor VIII and intended for the in vitro diagnostic quantitative determination of Factor VIII activity in citrated plasma, based on the activated partial thromboplastin time (APTT) assay, on the ACL TOP Family analyzers. HemosIL Factor VIII deficient plasma is indicated for use on patients who are suspected of congenital or acquired deficiency based on the activated partial thromboplastin time (APTT) assay results.	CRYO*check* Factor VIII Deficient Plasma with VWF is for clinical laboratory use as a deficient substrate in the quantitative determination of Factor VIII activity in 3.2% citrated human plasma based on the activated partial thromboplastin time (APTT) assay. 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 (clot-based measurement of FVIII)	Same
Methodology	Factor VIII 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 plasma deficient in Factor VIII. 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.	Same
Expression of results	Quantitative; results are expressed as percent activity. interpreted relative to a calibration curve.	Same
Instrument(s)	ACL TOP Family/ACL TOP Family 50 Series	Same

Differences		
Item	**Predicate**	**New Device**
Device Description	The HemosIL Factor VIII deficient plasma kit contains 10 x 1 mL vials of lyophilized human plasma that has been artificially depleted of factor VIII containing buffer and stabilizers. The residual factor VIII activity is less than or equal to 1% whereas von Willebrand Factor and the remaining intrinsic pathway factor levels are normal.	CRYO*check* Factor VIII Deficient Plasma with VWF is normal human citrated plasma which has been immunodepleted of factor VIII and to which an exogenous source of human von Willebrand Factor (vWF) has been added and buffered with HEPES. Factor VIII has been assayed at less than 1% of normal activity levels and vWF antigen and activity are >50%. It will be provided to users frozen in small-volume aliquots (25 vials of 1.0 mL, and 25 vials of 1.5 mL). Vials will be packaged into boxes; these will be frozen during the manufacturing process and will be shipped and stored frozen until use to preserve the integrity of the components.

Performance Summary:

All studies were performed using CRYO*check* Factor VIII Deficient Plasma with VWF in a modified APTT assay with Instrumentation Laboratories' APTT SynthASil reagent to measure FVIII activity 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* Factor VIII Deficient Plasma with VWF in a modified APTT assay 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 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 pooled results demonstrated a precision of <10% CV for all controls and the high FVIII activity plasma sample, and <0.5 SD for the low and very low FVIII plasma samples.

Aggregated Data (Lots 1, 2 and 3)					
Sample	Mean FVIII (%)	Within-Run Precision		Total Precision	
		SD	**%CV**	**SD**	**%CV**
CRYO*check* Reference Control Normal	100.4	3.5	3.4	5.7	5.7
CRYO*check* Abnormal 1 Reference Control	37.7	1.7	4.6	2.3	6.2
CRYO*check* Abnormal 2 Reference Control	11.3	0.4	3.7	0.6	5.2
High FVIII Plasma Sample	164	6.1	3.7	9.8	6.0
Low FVIII Plasma Sample	2.0	0.2	9.3	0.2	11.1
Very Low FVIII Plasma Sample	0.1	0.0	18.2	0.0	24.1

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 500, IL ACL TOP 700 CTS (K160276), and IL ACL TOP 750 CTS (K150877), analyzers using three lots of CRYO*check* Factor VIII Deficient Plasma with VWF in a modified APTT assay 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 FVIII activity. Each sample was measured in triplicate, twice a day for 5 days at each site. The pooled data across three sites demonstrated a reproducibility of <10% CV for all controls and the high FVIII plasma sample, and <0.5 SD for the low and very low FVIII plasma samples.

Pooled 3-Site Data														
Sample	N	Mean FVIII (%)	Repeatability (Within-Run)		Between- Run		Between-Day		Between-Lot		Between-Site		Reproducibility (Total)	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Reference Control Normal	270	98.97	3.00	3.03	2.07	2.09	1.78	1.79	1.92	1.94	3.95	3.99	5.98	6.04
Abnormal 1 Reference Control	270	37.40	1.25	3.33	0.63	1.68	0.61	1.63	0.80	2.14	0.44	1.16	1.77	4.75
Abnormal 2 Reference Control	270	11.87	0.41	3.48	0.18	1.55	0.28	2.43	0.33	2.81	0.66	5.54	0.91	7.68
High FVIII Plasma Sample	269	166.37	6.54	3.93	2.08	1.25	1.45	0.87	4.34	2.61	1.78	1.07	8.44	5.07
Low FVIII Plasma Sample	270	1.93	0.11	5.84	0.06	3.08	0.03	1.81	0.08	4.01	0.09	5.01	0.18	9.39
Very Low FVIII Plasma Sample	270	0.11	0.03	30.24	0.01	5.90	0.01	10.16	0.01	4.52	0.02	20.34	0.04	38.56

Linearity/Assay Reportable Range

A linearity study was conducted in accordance with CLSI EP06-2nd Ed using three lots of CRYO*check* Factor VIII Deficient Plasma with VWF in a modified APTT assay to quantify FVIII on an IL ACL TOP 700 CTS instrument (K160276). A high FVIII (~260%) plasma was combined with congenital hemophilia A patient plasma (0% FVIII) 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 230% FVIII activity

Reference Interval

A reference interval study was conducted by two operators on two IL ACL TOP 700 CTS (K160276) analyzers in accordance with CLSI EP28-A3c using three lots of CRYO*check* Factor VIII Deficient Plasma with VWF and citrated plasma samples from 136 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: 62 to 163 % FVIII 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). Three lots of CRYO*check* Factor VIII Deficient Plasma with VWF were stored at -40 °C and ≤-70 °C and tested at t=0 and regular intervals defined by the lot-specific pull schedule up to 37 months (real time study is ongoing). 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 FVIII activity levels were quantified in a modified APTT assay. The study has been completed up to 25 months and supports a shelf-life stability claim of 24 months when the product is stored at -40 °C to -80 °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). Three lots of CRYO*check* Factor VIII Deficient Plasma with VWF were maintained on board the analyzer (14.5 – 15.5 °C) for up to 25 hours and in a refrigerator (2–8 °C) for up to 25 hours. Each lot was used in a modified APTT assay to quantify five replicates of one normal and two abnormal reference controls and two patient plasma samples representing low and high levels of FVIII activity from each storage condition at defined timepoints. The data support a stability claim of 24 hours on board the instrument and at 2-8 °C.

Interferences

Interference studies were conducted according to CLSI EP07-A3 using a single lot of CRYO*check* Factor VIII Deficient Plasma with VWF in a modified APTT assay 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
Intralipid	≤2000 mg/dL
Bilirubin (conjugated)	≤4.0 mg/dL
Bilirubin (unconjugated)	40 mg/dL
Lupus Anticoagulant	≤1.8 dRVVT ratio
Warfarin	≤ INR ratio 2.72

Rivaroxaban, fondaparinux, dabigatran, emicizumab, unfractionated heparin, and low molecular weight heparin were shown to interfere with the quantification of FVIII activity.

Recovery of FVIII Replacements

A recovery study was conducted using a single lot of CRYO*check* Factor VIII Deficient Plasma with VWF in a modified APTT assay on an IL ACL TOP 700 CTS instrument (K160276). Congenital FVIII deficient plasma was spiked with six FVIII replacement therapies at seven concentrations and percent recovery was determined. CRYO*check* Factor VIII Deficient Plasma with VWF accurately evaluated (100 ± 25%) the potency of FVIII replacements including Advate, Afstyla, Elocate, Jivi, Novoeight, and Wilate at concentrations ranging from 0.05 to 1.0 IU/mL. There was an underestimation of Afstyla*, and a 2x correction factor was applied to the results based on manufacturer's recommendations.

Product	Mean Percent Recovery (%)
Advate	92.84
Afstyla*	97.38
Eloctate	94.90
Jivi	104.49
Novoeight	113.33
Wilate	94.92

** Per the manufacturer's recommendations, a chromogenic assay is recommended for measurement of Afstyla and results obtained by a one stage clotting assay will under recover by 50%.*

Method Comparison

A method comparison study was conducted at four sites (one internal and three external) according to CLSI EP09c to compare the accuracy of factor VIII activity measurement when using CRYO*check* Factor VIII Deficient Plasma with VWF in a modified APTT assay relative to a comparator device. Three hundred and sixty-six human plasma samples from normal ostensibly healthy individuals, from patients with congenital or acquired hemophilia A, patients with hemophilia B, patients with von Willebrand disease, hemophilia A patients on FVIII replacement therapies, and patients with other factor deficiencies were distributed across four sites and tested to quantify FVIII activity using a single lot of CRYO*check* Factor VIII Deficient Plasma with VWF on IL ACL TOP 500, IL ACL TOP 700 CTS (K160276), and IL ACL TOP 750 CTS (K150877) analyzers. A second aliquot of each sample was tested using a modified APTT assay with HemosIL Factor VIII Deficient Plasma on an IL ACL TOP 750 instrument (K150877).

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

	N	Slope		Intercept		Pearson Correlation Coefficient (r)
		Value	95% CI	Value	95% CI	
Site 1	115	1.15	1.12 to 1.19	0.17	-0.38 to 0.64	0.93
Site 2	125	1.19	1.16 to 1.22	-0.26	-0.48 to -0.09	0.97
Site 3	108	1.10	1.06 to 1.15	0.97	0.24 to 1.99	0.98
Site 4	18	1.22	0.95 to 1.31	1.19	-3.99 to 13.96	0.98
Overall	**366**	**1.16**	**1.15 to 1.18**	**-0.08**	**-0.25 to 0.13**	**0.96**

Absolute predicted biases at medical decision levels are reported below.

FVIII activity (%)	Predicted Bias (%)	Lower CI (%)	Upper CI (%)
1	0.37	-1.42	2.17
5	0.91	-0.79	2.62
50	6.97	5.85	8.09
100	13.70	11.84	15.56

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 FVIII activity of ninety-four plasma samples was measured using one lot of CRYO*check* Factor VIII Deficient Plasma with VWF on IL ACL TOP 300 and IL ACL TOP 700 (K160276) analyzers. Results were compared using weighted Deming regression analysis and support a fresh sample stability claim of 2 hours at room temperature and a frozen storage claim of 1.5 months at ≤-70 °C, including up to two freeze thaw cycles.

Conclusion

The performance testing results demonstrate that CRYO*check* Factor VIII Deficient Plasma with VWF is substantially equivalent to the predicate device, HemosIL Factor VIII Deficient Plasma (K110237) and that the assay is effective for its labeled intended use.