March 12, 2019

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

Re: K183440
Trade/Device Name: CRYOcheck FVIII Inhibitor Kit
Regulation Number: 21 CFR 864.7290
Regulation Name: Factor deficiency test
Regulatory Class: Class II
Product Code: GGP
Dated: December 10, 2018
Received: December 12, 2018

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/CombinationProducts/GuidanceRegulatoryInformation/ucm597488.htm); 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 http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/) and CDRH Learn (http://www.fda.gov/Training/CDRHLearn). 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 (http://www.fda.gov/DICE) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Leonthena R. Carrington -S

Lea Carrington
Director
Division of Immunology and Hematology Devices
Office of In Vitro Diagnostics and Radiological Health
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)*
K183440

Device Name
CRYOcheck FVIII Inhibitor Kit

Indications for Use *(Describe)*
The CRYOcheck FVIII Inhibitor Kit is for clinical laboratory use in conjunction with a Factor VIII activity assay to enable the performance of a modified Nijmegen-Bethesda assay using 3.2% citrated human plasma. It enables the determination of a functional FVIII inhibitor titer to aid in the clinical management of congenital hemophilia A in individuals aged 2 years or 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.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 79 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

510(k) Summary
CRYO*check* FVIII Inhibitor Kit

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: __K183440_____

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	December 10, 2018	
Device Trade Name	CRYO*check*™ Factor VIII Inhibitor Kit	
Regulatory Information	Regulation Number and Description	21 CFR 864.7290 Factor Deficiency Test 21 CFR 864.5425 Multipurpose system for in vitro coagulation studies
	Classification	Class II
	Product Code	GGP; Test, Qualitative and Quantitative Factor Deficiency; 21 CFR 864.7290; GGN; Plasma, Coagulation Control; 21 CFR 864.5425
	Classification Panel	Hematology
Predicate Device	Immucor FVIII Antibody Screen Assay (K082205)	
Indication for Use/ Intended Use	The CRYO*check* FVIII Inhibitor Kit is for clinical laboratory use in conjunction with a Factor VIII activity assay to enable performance of a modified Nijmegen-Bethesda assay using 3.2% citrated human plasma. It enables the determination of a functional FVIII inhibitor titer to aid in the clinical management of congenital hemophilia A in individuals aged 2 years or older. For in vitro diagnostic use.	
Device Description	The FVIII Inhibitor Kit is used in the CDC modification of the Nijmegen-Bethesda assay and contains the following components: *Imidazole Buffered Pooled Normal Plasma (IB-PNP):* Pooled normal plasma from a minimum of twenty donors with a factor VIII activity value of 95-113% and buffered with imidazole to a pH of 7.3 – 7.5. *Imidazole Buffered Bovine Serum Albumin (IB-BSA):* A 4% BSA solution buffered with imidazole to a pH of 7.3-7.5. *Negative Factor VIII Inhibitor Control:* Pooled normal plasma from a minimum of five donors buffered with HEPES to a pH of 6.2-8.2.	

	Positive Factor VIII Inhibitor Control: HEPES buffered (pH 6.2-8.2) immunodepleted FVIII deficient plasma to which anti-human FVIII antibodies have been added.	
Comparison to Predicate		
Item	**Predicate**	**New Device**
Proprietary and Established Names	Factor VIII Antibody Screen, Immucor FVIII Antibody Screen Assay	CRYO*check* FVIII Inhibitor Kit
Manufacturer	Genetic Testing Institute, Inc. (original applicant)	Precision BioLogic
Similarities		
Measurand	Antibodies to human Factor VIII	Factor VIII Inhibitor
Product Code	GGP Test, Qualitative and Quantitative Factor Deficiency	GGP Test, Qualitative and Quantitative Factor Deficiency GGN Plasma, Coagulation Control
Regulation Section	21 CFR 864.7290 Factor Deficiency Test	21 CFR 864.7290 Factor Deficiency Test 21 CFR 864.5425 Multipurpose system for in vitro coagulation studies
Classification	Class II	Class II
Panel	81 (Haematology)	81 (Haematology)
Intended Use	The Factor VIII Antibody Screen is a qualitative solid phase enzyme linked immunosorbent assay (ELISA) designed to detect IgG antibodies reactive with recombinant human VIII (FVIII) in human serum and plasma.	The CRYO*check* FVIII Inhibitor Kit is for clinical laboratory use in conjunction with a Factor VIII activity assay to enable performance of a modified Nijmegen-Bethesda assay using 3.2% citrated human plasma. It enables the determination of a functional FVIII inhibitor titer to aid in the clinical management of congenital hemophilia A in individuals aged 2 years or older. For in vitro diagnostic use.
Differences		
Assay Type	ELISA (Qualitative)	Quantitative
Device Description	The Factor VIII Antibody Screen assay is an ELISA with a colorimetric endpoint. The assay kit is made of a 96 welled microwell plate (in 1 X 8	The FVIII Inhibitor Kit is used in the CDC modification of the Nijmegen-Bethesda assay and

	strips), alkaline phosphatase conjugated goat antibody to human immunoglobulin G, p-nitrophenyl phosphate substrate, positive and negative control, Stop Solution, diluents, buffers, wash solutions, and plate sealers.	contains the following components: *Imidazole Buffered Pooled Normal Plasma (IB-PNP):* Pooled normal plasma from a minimum of twenty donors with a factor VIII activity value of 95-113% and buffered with imidazole to a pH of 7.3 – 7.5. *Imidazole Buffered Bovine Serum Albumin (IB-BSA):* A 4% BSA solution buffered with imidazole to a pH of 7.3-7.5. *Negative Factor VIII Inhibitor Control:* Pooled normal plasma from a minimum of five donors buffered with HEPES to a pH of 6.2-8.2. *Positive Factor VIII Inhibitor Control:* HEPES buffered (pH 6.2-8.2) immunodepleted FVIII deficient plasma to which anti-human FVIII antibodies have been added.
Methodology	Diluted patient sample is added to microwells coated with recombinant FVIII, and antibody, if present will bind. Unbound material is washed away, and an alkaline phosphatase labeled anti-human immunoglobulin reagent (anti IgG) is added to the wells and incubated. Unbound anti-IgG is washed away and then PNPP (p-nitrophenyl phosphate) substrate is added. After a 30 minute incubation period, the reaction is stopped, and the optical density of the color that develops is measured at 405nm.	Diluted heat inactivated patient plasma is mixed with an exogenous source of FVIII (IB-PNP) and prepared alongside a control mix, consisting of a diluent (IB-BSA) and IB-PNP. Following a 2 hour incubation, the FVIII activity of the test plasma relative to the control mix is determined and used to calculate FVIII inhibitor activity expressed as Bethesda units per milliliter.
Expression of results	Qualitative; results are reported as positive or negative.	Quantitative; results are expressed in Bethesda units per milliliter (BU/mL)

Performance Summary:

All studies were performed using the CRYO*check* FVIII Inhibitor Kit in conjunction with the Siemens FVIII chromogenic assay (K884544, original applicant Baxter Healthcare Corporation) on Siemens BCS XP instrument(s) (K970431, original applicant Behring Diagnostics Inc).

Multi-Reagent Lot Precision

An internal precision study was performed using three (3) different lots of CRYO*check* FVIII Inhibitor Kit by one operator on a Siemens BCS XP analyzer in accordance with CLSI EP05-A3. The study quantified the kit's Positive and Negative Control as well as four plasma samples from congenital hemophilia A patients representing negative, low, mid and high levels of FVIII inhibitor. 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 8 % CV for the positive samples and 0.1 BU/mL SD for the negative sample as summarized below.

Lot 1									
Sample	**Mean (BU/mL)**	**Within-Run**		**Between- Run**		**Between-Day**		**Within-Lot**	
		SD	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
Kit Negative Control	0.0	0.0	189.7	0.0	178.9	0.0	156.4	0.1	304.1
Kit Positive Control	1.8	0.1	7.9	0.1	5.2	0.0	0.0	0.2	9.4
Negative Plasma Sample	0.3	0.1	22.2	0.0	10.1	0.0	0.0	0.1	24.4
Low Plasma Sample	1.4	0.1	7.9	0.0	0.0	0.0	2.2	0.1	8.2
Mid Plasma Sample	5.6	0.5	8.8	0.2	3.5	0.2	3.1	0.6	9.9
High Plasma Sample	9.6	0.6	6.1	0.2	2.0	0.2	2.0	0.6	6.7
Lot 2									
Sample	**Mean (BU/mL)**	**Within-Run**		**Between- Run**		**Between-Day**		**Within-Lot**	
		SD	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
Kit Negative Control	0.0	0.1	306.3	0.0	111.1	0.0	0.0	0.1	325.8
Kit Positive Control	1.5	0.2	12.1	0.0	0.0	0.0	0.0	0.2	12.1
Negative Plasma Sample	0.2	0.1	32.4	0.0	13.1	0.0	7.5	0.1	35.7
Low Plasma Sample	1.1	0.1	7.6	0.0	0.0	0.0	2.9	0.1	8.2
Mid Plasma Sample	5.0	0.4	7.3	0.0	0.0	0.0	0.0	0.4	7.3
High Plasma Sample	7.9	0.7	9.3	0.0	0.0	0.3	3.6	0.8	10.0

Lot 3									
Sample	Mean (BU/mL)	Within-Run		Between- Run		Between-Day		Within-Lot	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
Kit Negative Control	0.0	0.1	209.8	0.0	161.2	0.0	0.0	0.1	264.6
Kit Positive Control	1.5	0.1	8.4	0.1	4.2	0.1	5.5	0.2	10.9
Negative Plasma Sample	0.3	0.1	23.9	0.0	8.4	0.0	12.8	0.1	28.4
Low Plasma Sample	1.1	0.1	6.7	0.0	4.3	0.0	2.3	0.1	8.2
Mid Plasma Sample	5.3	0.3	6.0	0.2	3.8	0.1	1.3	0.4	7.2
High Plasma Sample	8.4	0.6	7.6	0.4	4.5	0.1	0.6	0.7	8.9

Aggregated Data (Lots 1, 2 and 3)			
Sample	Mean (BU/mL)	Within-Laboratory	
		SD	%CV
Negative Plasma Sample	0.3	0.1	29.0
Low Plasma Sample	1.2	0.1	8.2
Mid Plasma Sample	5.3	0.4	8.3
High Plasma Sample	8.6	0.7	8.4

Multi-Reagent Lot Site to Site Reproducibility

Reproducibility studies were conducted at three sites (one internal and two external) by three different operators on three different Siemens BCS XP analyzers using a single lot of CRYO*check* FVIII Inhibitor Kit in accordance with CLSI EP05-A3. The study quantified the kit's Positive and Negative Control as well as four plasma samples from congenital hemophilia A patients representing negative, low, mid and high levels of FVIII inhibitor. Each sample was measured in triplicate, twice a day for 5 days for a total of 30 replicates per sample per site. The data across three sites demonstrated a pooled reproducibility of ≤16% CV for the positive samples and 0.1 BU/mL SD for the negative plasma sample as summarized below.

Pooled 3-Site Data											
Sample	Mean (BU/mL)	Within-Run		Between- Run		Between-Day		Between-Site		Across-Site	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Kit Negative Control	0.0	0.1	399.4	0.0	138.3	0.0	0.0	0.0	0.0	0.1	422.7
Kit Positive Control	1.8	0.2	8.9	0.1	3.3	0.1	3.4	0.2	12.4	0.3	16.0
Negative Plasma Sample	0.3	0.1	26.9	0.0	0.0	0.0	9.0	0.0	2.2	0.1	28.4
Low Plasma Sample	1.4	0.1	10.2	0.0	0.0	0.0	2.9	0.0	0.0	0.1	10.6
Mid Plasma Sample	5.5	0.4	7.8	0.1	1.9	0.1	2.2	0.0	0.0	0.5	8.3
High Plasma Sample	9.6	0.7	7.8	0.4	4.0	0.3	3.4	0.9	9.2	1.3	13.2

Linearity/Assay Reportable Range

A linearity study was conducted in accordance with CLSI EP06-A using one lot of CRYO*check* FVIII Inhibitor Kit. Factor VIII inhibitor positive plasma from a congenital hemophilia A patient was combined with congenital hemophilia A patient plasma containing no FVIII inhibitor to create twelve sample dilutions with estimated titers in the range of 0 to 100 BU/mL. The results support the linearity claim described below.

An expanded linearity study was also conducted using one lot of CRYO*check* FVIII Inhibitor Kit. A series of eighteen sample dilutions spanning a range of 0 to 1402.9 BU/mL was created by diluting a high titer contrived sample (FVIII inhibitor titer of 1402.9 BU/mL, comprised of FVIII monoclonal antibody in immunodepleted FVIII deficient plasma) with immunodepleted FVIII deficient plasma. The results support the linearity claim described below.

Linearity Range: 0.2 to 1402.9 BU/mL

Stability

Shelf Life Stability

A shelf life stability study was conducted in accordance with CLSI EP25-A. Three lots of CRYO*check* FVIII Inhibitor Kit were stored 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 the kit's Positive and Negative Control as well as four plasma samples from congenital hemophilia A patients representing negative, low, mid and high levels of FVIII inhibitor were quantified. The study has been completed up to 13 months and supports a 12-month shelf-life stability claim.

In-Use Stability

An in-use stability study was conducted in accordance with CLSI EP25-A. Three lots of CRYO*check* FVIII Inhibitor Kit were maintained at room temperature (18–25 °C) or in a refrigerator (2–8 °C) and used to quantify six replicates of the kit's Positive and Negative Control as well as three plasma samples from congenital hemophilia A patients representing negative, low and high levels of FVIII inhibitor at 0, 2, 4, 6 and 7 hours. The data support a 4-hour in-use stability of the product when maintained at room temperature or at 2-8 °C post thaw.

Detection Limit

The limit of blank (LoB) was determined following the CLSI EP17-A2 guideline by measuring four blank plasma samples obtained from normal healthy donors. Samples were measured in triplicate using three lots of CRYO*check* FVIII Inhibitor Kit over five days. The LoB was determined to be 0.1 BU/mL.

The limit of detection (LoD) was determined following the CLSI EP17-A2 guideline by measuring four low titer plasma samples obtained from congenital hemophilia A donors. Samples were measured in triplicate using three lots of CRYO*check* FVIII Inhibitor Kit over five days. The LoD was determined to be 0.2 BU/mL.

The limit of quantitation (LoQ) study was determined according to the CLSI EP17-A2 guideline. Aliquots of each low titer sample used in the LoD study were sent to an external laboratory for testing in three replicates on three different days to determine assigned values using a validated, laboratory-developed, CDC-modified Nijmegen-Bethesda assay. The LoQ was determined to be 0.2 BU/mL.

Interferences

Interference studies were conducted according to CLSI EP7-A2 using a single lot of CRYO*check* FVIII Inhibitor Kit. Patient 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	≤ 500mg/dL
Bilirubin	≤ 500mg/dL
Intralipid	≤ 29mg/dL
vWF	≤ 20 µg/mL

Lupus anticoagulant autoantibodies may interfere with the quantification of low titer FVIII inhibitors.

Rheumatoid Factor at ≥ 82 IU/mL showed interference with the quantification of FVIII inhibitors.

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 the CRYO*check* FVIII Inhibitor Kit relative to a comparator device. Aliquots of human plasma samples from individuals with congenital hemophilia A (N=210) were distributed across three sites and tested using a single lot of CRYO*check* FVIII Inhibitor Kit. A second aliquot of each sample was tested at a central reference laboratory using a chromogenic CDC-Modified Nijmegen-Bethesda Assay which has been implemented as a validated Laboratory-Developed Test on a Siemens BCS XP instrument. The data demonstrated positive agreement of 100% (95% CI, 97-100%) and negative agreement of 99% (95% CI, 93-100%), as summarized below.

		CRYO*check* FVIII Inhibitor Kit results		
		Positive	**Negative**	**Total**
Comparator device results	**Positive**	133	0	133
	Negative	1	76	77
	Total	134	76	210

Results were compared by Passing-Bablok regression analysis as well as Bland-Altman plots. Regression statistics show that the CRYO*check* FVIII Inhibitor Kit performed equivalently to the comparator method.

	N	Slope		Intercept		Pearson Correlation Coefficient
		Value	95% CI	Value	95% CI	
Site 1	68	1.543	1.404, 1.660	-0.224	-0.434, -0.127	0.977 (r^2=0.954)
Site 2	72	1.065	0.998, 1.190	-0.113	-0.138, -0.043	0.985 (r^2=0.969)
Site 3	70	1.373	1.225, 1.455	-0.075	-0.159, -0.023	0.980 (r^2=0.960)
Overall	210	1.341	1.265, 1.406	-0.145	-0.180, -0.070	0.970 (r^2=0.940)

Absolute predicted biases at medical decision levels are reported below.

Titer (BU/mL)	Predicted Bias (BU/mL)	Lower CI (%)	Upper CI (%)
0.6	-2.0	-4.8	0.8
1	-1.9	-4.6	0.9
5	-0.3	-3.0	2.5
10	1.7	-0.9	4.4

Sample Integrity

Sample integrity was assessed in two studies. In the first study, three test plasma samples were created by spiking anti-FVIII monoclonal antibody into immunodepleted Factor VIII deficient plasma representing negative, low and high levels of FVIII inhibitor and were quantified freshly prepared at t=0 and after 1) 25 hours storage at 2-8 °C, 2) freezing at -80°C and transfer to 2-8 °C for up to 25 hours, 3) freezing at -80°C and transfer to -20°C for up to 15 days, 4) freezing at -80°C, transfer to -20°C and up to three freeze/thaw cycles at -20°C and 5) freezing at -80°C and up to three freeze/thaw cycles at -80°C. The titers of immunodepleted FVIII-deficient plasma samples spiked with monoclonal anti-FVIII antibody measured consistently across each of these sample storage conditions, demonstrating robustness of FVIII measurements in fresh and frozen plasma samples including after multiple freeze/thaw cycles.

In the second study, a retrospective analysis was performed examining FVIII inhibitor titer results for four plasma samples from congenital hemophilia A patients representing negative, low, mid and high levels of FVIII inhibitor quantified using three lots of CRYO*check* FVIII Inhibitor Kit. The results demonstrated sample stability of 12 months when stored frozen at <-70°C.

Conclusion

The performance testing results demonstrate that the CRYO*check* FVIII Inhibitor Kit is substantially equivalent to the predicate device, Immucor FVIII Antibody Screen Assay (K082205) and the comparator assay (validated Laboratory-Developed test), and that the assay is effective for its labeled intended use.