Canadian Blood Services
BLOOD PLASMA STEM CELLS ORGANS & TISSUES

1800 Alta Vista Drive
Ottawa ON
K1G 4J5
Canada

2019-03-01
CBS Control #: CBS6276
HPFB File #: C1892-100390
REF: H-1819-SAS-GMP

Mr. Ian Findlay
Regional Regulatory Compliance & Enforcement Officer
Health Canada Product Inspection and Licensing Division
Regulatory Operations and Regions Branch
Health Canada
300-391 York Avenue
Winnipeg, Manitoba
R3C 4W1

Dear Mr. Findlay:

Re: Responses to Health Canada GMP Inspection of Wholesaler Activities at Regina Operations on 2019-01-10

The following are the actions undertaken by Canadian Blood Services in response to the observations contained in the Health Canada Exit Notice dated 2019-01-29.

C.02.012 - Manufacturing control

1. **The self-inspection and procedure presented for inspection to Health Canada Inspectors, i.e. Audit Report REF: I-1819-PPS (Page 1-3 of 15) and SOP 08-031 rev 7 "Quality Audits" were inadequate. Specifically,**
   A. **There was no evidence the self-inspection program defined in SOP 08-031 was specific to ensuring compliance with Division 2, Part C of the Food and Drug Regulations.**
      i. SOP 08-031 did not indicate GMP inspection in key areas such as the Audit Frequency Table (minimum self-audit frequency based on regulation/standard)

      ii. Risk rating of inspection observations in SOP 08-031, section 1.4 was not against GUI-0023, "Risk classification guide for drug good manufacturing practices observations"

      Combined response for 1ai and 1aii:

      Although the requirements for the frequency of wholesale audits (GMPs) were considered under the category for blood (Audit frequency table) and that observations were classified according to GUI-0023 as indicated in the audit plan, we acknowledge that this needs clarification in SOP 08 031, Quality Audits. As such SOP 08 031 will be revised by 2019-06-30 to include GUI-0023 in the references section and the audit frequency for wholesale activities in the audit frequency table.

LA

iii. It was not clear from the SOP or Audit Report REF: I-1819-PPS, that the team performing self-inspections included personnel who were suitably trained and qualified in GMP.

*Canadian Blood Services' Quality Auditors are trained and qualified (SOP 08 260, Quality Auditor Training) to be effective auditors, i.e. to have the right skills, competence, attitude and behavior expected of an auditor. They are trained to audit against requirements. That way Canadian Blood Services' Quality Auditors can audit all and any of our regulated and accredited activities by preparing and using detailed checklists that take into consideration the requirements of applicable regulations (e.g. Blood Regulations, Good Manufacturing Practices, CTO Regulations), standards (e.g. Foundation for the Accreditation of Cellular Therapies, AABB for Cellular Therapy Services, World Marrow Donor Association) and any additional corporate requirements. For the audit of Canadian Blood Services' wholesale activities, the checklists took into consideration requirements of Division2, Good Manufacturing Practices (**Attachment #1**). Therefore, our auditors are qualified and competent auditors that can audit against any set of requirements, including those of Good Manufacturing Practices.*

B. The May/June 2018 (most recent) self-inspection in Audit Report REF: I-1819-PPS (Page 1-3 of 15), specifically excludes the Regina site under the Scope. It was not clear that GMP self-inspection of the Regina site was routinely performed according to a defined frequency.

Audit # I-1819-PPS was conducted from May 21 to June 15, 2018. During that time Regina production was being consolidated into the Calgary site. A Health Canada inspection was also planned to start on June 18, 2018. It was therefore decided not to include Regina as part of the audit. A Wholesale audit of Regina Operations will be conducted in Q1 of fiscal year 2019-2020.

To clarify that sites are inspected according to a defined frequency, SOP 08 031, Quality Audits will be revised by 2019-06-30 to include 3 years as the audit frequency for wholesale activities.

C. Neither SOP 08-031, nor Audit Report REF: I-1819-PPS demonstrated that all applicable GMP Requirements set out in the Food and Drug Regulations (FDR) had been addressed in the performed self-inspection i.e. that the self-audit included an assessment of the firms Premises C.02.004; Personnel (GMP training) C.02.006, Manufacturing Control C.02.011 - 012; Quality Control Department C.02.013 - 015; and Records C.02.021 - 024.

As described in the audit plan, the audit was conducted against requirements described in GUI-0001 - Good Manufacturing Practices Guidelines. The scope of the audit also indicates that the elements mentioned in the observation are all part of the audit and the audit checklist includes the applicable sections of the GMPs to be verified (in accordance with Chart 1.0, of GUI-0001).

<u>C.02.015 - Quality control department</u>

2. The quality control department's handling of complaints and/or information received about drug quality was inadequate.

A. In two instances, the firm received Schedule D drug products (Plasma Protein Products) that had undergone temperature excursion during transport, but were deemed suitable for continued use by the quality department. There was no documented scientific/technical rationale available to justify the allowable

LA

temperature excursions outside of drug product labelled storage conditions in the two instances. Specifically,

i. Quality Event Report (QER) #30-18-118329; 40 vials of Kovaltry (rFVIII) 3000 IU/vial (DIN 02451492) were exposed to freezing temperatures (min -5°C) for 6.1 hours. The product monograph states "Stored under refrigeration (2°C - 8°C). Freezing must be avoided."

ii. QER #30-18-118345; 19 vials of Nuwiq (rFVIII) 250 IU/vial (DIN 20432951) were exposed to temperatures above refrigeration (max 9.1°C) for 13.2 hours. The product monograph states "Store under refrigeration (2°C - 8°C) until indicated expiry date. Nuwiq may be stored at room temperature (up to 25°C) for up to one month. Once the product has been taken out of the refrigerator it must not be returned to the refrigerator. Please record the beginning of storage at room temperature on the product carton." There was no evidence the product monograph directions for non-refrigerator conditions were followed.

B. The firm's SOP 12-808, rev 4 "Managing Excursions Reported to Plasma Products & Services - Head Office" was deficient. Step 1.3 "Determine Acceptability" by the HO QA requires "Determine acceptability for release, based on vendor supplied information and supporting documentation or forward to manufacturer for decision." The SOP does not require the scientific/technical justification demonstrating that product quality is not affected to be documented in the QER.

Combined response for observations 2a and 2b:

*In both instances, products were released based on information and evidence provided by the manufacturers (see **Attachment #2** for Kovaltry release package).*

SOP 12 808, Managing Excursions Reported to Plasma Products & Services - Head Office will be revised by 2019-07-29 to require that scientific and technical rationale be included when products are deemed acceptable for release by quality assurance.

C.02.024 - Records

3. The controls were inadequate for creating, modifying, reviewing, storing, and/or retrieving records.

The firm was unable to demonstrate adherence to the requirement under C.02.024; Every wholesaler shall a. maintain records of the results of the self-inspection program required by section C.02.012 and of any action taken in connection with that program;

The firm's SOP for Health Canada inspection was inadequate. Specifically, SOP 08-087 "Inspection Activities" which stated under Attachment 2, "records Inspector(s) are not permitted to review, unless authorized by the Director Regulatory Affairs.

i. Audit Observations

ii. Audit Reports (evidence that a report exists may be provided without disclosing details of the reports contents)."

The firm's position that records of the results of your self-inspection program, evaluation and conclusions, and corrective measures implemented, were not required to be provided during the course of this Health Canada GMP inspection, was not consistent with Section 23 (3) of the Food and Drugs Act.

We are of the opinion that, as is the case for all Health Canada inspections, we provided the inspector with all reasonable assistance and with any information he may have reasonably required.

LA

To demonstrate compliance to C.02.024 we provided a copy of SOP 08 031 that described the management of quality audits and pages 1-3 of Audit Report (REF: I-1819-PPS) that provides further evidence to the goal and scope of an audit, to the documentation of observations and to the approval of an audit.

Our audit program is designed to encourage openness and to provide meaningful audits. To that end and to maintain the integrity of the process we do not share quality audit reports with external parties. This is not a unique approach to Canadian Blood Services. In fact, the USFDA has a policy that recognizes this and they do not review quality audit reports[1].

We believe we can demonstrate compliance to C.02.024 without disclosing our audit reports and are willing to work with RORB to look at alternative ways to provide you with what is deemed to be satisfactory evidence.

[1]CPG Sec. 130.300 FDA Access to Results of Quality Assurance Program Audits and Inspections, June 2007.

C.02.015 - Quality control department

4. The guidelines and/or procedures were inadequate in ensuring storage and/or transportation conditions would maintain the quality R safe distribution of the drug.

The assessment of the Pelican BioThermal Credo Cube shipping container was incomplete. Winter profile (CBS B profile - in laboratory) was completed as per report TR-CBS-16-222-1. Additionally, the firm was in process of assessing those same Credo containers for blood products (refrigeration and room temperature shipments) according to the Shipping Process Project (route shipping profiles - seasonal). However the following deficiencies were noted:

i. No records were provided demonstrating that summer shipping conditions were assessed.

We acknowledge our difficulties during the inspection to provide some of the records in a timely manner. The evidence for the summer shipment conditions is documented in the following reports:

16L Shipping Container

- *ESP020163P.2, (2-8°C) Summer*
- *TR-CBS-16-272-1, (2-25°C) Summer and Winter*

8L Shipping Container:

- *TR-CBS-16-006-1 (Rev A), 2-25°C and 2-8°C - Summer*

ii. While the Credo Container Shipping Process Project (route shipping profiles - seasonal) was in progress, a final report was not available/provided to confirm the suitability of the container system for shipments from Regina.

The insulated shipping containers have been fully qualified for all shipping routes (including those from Regina) and all packing configurations. Approved qualification protocols and final qualification reports are available for:

- *16L Shipping Container, 2-25°C Packing Configuration*
- *16L Shipping Container, 2-8°C Packing Configuration*
- *8L Shipping Container, 2-25°C Packing Configuration*

LA

- *8L Shipping Container, 2-8°C Packing Configuration*
- *EPS Shipping Container, Frozen Packing Configuration*
- *8L Shipping Container, Frozen Packing Configuration.*

iii. The Shipping Process Project did not assess shipping of frozen (< -18°C) products, which are a type of drug product shipped from Regina.

The insulated shipping containers have been fully qualified for frozen products for all shipping routes (including those from Regina). All testing was performed against summer profiles which represent the worst-case scenario. Approved qualification protocols and final qualification reports are available for:

- *EPS Shipping Container: T2547-47 OQ Report - Frozen i1.4*
- *8L Shipping Container: TR-CBS-16-284-1 (Rev B)*

C.02.021 – Records

5. Documents were not available on the premises.
In several cases, required records under Division 2 of the Food and Drug Regulations were not available for inspection. For example for the 2018 "Installation and Performance Qualification of the Vaisala view/Linc" electronic storage temperature monitoring system in report IPQ-CMS-001 Version 3.0, only the firm's approval page (#36 of 43 pages) was available for inspection.

While we acknowledge that Canadian Blood Services generally had a robust and complete record-keeping system, those records should be maintained at the locations in Canada that are identified in your establishment licence or available on site during the course of a GMP inspection.

Canadian Blood Services maintains all records as required by the Food and Drug Regulations. As a national organization, records are maintained by the responsible department which may not be physically associated to only one site; however, records (or copy of) may be requested and made available. Every effort will be made in future inspections to provide all records requested in a timely manner.

If you require clarification or further information, please do not hesitate to contact the undersigned. **Please reference the above CBS control number in any correspondence.**

Sincerely,

Christian Choquet

Dr. Christian Choquet
Vice-President
Quality & Regulatory Affairs
Fax Number: 613-739-2505

cc: Ms. Joy Bregg
Regulatory Operations and Regions Branch

LA