Canadian Blood Services
BLOOD PLASMA STEM CELLS ORGANS & TISSUES

1800 Alta Vista Drive
Ottawa ON K1G 4J5

blood.ca

2024-12-06
CBS Control #: 6853
HPFB File #: C1892-100390
REF: H-2425-BRP-W

Craig Turk
Regional Regulatory Compliance and Enforcement Officer
GMP Inspection, Central
Regulatory and Enforcement Branch (ROEB)
Health Canada
Government of Canada
2301 Midland Avenue
Toronto, ON M1P 4R7

Dear Craig:

Re: Responses to Health Canada Inspection of Wholesale Activities at Brampton Operations
2024-10-30 to 2024-10-31

C.02.015 Quality Control Department

1. **Deficiencies were identified with the firm's management of the qualifications of their product storage areas. For example:**
   1) **There was no requirement to perform requalification activities for the drug product storage areas, nor was there a requirement to evaluate existing qualifications at a specific frequency, with supporting data, to ensure that they were still valid. For example, the firm had not assessed whether the temperature mapping studies performed in 2013 for the Distribution walk-in refrigerator (R000021228) and 2016 for the Logistics walk-in freezer (R000015887), were still valid.**

      Canadian Blood Services will implement a periodic review process to assess the need to re-validate our drug storage areas. This process will provide Canadian Blood Services with assurances that our drug storage areas remain in control (temperature and humidity) and continue to function as designed. If this review finds that our drug storage areas are not in control, corrective action will be taken and where required re-validation.

      The process will be designed, and implementation plan will be developed 2025-06-01.

   2) **Modifications to the layout of the Logistics walk-in refrigerator (R000015974) had occurred without a documented assessment against the existing qualification**

(IOQ-WRF-001-2017-03-24-115938). Note: there was also no change control available for this modification.

DEV-24-011182 was initiated 2024-11-13.

To investigate the impact of this uncontrolled change a validation request form was initiated on 2024-11-13 and completed on 2024-11-19. The resulting validation assessment indicated the removal of the cage did not have significant impact on the operation of the walk-in cooler to maintain the required temperature as it was a fencing material that is perforated. The full validation assessment is attached to DEV-24-011182.

Follow up was performed at the time of the inspection with facilities staff to ensure that they are aware and follow the requirements of WI-01405 Standard Change Initiator, specifically the requirement to ensure all assessments and approvals are captured in a change request prior to executing any change in a GMP environment such as the removal of a cage in a temperature mapped area.

In addition, refresher training to Quality Annual Retraining and of the change control process (WI-01405 Standard Change Initiator) will be completed by no later than 2024-12-20.

3) **The firm's approach to qualifying their product storage areas was not always justified. For example:**
   a) **There was no documented rationale for the firm's choice of duration for their mapping studies. For example, the Logistics and Distribution warehouse (R000015973 and R000031466) mapping studies occurred over a twenty-four hour period without a rationale for this duration.**

A risk-based approach to the mapping strategy for the product storage areas is built on the fact that the Brampton facility's heating, ventilation and air conditioning (HVAC) system were designed and commissioned, with considerations of the ambient environmental conditions and internal operational requirements. The mapping studies provided the documented evidence that the performance of the HVAC system met these requirements. The mapping studies also provided the information to identify the installation locations of monitoring sensors. The key to this risk-based mapping strategy is to ensure the mapping studies cover the mode of operations expected of the HVAC system in delivering and maintaining a stable internal operating environment. Therefore, considering the startup activities and test runs performed during commissioning, a 24-hour mapping during validation is deemed sufficient.

To clarify the current approach, the master protocol IOQ-ECA-001 will be updated, by 2025-03-31, to clarify this risk-based approach and to provide rationale on the duration of mapping studies which can be considered appropriate.

b) **The firm did not record external temperatures in order to assess how external conditions could impact internal temperature fluctuations during their mapping studies. For example, the studies performed for the Logistics and Distribution warehouses (IOQ-ECA-001-2023-07-17-103328 and IOQ-ECA-001-2024-03-11-164343, respectively) did not record the external temperatures at the time of the studies.**

A risk-based approach to the mapping strategy for the product storage areas is built on the fact that the Brampton facility's heating, ventilation and air conditioning (HVAC) system was designed and commissioned, with considerations of the ambient environmental conditions, and internal operational requirements. The HVAC system actively monitors to maintain the internal temperature of the warehouse. The mapping studies provided documented evidence of the HVAC system's performance in both heating and cooling modes. This evidence, along with the design and commissioning process, demonstrated the system's ability to maintain the required internal temperature for storage. Additionally, the worst-case locations based on the two mappings were identified for the area and on-going temperature monitoring sensors installed in those locations. The key to this risk-based mapping strategy is to ensure the mapping studies cover the expected modes of operation of the HVAC system in delivering and maintaining a stable internal operating environment. Consequently, monitoring the external temperature is not required during the mapping studies.

To clarify the current approach, the master protocol IOQ-ECA-001 will be updated, by 2025-03-31, to describe this risk-based approach and to provide guidance on the timeframe during which mapping studies with specific HVAC mode of operation can be considered appropriate, e.g. November to March for heating mode operation.

c) **For the temperature mapping of the Distribution warehouse (R000031466), extreme seasonal variation may not have been considered, as the studies were conducted in March and September, without a documented rationale.**

A risk-based approach to the mapping strategy for the product storage areas is built on the fact that the Brampton facility's heating, ventilation and air conditioning (HVAC) system were designed and commissioned, with considerations of the ambient environmental conditions and internal operational requirements.. The mapping studies provide documented evidence of the HVAC system's performance in responding to ambient environmental changes and internal operational demands, in addition to the design and commissioning process. These studies also help identify the optimal locations for monitoring sensors. The key to this risk-based mapping strategy is to ensure the studies cover the mode of operations expected of the HVAC system in delivering and maintaining a stable internal operating environment.

To improve on the current approach, the master protocol IOQ-ECA-001 will be updated, by 2025-03-31, to clarify this risk-based approach and to provide guidance on the

timeframe during which mapping studies with specific HVAC mode of operations can be considered appropriate e.g. November to March for heating mode operations.

d) **IOQ-WRF-001-56-2013-199 for the Distribution walk-in refrigerator (R000021228), did not have a written rationale available to justify the placement of the current temperature monitors in their current locations.**

In section 13.0 of protocol IOQ-WRF-001-56-2013-199 version 7.0 the following instructions are provided:

- *At the completion of the temperature mapping, a review must be made of all measurement points to determine overall acceptability of the mapping results and indication of warm/cold locations based on minimum, maximum instantaneous readings along with average results.*
- *Create temperature graphs from the measurement point data that can be used to assist the review process and determine overall acceptability.*
- *Review the probe placement diagram and mapping data to identify the worst-case locations. Indicate the warm/cold probe location directly on the diagram and ensure the sensors for the system of record have been placed in the appropriate volume of fluid and in the worst-case temperature locations.*

The worst-case locations were identified and indicated on a diagram attached to the protocol as reference document number RDN-006. The placement of the temperature monitors, which have remained unchanged, reflects the work-case locations identified on the diagram.

2. **1) Some the firm's Pest Monitoring Inspection Reports (FORM 1000104164) were deficient due to being incomplete or lacking sufficient detail about the events that had occurred. For example:**
   a) **The "Final Review" section of the forms was not completed. For example, it was incomplete for July 05, 2024, August 01, 2024 and August 16, 2024 reports.**
   b) **Follow-up actions from the firm's comments on the forms were not documented. For example, the September 04, 2024 form had a comment recommending the replacement of a door sweep and the June 07, 2024 form had a comment stating that a spray was needed to eliminate carpenter bees on the perimeter fence; however, it was not recorded on the form whether the actions were completed.**

Combined response for a) and b):

DEV-24-011664 was initiated 2024-11-26.

Brampton facilities staff will be retrained to WI-00659 Pest Control with special attention to section 3 step 4 which requires:

a) Final Review section to be completed prior to filing, and,

b) documentation of completion of recommended actions.

This will be completed by staff by no later than 2024-12-20.

In addition, all Pest Control Inspection Report forms since 2024-01-01 will be reviewed to ensure Final Review sections were completed and any follow-up actions were completed and documented correctly. This review will be completed by 2024-12-20.

3. **2) The records documenting the annual cleaning and defrosting of the walk-in freezers were insufficient to ensure product traceability and proper equipment functionality. Specifically:**

   a) **Products removed from the freezer and placed in a different temporary freezer were not recorded. The location to which the products were moved was also not recorded.**

   The original storage locations for all wholesaled drug products are recorded electronically in SAP.

   Prior to the annual cleaning and defrosting of walk-in freezers completed by facilities, all products are removed by distribution personnel and placed into known validated alternate location(s) as per WI-00673 viewLinc Operation. The product names are documented on form F800125 viewLinc Alternate Storage Location. This work instruction also describes the management of temperature alarms for the duration of the cleaning and maintenance work. Upon completion of cleaning and maintenance work, the viewLinc temperature monitoring alarms are re-enabled, and product is returned to its original storage location.

   The batch/lot number of products moved out of, or returned to the original location, is not recorded, as unless shipped to customers, the product would be in either the original or alternate locations, under proper storage conditions.

   In the event a storage location (original or alternate) would be compromised an alarm would occur and product would be moved to the alternate storage location identified on F800125 viewLinc Alternate Storage Location and WI-00518 Deviation / Minor Quality Event Management process would be initiated. If product quality was impacted the entire batch identified would be recalled.

   In the event a storage location (original or alternate) would be compromised over a period of time, WI-00518 Deviation / Minor Quality Event Management process would be initiated, and investigation would occur. ViewLinc records and equipment cleaning and maintenance records for both the original and the identified alternate storage locations would be pulled and assessed to determine if any product had been stored in the storage location during the time the unit had been compromised. The product stored in the physical storage location can be identified because the name of the product is

documented on F800125 viewLinc Alternate Storage Location and the product and batch would be identified via SAP, the complete batch would be identified, quarantined and recalled.

In the event of a manufacturer's recall, all product can be identified and tracked via SAP and F800125 viewLinc Alternate Storage Location.

Form F801690 Annual Cleaning of Walk-In Cooler/Freezer Units will be assessed for improvement and revised to include where the product was relocated to as identified on F800125 viewLinc Alternate Storage Location. In addition, a reference to F800832 Facilities Risk Assessment for Walk-In Refrigeration Maintenance and viewLinc will be added to connect the records and processes. This will be completed by 2025-03-31.

b) **The records did not clearly indicate the duration of the work, how long the unit was not operating under its typical conditions and how long the product was stored in the temporary location.**

The total duration of work and how long the unit was not operating during cleaning was not noted on F800832 Facilities Risk Assessment for Walk-In Refrigeration Maintenance, however the duration can be determined by reviewing the viewLinc records for the storage location. The alarm monitoring in viewLinc would have been silenced and then returned to normal upon completion of the work. The estimated duration of work and start time are captured on F800832 Facilities Risk Assessment for Walk-In Refrigeration maintenance.

Form F801690 Annual Cleaning of Walk-In Cooler/Freezer Units will be assessed for improvement and revised to include at a minimum the time the product was removed from the unit, and that the unit is empty prior to disabling the viewLinc monitoring and conducting the maintenance activity. A reference to F800832 Facilities Risk Assessment for Walk-In Refrigeration Maintenance and viewLinc will be added to connect the records and processes. This will be completed by 2025-03-31.

c) **The functional tests to be completed after the walk-in freezer was restored to functionality were not specified in any work instructions.**

WI-00669 Refrigeration Inspection and Maintenance describes the procedure for the inspection and maintenance of walk-in refrigeration equipment that are integrated into Canadian Blood Services' sites. The unit's functional tests and return to operational use is captured in the Service Providers Note. ViewLinc alarm history provides the return to operational use. As well, WI-00534 RAM Management Equipment by Owner describes how equipment owners/operators proceed with preventative/ demand/ and validation work and describes the use of L800063 Out of Service Label. Facilities only will remove the Out of Service Label when the unit has stabilized, and the alarms are turned back

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on. The equipment owner would not complete F800832 Facilities Risk Assessment until the Out of Service Label was removed, and alarms are reestablished.

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,

David Howe
A/Vice-President
Quality & Regulatory Affairs