Canadian Blood Services
BLOOD PLASMA STEM CELLS ORGANS & TISSUES

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2025-01-16
CBS Control #: 6853
Drug Inspection Program File #: 85002-100390DDD
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: Further to the Responses to Health Canada Inspection of Wholesale Activities at Brampton Operations 2024-10-30 to 2024-10-31

The following are the actions taken by Canadian Blood Services in response to the Health Canada Follow-up letter dated 2025-01-02, requesting additional information to the responses to the Health Canada Exit Notice dated 2024-11-14.

1.3 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.

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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.

Health Canada Follow-up letter dated 2025-01-02:

1.3 a) – c) The rationale for limiting the mapping to just 24 hours did not provide adequate justification to support the long-term stability of temperature distribution within the storage area. Furthermore, the justifications did not outline how external temperatures and extreme seasonal variations could affect the HVAC system's performance and, in turn, influence the overall temperature distribution within the space.

Canadian Blood Services Follow-up Response:

The 24-hour mapping covers a full operational day of the area. It captures daytime temperatures which are typically warmer and overnight temperatures which typically lower than the day. A 24-hour mapping would capture the operation and temperature distribution throughout the day. The mapping is conducted during the colder months when the HVAC system is in heating mode and during the warmer months when the HVAC system is in cooling mode as dictated in the protocol.

For the Distribution area protocol IOQ-ECA-001-2024-03-11-164343:

- *Heating mode mapping occurred between 2024-03-23 8:45 am to 2024-03-24 8:45 am.*
- *From review of the historical temperature data from Environment Canada (Pearson International airport weather station operated by NAVCAN) the temperatures on those days ranged between -7.5°C and 1.6°C. The temperatures are indicative of winter. Refer to attachment 1 for the historical temperature data.*
- *The cooling mode mapping occurred between 2024-09-10 1:00 pm to 2024-09-11 1:00 pm.*
- *From review of the historical temperature data from Environment Canada (Pearson International airport weather station operated by NAVCAN) the temperatures on those days ranged between 13°C and 23°C. Refer to attachment 1 for the historical temperature data.*
- *The HVAC operation and mapping date/time were indicated on the executed protocol at the time of both mappings.*

For the Logistics warehouse protocol IOQ-ECA-001-2023-07-17-103328:

- *Cooling mode mapping occurred between 2023-08-02 10:30 am to 2023-08-03 11:30 am. The HVAC operation and date and time were indicated on the executed protocol.*
- *From review of the historical temperature data from Environment Canada (Pearson International airport weather station operated by NAVCAN) the temperatures on those*

days ranged between 18.9°C and 24.5°C. The temperatures are indicative of summer. Refer to attachment 2 for the historical temperature data.

- *The heating mode mapping occurred between 2024-02-28 8:30 amp to 2024-02-29 9:30 am.*
- *From review of the historical temperature data from Environment Canada (Pearson International airport weather station operated by NAVCAN) the temperatures on those days ranged between -6.6°C and 16°C. Refer to attachment 2 for the historical temperature data.*
- *HVAC operation and mapping date/time were indicated on the executed protocol at the time of both mappings.*

Temperature distribution over the 24-hour mapping period is demonstrated with multiple probes placed within the area recording temperatures at a frequency of 5 minutes. Based on the 24-hour temperature mapping data, a review is performed and the worst case locations are identified based on minimum, maximum and average temperatures recording during the study.

The continous monitoring probes of both the primary (Vaisala viewLinc system) and secondary system (Digital Touchsreen recorder) are installed in those worst-case locations determined during the mapping. The area is then continuously monitored in those locations with both high and low temperature alarms configured within the acceptable temperature requirement. Any issues with the performance of the environmental area would be recorded through the continous monitoring at those worst-case locations. Monitoring these areas throughout the year provides reassurance that the area is maintaining the required temperature throughout all seasons and provide active response during unseasonable conditions.

The primary and secondary monitoring systems are actively maintained with an annual preventive maintenance procedure which includes verification probe temperature accuracy.

The Distribution drug product storage area is a designated area within the wider Distribution room that was mapped and used to store drug products. This area was initially mapped as it was a newly designated area for drug product storage to streamline the picking process and consolidating the storage within Distribution as part of Change request StCR-23-000630. The initial mapping in March 2024 was completed prior to use of the space for drug product storage and was the earliest available time for the mapping to occur. The area has an acceptable temperature range to 15 to 25°C with the high temperature alarm set to 24.5°C and the low temperature alarm set to 15.5°C. Review of the primary continous monitoring trend data since the area was initially mapped in 2024-03-23 to present day shows the area is in control. See table 1.

Table 1:

Distribution drug product storage area viewLinc Trend Data Summary (from 2024-03-23 to 2025-01-06)					
#	**Location**	**Average (°C)**	**Minimum (°C)**	**Maximum (°C)**	**Standard Deviation**
1	BRM1514 Room 1155 Temperature 1	22.05	18.12	23.62	0.48
2	BRM1514 Room 1155 Temperature 2	20.90	18.27	22.57	0.42

The trend data demonstrates that the area has maintained temperature with acceptable temperature range of 15 to 25°C without any temperature excursions noted for the area. Refer to attachment 3 for the primary system trend date for the Distribution drug product storage area.

The Logistics drug product warehouse has an acceptable temperature range of 15° to 25°C with the high temperature alarm set to 24.0°C and the low temperature alarm set to 16.0°C. There are a total of 4 continuous monitoring locations in the warehouse. Review of the primary continuous monitoring trend data since the warehouse was last mapped in 2023-08-23 to present day shows the area is in control. See table 2.

Table 2:

Logistics drug product warehouse viewLinc Trend Data Summary (from 2023-08-23 to 2025-01-06)					
#	**Location**	**Average (°C)**	**Minimum (°C)**	**Maximum (°C)**	**Standard Deviation**
1	BRM3416 Bulk Storage Room 1063 Temperature 1	20.76	18.64	23.39	0.74
2	BRM3416 Bulk Storage Room 1063 Temperature 1	19.81	16.84	22.54	0.88
3	BRM3416 Picking Shelves Room 1063 Temperature 1	21.46	19.21	24.07	0.69
4	BRM3416 Picking Shelves Room 1063 Temperature 2	20.05	17.29	23.03	0.83

The trend data demonstrates that the Logistics drug product warehouse has maintained temperature within the acceptable temperature range of 15 to 25°C without any temperature excursions noted for the area. Refer to attachment 4 for the primary system trend date for the Logistics drug product warehouse.

In summary, the use of 24-hour mapping to characterize the temperature profile of the storage areas have been demonstrated to provide an overall temperature distribution of the storage areas, effective in terms of identifying worst case locations and ensuring that the spaces remain in control during continuous monitoring.

Protocol IOQ-ECA-001 has been in use by Canadian Blood Services since 2011-08-24. However, given the concerns currently identified for mapping duration, going forward protocol IOQ-ECA-001 will be revised to conduct a mapping for 7 consecutive days. Additionally, the protocol will have an assessment of the ambient conditions during the mapping to provide re-assurance that the mapping aligned with cooling mode during the summer months and the heating mode during the winter months.

The revised protocol will be implemented by 2025-03-31.

2.2) 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 the 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 products 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.

Health Canada Follow-up letter dated 2025-01-02:

For traceability purposes, it is expected that the batch/lot numbers would be recorded as part of this process.

Canadian Blood Services Follow-up Response:

To provide traceability an SAP inventory report for the storage type identifying the batch/lot and Plasma Protein and Related Product will be run prior to and post the cleaning/ maintenance event and retained. WI-00616 Storage Location requirements for Plasma Protein and Related Products will be updated to include the SAP Inventory report by 2025-07-07.

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

Health Canada Follow-up letter dated 2025-01-02:

Please clarify if the instructions for functional tests, as referenced in the "Service Providers Note" are described in WI-00699 or any other procedure. Please also clarify where the "Service Providers Note" is documented, where the review of this note is documented, and who is responsible for the review.

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<u>Canadian Blood Services Follow-up Response</u>:

Functional tests, which are part of maintenance activities are performed following refrigerator/freezer cleaning activities to provide assurance that the equipment is running within its validated state prior to the reintroduction of drug products.

Canadian Blood Services issues a work order when quarterly or demand maintenance is required. Cleaning activities are combined with other maintenance such as unit defrosting, component repair etc. to minimize downtime. Canadian Blood Services has Work Plan Templates, which are predetermined, approved and controlled, for equipment that are followed by the Service Provider when completing maintenance. The Service Provider completes their documentation of the completed Work Plan Template on their Service Provider Notes. Work Plan Templates can be obtained from the RAM system. None of the Work Plan Templates have instructions to change parameters.

WI-00564 RAM Management of Equipment by Owners identifies when a change request and a validation assessment is required.

The Work Instructions for reviewing the functional test performed, which includes both the post maintenance monitoring to ensure the equipment functions as expected, and ViewLinc information to determine if the equipment is stable prior to return to use, as well as the Service Provider Notes, are in WI-00669 Refrigeration Inspection and Maintenance. Throughout WI-00669 the user is refered to WI-00534 RAM Management of Equipment by Owners for instructions regarding Service Provider Notes. WI-00534 section 2, step 2, outlines the review of the Service Provider Notes by Equipment Owners. F800832 Facilities Risk Assessment for Walk-in Refrigeration Maintenance Section B, Post Work Inspection, is completed after all work has been completed and reviewed prior to uploading the records into RAM as per WI-00534. Section B captures the signature of the reviewers (Equipment Owners). A unit is not placed back into service until all work and functional testing is completed and reviewed.

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

David Howe (2025-01-16 16:32 EST)

David Howe
A/Vice-President
Quality & Regulatory Affairs