Canadian Blood Services BLOOD PLASMA STEM CELLS ORGANS & TISSUES

1800 Alta Vista Drive
Ottawa ON K1G 4J5

blood.ca

2025-01-10
CBS Control #: CBS6851
Drug Inspection Program File #: 84907-100390K
REF: H-2425-OTT-W

Craig Turk
Regional Regulatory Compliance & Enforcement Officer
GMP Inspection Central
Regulatory Operations and Enforcement Branch (ROEB)
Health Canada
Government of Canada

Dear Craig:

Re: Further to the Responses to Health Canada Inspection of Wholesale Activities at Ottawa Operations on 2024-10-09

The following are the actions taken by Canadian Blood Services in response to the Health Canada Follow-up letter dated 2024-12-18, requesting additional information to the responses to the Health Canada Exit Notice dated 2024-10-24.

C.02.015 Quality Control Department

1.3 a) Deficiencies were noted with regards to the qualification of the double-door refrigerator (R000024415) in 2020. For example:
i) The bulk of the qualification took place at the Canadian Blood Services Ottawa-Head Office location, including that of temperature mapping, with only alarm tests and setpoint temperature checks performed at Canadian Blood Services Ottawa Operations.

The Installation and Operational Qualification (IOQ) protocol is structured to allow for the initial set-up and mapping to be performed off-site at an interim Canadian Blood Services location different from the final installation site. The protocol was designed to provide a turnkey approach for operational staff at local sites where the initial set-up and mapping was completed at the Head Office Alta Vista site providing reassurance the unit was operational prior to use. Activities for the IOQ at the interim location include verifying on-board parameters such as operating setpoint, on-board high and low alarm settings and temperature mapping of the internal chamber. After interim approval of the results, the refrigerator is relocated and installed at the final installation location.

The final section of the IOQ was completed upon relocation and it was verified that the unit was installed at the final installation location as per install requirements. Verification also included confirming that the setpoint was set to the same value that was verified and mapped in the interim location. Additionally, the operation of the unit was verified by maintaining the temperature requirements through monitoring for a period of 12 hours including the on-off cycles of the compressor through the operating setpoint of 4 degrees

Celsius using the installed on-going primary and secondary monitoring points.

The mapping performed at Alta Vista site is representative of the final location for the following reasons:
- The setpoint (4 degrees Celsius) which the unit was mapped to remained unchanged at the final location.
- There were no changes or modifications to the refrigeration system components at the final location.
- There were no changes to any other features including the door, door seal and to the internal arrangement of shelving of the unit.
- At the final installation location, the verifications performed confirmed that the unit was installed in a suitable location and that the operation of the unit had not been affected or altered after the move and that the unit was maintaining the required temperature range. In the event the unit was not maintaining temperature during the relocation verification section then a deficiency in the protocol would be initiated and if the unit would require a setpoint adjustment as a corrective action then re-mapping of the unit would then be done as per the IOQ at the relocated site.

Based on the above summary, there is no risk to the current operation of the refrigerator not meeting temperature requirements. Protocol IOQ-FRG-003 will be updated by 2025-02-07 to provide the rationale for the varying locations of the operational and installation qualification activities.

Health Canada Follow-up letter dated 2024-12-18:

The written justification for performing the bulk of the qualification activities at the Ottawa - Head Office location as opposed its final installation location, does not adequately demonstrate or provide assurance of uniform temperature distribution or its performance at the final location. Environmental factors at the new location, such as room temperature, ventilation, and vibrations during transport, which can impact temperature uniformity and performance, were not adequately evaluated.

Canadian Blood Services Follow-up Response:

The mapping and checks performed at the Ottawa – Head Office site can be considered representative of the new location for the following reasons:

- *The Helmer Horizon Series HBR256-GX Refrigerator is designed to operate under the following environmental conditions:*
    - *Indoor use only at ambient temperature range: 15 to 32°C, and*
    - *Ambient temperature range: 15 to 32°C.*

The mapping performed at the Ottawa – Head Office site was performed indoor in an environmentally controlled area where the temperature is maintained at approximately 20°C. The temperature at the relocated site, Concourse Gate, room L117 is set to be maintained at a temperature of approximately 22°C. Both areas are set to be maintained well within the designed operating range specified by the vendor.

- *Following completion of the initial IOQ sections at the Head Office site, the units are packed back into the original crates/boxes prior to relocation. There are no modifications applied to the unit and are shipped whole.*
- *Any risk exposed during transportation is mitigated by verifying the unit is maintaining the temperature afterwards for 12 hours along with an inspection. The critical components that potentially impact the performance of the refrigerator are typically the controller, circulating fans and the refrigeration system. If these critical components, were not functioning properly, it would become apparent during the 12-hour monitoring using both the primary and secondary monitoring points.*

As such, Canadian Blood Services believes its practice of requalification following an initial off-site qualification provides adequate assurance that the refrigerator has been qualified appropriately.

To address concerns regarding temperature uniformity, Canadian Blood Services will perform a full load chamber mapping of refrigerator Asset ID R000024415 at its current installed location. The data obtained with this full load chamber mapping will also be used to compare to the original empty chamber mapping performed at Head Office. The analysis will be used to provide additional information to support our original assertion regarding empty chamber mapping performed off-site being representative of the final installation location.

Mapping and data review for refrigerator Asset ID R000024415 to be completed by 2025-05-30.

b) There was no rationale in the protocol (IOQ-FRG-003-2020-10-15-161858) for only performing the qualification on the empty chamber and not that of a full chamber. There was also no rationale for why the temperature mapping only occurred over a twelve hour period.

The rationale for empty chamber temperature mapping is that there was no meaningful difference observed between empty and loaded chamber temperature mapping. This conclusion was the result of a study performed titled Helmer Horizon Series Blood Bank Refrigerator Development Summary Report SR-IOQ-FRG-002 version 1.0, 2019-06-17 which tested both empty and loaded chambers. The study validated that the empty chamber test scenario is suitable to demonstrate acceptable refrigerator performance. Mapping data obtained with probes in air and empty is worst case scenario as there is no thermal mass to stabilize the chamber. The 12 hours of temperature mapping captures the on-off cycles of the compressor through the operating setpoint of 4 degrees Celsius and is suitable to demonstrate acceptable refrigerator performance for a sustained period without going into alarm. Temperature data obtained in IOQ-FRG-003-2020-10-15-161858 successfully demonstrated that the unit was able to maintain temperature within the required range.

Protocol IOQ-FRG-003 will be updated by 2025-02-07 to provide rationale/clarification on mapping strategy.

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Health Canada Follow-up letter dated 2024-12-18:

While mapping an empty fridge is useful for understanding the fridge's baseline cooling ability and assessing its performance under minimal thermal load, it does not provide sufficient data for real-world scenarios where the fridge operates with a full or partially full load at its final location.

Canadian Blood Services Follow-up Response:

For refrigerator Asset ID R000024415, Canadian Blood Services will perform a full load chamber mapping at its current installed location.

The data obtained with this full load chamber mapping will also be used to compare to the original empty chamber mapping. The analysis will be used to provide additional information to support our original assertion regarding empty chamber mapping being the worst-case scenario.

Mapping and data review for refrigerator Asset ID R000024415 to be completed by 2025-05-30.

For asset R000024415, the risk to product quality is minimal as the chamber temperature is continuously monitored and the unit follows a regular preventive maintenance/calibration schedule; additionally, the temperature requirement of the unit, 2 to 6°C, is within the drug product storage requirements of 2 to 8°C.

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 (2025-01-10 12:12 EST)

Mr. David Howe
A/Vice-President
Quality & Regulatory Affairs