Canadian Blood Services
BLOOD PLASMA STEM CELLS ORGANS & TISSUES

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2024-11-20
CBS Control #: CBS6851
HPFB File #: C1892-100390
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: Responses to Health Canada Inspection of Wholesale Activities at Ottawa Operations 2024-10-09

The following are the actions undertaken by Canadian Blood Services in response to the observations contained in the Health Canada Exit Notice dated 2024-10-24.

C.02.015 Quality Control Department

1. **The temperature and/or humidity control was inadequate. The calibration, inspection, and/or qualification of the equipment, including computerized systems, was inadequate.**
a) The placement of the temperature monitor in the ambient storage area was not justified, for example, through worst-case locations established from temperature mapping studies.

The Distribution room has been continuously monitored for temperature using the central continuous monitoring system as per work instruction WI-00673 "ViewLinc Operation" with the probes in the area having the high and low alarm setpoints at 23.5°C and 20.5°C, respectively. Site representatives reviewed the floor plan and verified that there are currently three continuous monitoring probes monitoring the area. The three probes are currently located in areas that can potentially capture temperature excursions. One probe is in the immediate location of where the PPRP is being stored and close by a sliding door to the outside hallway. A second probe is situated across the room and located near an opposite door that leads to the hallway. The final probe is in the quarantine room and is located near freezers which would be potentially exposed to heat out put of the equipment.

Change Request StCR-24-000609 was initiated on 2024-10-30 to include the scope of Distribution rooms to be mapped and the installation of additional on-going monitoring points, as applicable.

Canadian Blood Services will perform temperature mapping as per current protocol IOQ-ECA-001 for the defined area of the Distribution room. The executed protocol will include seasonal mappings in both heating and cooling modes of the defined area and will include a rationale of the final placement of the on-going temperature monitoring probes based on the mapping data. The planned completion date including review of the executed protocol is 2025-10-31.

b) There was no requirement to perform re-qualification activities for the drug product storage areas, nor was there a requirement to evaluate existing qualifications at an appropriate 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 2003 and 2004 for the refrigerators (R000021268, R000021267, R21269) and freezers (R000021275, R000021276), 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 by 2025-06-01.

c) 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.

ii) 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.

iii) The results from the temperature mapping that was performed were not used to justify worst-case locations to support the placement of the temperature monitors. Specifically, the monitoring locations were pre-established prior to the start of the mapping study, with the results from those locations compared to that of the temporary locations set-up during the study.

Canadian Blood Services' practice for off-the-shelf upright refrigerators/freezers is to install the primary and secondary continuous monitoring probes next to the pre-installed vendor bracket where the on-board probe is installed. This area provides a location that does not require any modification of the unit and does not interfere with any of the shelving or potential damage to the monitoring probe. There is no risk to the operation of the unit or storage of product in the unit for the following reasons:
- Pre-established area designated by the vendor for the refrigerator as per user manual (Refrigerator Instructions for Use i.Series® / Horizon Series™ Upright - Undercounter - Pass-Thru, 360414/D) and does not interfere with shelving or require any modification of an off-the-shelf refrigerator.
- Bracket is installed in the middle of the topmost shelf. Mapping data obtained in air and empty is worst case scenario as there is no thermal mass to stabilize the chamber. Data demonstrated that the top shelf is the worst-case warm location with averages between 4.16 to 4.38 degrees Celsius and maximum readings between 4.85 to 4.92 degrees Celsius.
- The unit has an internal volume of less than 2.0 cubic meters and one monitoring probe can ensure the unit is maintaining the required temperature range.

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

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,

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