Canadian Blood Services
BLOOD PLASMA STEM CELLS ORGANS & TISSUES

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Canada

2020-01-14
CBS Control #: CBS6367
HPFB File #: C1892-100390
REF: H-1920-BRM

Ms. Urbee Shome-Pal
Compliance Specialist
Regulatory Operations and Regions Branch
Health Canada
180 Queen Street West, 10th Floor
Toronto, ON M5V 3L7

Dear Ms. Shome-Pal:

Re: Further to the Responses to the Health Canada Inspection of the Licensed Activities at Brampton Operations from 2019-04-29 to 2019-05-03 and from 2019-05-28 to 2019-05-31

The following are the actions taken by Canadian Blood Services in response to the Health Canada letter dated 2019-11-29, requesting additional information for observations to the Exit Notice for Health Canada's Inspection of licensed activities at Brampton Operations.

Section 94 - Quality Management System

1. **The system for identifying and investigating errors and accidents was not sufficient. For example:**
   a) There was no documented process in place to consider all factors (i.e. processes, equipment, supplies, personnel, etc.) that could have contributed to the errors or accidents documented as Quality Event Reports (QERs). Furthermore, there is a lack of instructions around how to conduct risk assessments consistently and there is no requirement to assess if a CAPA would be required if a QER is given a low risk assessment. Specifically,
      (i) For QER 56-18-136411, Hospital received four units that were damaged. One leaked upon thawing. Risk assessment was indicated as low.
      (ii) For QER 56-18-122125, Hospital reported receiving a shipment of 13 RBC units in which one bag leaked and contaminated the rest of the bags with red cells. Units were discarded. Risk assessment was indicated as low.
      (iii) For QER 56-18-117249; Hospital reported 2 RBC units with suspected hemolysis. Hemolysis confirmed. The units were returned and discarded. Risk assessment was indicated as low.
   For all of the above examples and for all the QERs reviewed, if the risk was assessed as low, there was no root cause analysis conducted or an assessment of whether any further actions or CAPA would be required for the incidents.

   Canadian Blood Services Response:

   Instructions on how to conduct risk assessments are provided in SOP 08 812 "Quality Event Management – Quality Assurance Assessment and Review" and in section 9 of the quality event

report itself. The risk assessment performed by quality assurance includes an evaluation of the probability of occurrence, detectability, and severity of impact of product and patient/donor. The outcome of the risk assessment is documented on the quality event report.

Every quality event classified as medium or high risk results in the initiation of a CAPA. The CAPA, managed per SOP 08 175 "CAPA Management", will investigate the event, which includes processes, equipment, supplies, personnel, etc., as required by the use of tools such as 5 Whys, MEEpP or fish bone analysis.

Based upon the review of the quality event reports, it was found all risk assessments were completed appropriately and correctly classified as "Low" risk.

By their definition, low risk quality events are those which present no or minimal risk to patient, donors or staff based on worst case scenario. At this time, Canadian Blood Services has chosen to focus its corrective and preventive action resources on events that are more potentially impactful (i.e. medium and high risk). At a later point in time (to be determined), Canadian Blood Services will implement a strategy for the management of low risk quality events.

Health Canada Follow-up letter dated 2019-10-01:

The CBS response does not address the portion of this observation where it speaks to the lack of a documented process to consider all factors that could have led to an error or accident. It was stated during the September 19, 2019 meeting with CBS and HC that a new process for electronic documentation of QERs will be implemented in Oct 2019. Please confirm whether or not this new process will address this gap and how it will do so. The response also indicates that CBS will implement a strategy for low risk quality events at a later point in time. Health Canada would like a firmer commitment by CBS on this matter and is therefore requesting a timeline for the implementation of this strategy. Additionally, please also provide a copy of SOP 08 812 highlighting the sections that provide instructions on how to conduct a risk assessment.

Canadian Blood Services Response:

The automated Quality Event Management process will be implemented on 2019-10-28, at which time the initiator will be prompted to enter specific information related to the description of the quality event. The mandatory information will include: a general description; the location or department where the event was discovered; how the event was discovered; the specific requirement or result that was not met; and the procedure associated with the process. This will further provide information to consider all factors that could have led to an error or accident and enable thorough investigations and accurate risk assessments to be completed.
Previous reviews of quality event reports randomly sampled were performed on two separate occasions, and 157 reports were reviewed each time. Each review has shown that in all cases product containment and disposition and the risk assessment levels were appropriate and CAPAs were correctly initiated where required.

As mentioned previously, we have chosen to focus our limited resources on corrective and preventive action on events that are more potentially impactful (i.e. medium and high risk). Other than to share our intent to conduct by 2020-01-31 a review of low risk QER that are reportable, nothing more definitive has yet been determined with regard to a strategy for the management of low risk quality events through the CAPA process. We fully intend to define such a strategy but as we have to balance the need to advance with our limited resources more pressing and higher priority corporate initiatives, this has yet to be determined.

Please refer to Section 2 of the attached SOP 08 812, Quality Event Management – Quality Assurance Assessment and Review version 6 for instructions on performing a risk assessment and Section 9 of the attached Quality Event Report.

Health Canada Follow-up letter dated 2019-11-29:

Has any thought been given to expanding the scope of the current parameters that lead to a risk assessment rating? The clarifications, corrective actions and additional information provided will be monitored and verified at subsequent CBS inspections.

Canadian Blood Services Response:

Can you clarity what is meant by "current parameters that lead to a risk assessment rating"? Is the suggestion to consider parameters other than probability of occurrence, detectability, and severity of impact? If that is the case, there is no plan to extend the risk assessment beyond those parameters as this is considered best practices.

2. **The system that identifies, documents and tracks all critical equipment or supplies was not sufficient. For example:**
   b)
   c) For April 9, 2019 production records, the equipment IDs for some equipment were not tracked. For example, Macopresses (Extractors), GSE Scales and Sealers. This would also apply to all production records after the implementation of the new production process flow and related production batch forms.

Canadian Blood Services is able to identify GSE Scales, Macopress (Extractors) and Compodocks utilized each day through the daily maintenance records. Sealers are not documented on the production records as tubing seals are inspected as they are made. In the event that a piece equipment is taken out of service, an "out of service" tag is attached to prevent further use of the equipment. In addition, a Quality Event is initiated and, as part of the process, an assessment of the impact on components produced is conducted.

Health Canada Follow-up letter dated 2019-10-01:

Please confirm whether or not compodocks are being tracked on production records. Additionally, would the centrifuges, which are being tracked on production records also have associated daily maintenance records? If so, then why are some critical equipment being tracked and not others? Please provide a rationale.

Canadian Blood Services Response:

Compodocks are being tracked on the production records. The centrifuges do not have a daily maintenance record as the maintenance is performed weekly. The decision to track specific equipment on the production records and not others is based on the potential impact to the products being produced.

Health Canada Follow-up letter dated 2019-11-29:

The response and rationale provided for this observation have been discussed internally and with BGTD and are not deemed satisfactory with respect to not tracking critical equipment, such as Macopresses (Extractors) on production records. It is unclear what is meant by, "The decision to track specific equipment on the production records is based on the potential impact to the products being produced." Please further elaborate upon this statement.

Furthermore, the Blood Guidance Document states the following:
• Section 117 - p. 168 - " ... records must be maintained concurrently with the performance of each significant step in the processing ... " "In addition, for processing and transformation records, the lot number of critical supplies and the identity of the critical equipment associated with the activities must be part of the records."

• Section 118, p. 169 - "Each unit of blood has a donation code that uniquely identifies it. The donation code enables the traceability of a given unit of blood and any associated information about that unit of blood throughout any processing or transformation steps and the chain of distribution. The donation code must be a part of all records related to the processing, distribution, transformation and transfusion of the unit of blood."

In light of this, we are requesting corrective actions on your end to ensure that these critical equipment are tracked on production records and your processes are updated to reflect this change. Please provide an updated corrective action plan and associated timelines.

Canadian Blood Services Response:

The interpretation given in the Guidance document for section 117 is a broadening of the actual regulatory requirements of the Blood Regulations as this section talks strictly to having accurate, complete, legible, indelible and readily retrievable records. Nevertheless, we do have concurrent records for each significant step in processing, albeit some of them are electronic records not paper records. Those are production records, batch records, pooled platelet records, maintenance records and electronic records from the Macopresses' data management system.

In addition, the identity of the critical equipment associated with each activity are part of the records, either electronic records or paper records:

- *Macopresses while not documented on the production records are connected to the data management system which collects information about each extraction. This includes the donation number, the extraction program, the extraction time, the Macopress ID, and the date and time of the extraction.*
- *All centrifuge IDs are documented on batch records for components being processed.*
- *All 5 sterile dockers (Compodocks) used for the manufacturing of each platelet are documented on the associated pooled platelet record which includes the pooled platelet number.*
- *Production scales are documented on the daily Component Scale Verification Log*
- *Sealers used in each production site are documented on maintenance records.*

The donation number label is part of the above records except for the production scales and the sealers.

The approach or the records by which the identity of each equipment is documented, and the donation number label captured, is based on the likelihood of potential issues with each type of equipment and the detectability of such issues during our in-process controls. We recognize and accept the risk that based on the chosen approach a quality event may result in the quarantine, re-work, recall or discard of a greater number of units than those directly impacted by the issue. However, this does not impact our ability to take appropriate actions regarding affected units and to identify equipment used in production during a specific time period. As such our interpretation is that we are compliant with the Blood Regulations with regard to the traceability of both equipment used in manufacturing and the identity of products produced using such equipment during a specified time period. We do not intend to take any corrective actions at this time.

If the RORB and/or BGTD have further questions on this issue, we propose to have a face-to-face meeting to further discuss.

For any other information, please do not hesitate to contact the undersigned. **Please refer to the above control number in all correspondence.**

Sincerely,

Christian Choquet

Dr. Christian Choquet
Vice-President
Quality & Regulatory Affair
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cc: Shelley Smyth
A/Supervisor – Blood Tissues, Organs and Xenografts
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