Canadian Blood Services BLOOD PLASMA STEM CELLS ORGANS & TISSUES

1800 Alta Vista Drive
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2021-12-09
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Sejal Shah
Regional Regulatory Compliance and Enforcement Officer
Regulatory Operations and Enforcement Branch (ROEB)
Health Canada
GMP Inspection, Central
2301 Midland Avenue
Toronto, Ontario
M1P 4R7

Dear Sejal:

Re: Responses to Health Canada Inspection of Wholesale Activities
at Dartmouth Operations
2021-10-18 to 2021-10-20

The following are the actions undertaken by Canadian Blood Services in response to the observations contained in the Health Canada Exit Notice dated 2021-11-10.

C.02.004 - Premises

1. **There was a lack of clearly marked quarantine areas for the storage of quarantine and returned products according to their labelled storage requirements. For example:**
   a. There was no designated or defined storage area for returned product awaiting final disposition for resale or destruction.
   b. Contrary to procedure WI 12 022- Inspection of Plasma Protein Products Received at a Site, an orange label was applied to all quarantined boxes prior to their storage in either the room temperature storage area, fridge or freezer, which was not outlined in the procedure. Room temperature storage and freezer storage areas did not have identified areas for quarantine materials.
   c. Large size products requiring refrigerated storage or products requiring freezer quarantine locations were placed the 'WIP' (Work in Progress) walk-in units which were also used as back-up or overflow storage units. These WIP walk-in units did not contain specific labelled storage areas for the various types of product.
   d. The room temperature storage area contained a small metal cage for quarantined products, however the cage was not routinely utilized.

   Associated procedures will be assessed and revised by 2022-06-27 to include requirements for identification of quarantine locations including physical markings as well as segregation requirements of returns or other unsuitable or potentially unsuitable products.

   In the interim, staff will be reminded of the appropriate placement of quarantine and returned products. This will be completed by 2021-12-23.

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2. **The controls for product storage, receipt and shipment were inadequate to prevent potential mix-ups between products. For example:**

   a. Storage racks for room temperature plasma protein products were not always labelled with the product name, strength and size including:

   i. Albumin 5% Solution

   ii. Albumin (human) 25%

   iii. C1- Esterase 2000IU

   b. Products were placed on the shelf above the product label, however the labels did not prevent the misplacement of drugs in the correct location. For example, Hizentra 2g boxes were placed above the label for "Hizentra 20% 20ml/4g".

   c. Octaplex 500 IU KI01A2841 (Expiry 12/2023 x 4 boxes) were physically placed in the quarantine refrigerator with an orange "quarantine" label on the boxes, however the online inventory system (SAP) incorrectly showed the location of the product as the "PPP Quarantine Room Temperature" area.

   d. The Walk-in fridge had no obvious separation between Plasma Protein Products and Blood Products that were being stored together.

   Storage racks were relabeled with all relevant product information such as product name, strength and size.

   The Supervisor reminded the distribution team that the location chosen in SAP has to reflect the storage location of quarantined PPRP products. This was discussed during team huddles from 2021-11-15 to 2021-11-18 and through a follow-up email on 2021-11-26. In addition, a verification will be completed by 2021-12-15 to confirm that all quarantined PPRP products have been stored in the correct locations as per SAP.

   Signage was posted in the walk-in fridge to indicate storage areas for Plasma Protein Related Products and Blood Components by 2021-11-30.

C.02.012 - Manufacturing control

3. **There were inadequate controls and procedures for the handling and storage of recalled products. Specifically,**
   a. There was no procedure defining the storage locations for recalled product.
   b. There were no physically segregated areas for the placement and control of recalled product.

   Work instructions will be revised by 2022-06-27 to include requirements for having pre-designated labelled storage locations as well as the segregation and labelling requirements for quarantined, recalled and returned products.

   In the interim, staff will be reminded of the appropriate placement of recalled products. This will be completed by 2021-12-23.

C.02.015 - Quality control department

4. **The investigation of complaints was inadequate, for example:**
   a. Complaint DAR-2021-063 was received when a drug product was delivered a day later than expected. The Phase Change Materials were validated for only 27 hours in the delivery boxes, however there was no documented evidence of the time the product was received by the customer.

Work Instruction 08 029 "Management of Hospital Customer Feedback" focuses on resolving the immediate issue at hand and managing responses to the customer. Any customer feedback that includes product impact would necessitate the initiation of a deviation per 09 230 "Deviation/Minor Quality Event Management".

09 230 will be updated to ensure that every deviation that involves plasma protein products includes an investigation into the probable root cause(s) of the event and any follow up activities performed after the investigation will be documented. Each deviation will undergo a risk assessment, and should it be evaluated as a medium or high-risk event, a CAPA will be initiated, and root cause investigation conducted per current process.

All actions will be implemented by 2022-03-31.

5. **Deviation investigations were deficient. For example:**
   a. Deviation reports were documented with only a record of events and lacked any investigations into the root cause.
   b. The level of risk determination for deviations were based on the subjective analysis by the quality assurance associates, using a checklist. There was an inadequate consideration for any scientific justification.
   c. Only deviations with a risk level of medium or high were qualified to generate a CAPA. For example, Deviation DEV-21-007480 was initiated when the incorrect product was delivered to a hospital and was classified as a low risk level and therefore no CAPA was required.
   d. DEV-21-004323 was initiated when the drug product arrived at the facility with the temperature monitor in alarm, however there was no documented evidence on the report which described the justification for acceptance of the product into saleable stock.
   e. DEV-21-001824 was initiated when the drug product was incorrectly stored in room temperature conditions when it required refrigerated conditions. The investigation was inadequate as there was no documented evidence on the personnel involved in incorrectly storing the product, the quarantine fridge it was moved to (quarantine fridge or WIP walk-in fridge) or the manufacturer's temperature excursion acceptance criteria (vendor letter).
   f. DEV-21-002674 was initiated when a partial order was incorrectly sent to the wrong client, however there was no investigation into the root cause.

   All Deviation/Minor Quality Event work instructions (WI 09 230, 09 231, 09 232, 09 233) currently contain guidelines around the quality of documentation. These will be revised and made into requirements to reinforce expectations.

   A separate training module for all roles within the Deviation/Minor Quality Event management process that reinforces quality documentation requirements will be created and implemented.

   Every deviation that involves plasma protein products will include an investigation into the probable root cause(s) of the event and any follow up activities performed after the investigation will be documented. Each deviation will still undergo a risk assessment, and should it be evaluated as a medium or high-risk event, a CAPA will be initiated, and a root cause investigation conducted per current process.

   All actions will be implemented by 2022-03-31.

6. **There was inadequate control for the disposition records of drug products through SAP, for example:**
   a. All lab assistants had the authorization to be able to move products to and from quarantine through the online electronic inventory system (SAP), regardless of having the appropriate training and/or approvals.

   SAP roles are defined such that each job or task function has a pre-defined set of transactions they can access in the system. Access to these SAP transactions is granted on a per-person basis, based on a formal access request approved by the manager. Further approval is performed by IT security to ensure appropriate segregation of duties is in place compared with other SAP functionality the requestor may have. Such requests to access SAP are covered under Work Instruction 07 437 SAP Access Requests to Production Systems v2. Access to SAP is not granted automatically to a person or group of persons when they take on a new role, each access request must be submitted for a named user, followed up by the appropriate training. As such, access to the SAP Inventory Management process which controls movements of product in and out of quarantine, is granted to a specific individual(s), based on role and job duties, for the specific site they work out of only. Training is required to be completed either prior to granting SAP access or when on-the-job training will be completed.

   A review of SAP users who have the Inventory Management access will be completed and compared to the appropriate training matrices. This comparison, and any necessary absence training or SAP user access removal, will be completed by 2022-01-30.

C.006 – Personnel

7. **Personnel were trained on SOP 13 036 ViewLinc Operations v4 despite v5 being in effect.**

   DEV-21-008951 was initiated on 2021-12-01.

   The training was updated to the correct version of SOP 13 036 ViewLinc Operations v5 on 2021-05-11. Managers were notified on 2021-11-24 of staff who might have trained to the incorrect version. They were instructed to ensure that staff were trained to version 5 of SOP 13 036 and to initiate a quality event for those who trained to version 4 of SOP 13 036.

   The owner of the training for SOP 13 036, ViewLinc Operations, properly notified the DualCode administrator of the need to update the training on the system. The process for requesting updates to training items on DualCode is email based and at the time, incoming e-mails were managed by one employee who retired without having actioned this particular request. To mitigate recurrence, requests are now submitted to a group email box that is being monitored by three learning management system analysts. Since the time of implementing this group email, no update requests have not been actioned.

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C.02.024 – Records

8. **The documented information was inadequate, for example:**
   The 'Packing Slip' for deliveries had a section for 'requested delivery date, date issued and time issued', however it was not clearly defined that the 'time issued' referred to the time the phase change material was added into the delivery box.

   The "time issued" field is automatically generated on the packing slip from our SAP inventory management system. As per Work Instruction 12 017 Packing Sales Orders Distributed in SAP, the time packed, which includes the packing of the phase change material, is manually recorded on the packing slip in the "time issued" field.

   Work Instruction 12 017 will be revised by 2022-06-30 to clarify the meaning of the "time issued" field. This will ensure consistent and accurate reporting of such times.

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,

Christian Choquet

Dr. Christian Choquet
Vice-President
Quality & Regulatory Affairs
Fax Number: 613-739-2505

c.c.: Melanie Bhangoo, Manager, GMP Inspection
GMP Inspection Central
Regulatory Operations and Enforcement Branch