Canadian Blood Services
BLOOD PLASMA STEM CELLS ORGANS & TISSUES

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2020-01-14
CBS Control #: CBS6378
ROEB File #: HC6-61-7918-3-2
REF: H-1920-HO-W

Ms. Shelly Chen
Regional Regulatory Compliance and Enforcement Officer - GMP Inspection Central
Regulatory Operations and Enforcement Branch (ROEB)
Regulatory Operations and Regions Branch
Health Canada
2301 Midland Avenue
Toronto, ON M1P 4R7

Dear Ms. Chen:

**Re: Responses to Health Canada Inspection of Wholesale Activities at Head Office 2019-11-06 and 2019-11-07**

The following are the actions undertaken by Canadian Blood Services in response to the observations contained in the Health Canada Exit Notice dated 2019-12-05.

**C.02.015 - Quality control department**

1. **The handling of deviations and complaints was inadequate. For example:**
   a. **Not all deviations and complaints that had impact or potential impact to product quality were investigated to identify the root cause of the deficiencies. Consequently, appropriate corrective and preventative actions (CAPA) could not be established and implemented in a timely manner. For example, there was no investigation performed for the following deviations:**
      i. **Deviation QER#56-17-115035 initiated for customer complaint BRA-2017-224 in which refrigerated product Gammagard Liquid was shipped with incorrect pack-out.**
      ii. **Deviation QER-56-17-113026 initiated for customer complaint BRA-2017-186 in which Benefix product was shipped with incorrect packing configuration.**
      iii. **Deviation QER-56-17-113767 initiated for customer complaint BRA-2017-199 in which Albumin product was received at incorrect temperature and packing configuration.**

*Combined responses 1ai, 1aii and 1aiii:*

*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). 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. A strategy for the management of low risk quality events will be developed by the end of June 2020.*

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b. **Risk assessment evaluation of deviations was deficient. For example:**
   i. **The evaluation of the probability of recurrence was subjective to QA's knowledge/memory of past deviations. There was no requirement to conduct a search in the deviation database to determine whether similar events had occurred in the past.**
   ii. **There was no evaluation of the impact to product quality or the potential impact to other products. For example, in Deviation QER-56-17-113026 (product shipped with incorrect packing configuration), the product was impacted and therefore discarded; but the impact assessment stated low impact.**

*Combined responses 1bi and 1bii:*

*The risk assessment component of the quality event management process and the associated risk assessment tools will be assessed by the end of June 2020 to ensure that they result in adequate evaluation of product impact.*

c. **CAPA # 120-18-111997 related to reoccurring shipping deviations such as incorrect product, batch, and quantity as were reported through customer complaints was deficient in that:**
   i. **There was no assurance that true root causes would be determined through a retrospective investigation conducted one year after the deviations.**
   ii. **The CAPA failed the effectiveness check, but no further investigation/CAPA was performed except at BC and Yukon sites.**
   iii. **It identified some potential reasons as to why effectiveness checks failed, such as scope of investigation was too broad and inappropriate evaluation criteria for effectiveness check, but there was no follow-ups to address these gaps.**

*Combined responses 1ci, 1cii and 1ciii:*

*Since the time of this CAPA's initiation, a dedicated organizational CAPA team has been established with the objective of driving more timely and more thorough investigations of quality events and the identification of more robust corrective actions. This centralization of CAPA work includes the establishment and ongoing monitoring of CAPA performance. Investigations are now being completed on average around 60 days.*

*The further investigation/ CAPA performed at the BC and Yukon sites was in fact taken over by the national CAPA team (CAPA-18-000017). As a result of this investigation, the transfer order form was revised and implemented on 2019-12-05. An effectiveness check will be conducted for a period of 3 months post implementation. Any further action will be determined during the review of the results of the effectiveness check.*

d. **Deviation QER-120-18-113402 was initiated for Fibryga diluent being stored and transported at 2-8C while labelled storage condition was 15-30C. The impacted product was released prior to receiving supplier's supporting documentation. A written justification was not available.**

*It was identified following the inspection, that we had received on 2018-11-21 a disposition letter from our supplier, originating from the diluent manufacturer, that stated that there was no impact to the diluent when stored at 2° to 8°C. Based on this information, the product was released by Canadian Blood Services on 2018-11-22. Unfortunately, this letter was not identified during the inspection. The letter has now been filed with the deviation.*

*Work Instruction 12 808, Managing Excursions Reported to Integrated Supply Chain Planning - Head Office and the associated form F800174, Plasma Protein Product Excursion Form will be revised by 2020-03-02 to require that the rationale and associated evidence, such as communications from suppliers, for decisions of acceptability be included in the documentation for release.*

**e. There was no procedural requirement to conduct deviation trending analysis periodically.**

*The review of deviation trends is performed as part of our management system reviews conducted both at the local and national level. The requirement to review quality data is covered in the quality management process procedure QMS-1005-01, "Quality Management Process – Quality Management System Review Committees". The requirement will be strengthened in this procedure and is also being included in the quality management system process procedure for the Quality Event management process currently being developed. Both will be implemented by the end of March 2020.*

**2. Contrary to the change control procedure, not all changes were properly documented, evaluated and approved by Quality. For example:**
- **a. A change control was not initiated for introducing new product Obizur and Alprolix.**
- **b. CR16092 was initiated for introduction new product Adynovate; however, it did not contain an assessment of the change and an implementation plan.**

*Combined responses 2a and 2b:*

*When Obizur and Alprolix were introduced the change control process was just not followed as required while at the time of CR16092, criteria were incorrectly assessed and as a result, the impact assessment and implementation plan were not completed as expected. Since then, the change control process has been revised and clarified in that all changes, except those that are editorial in nature (e.g. a correction to a document typographical error), must go through the change control process and all changes require an impact assessment and an implementation plan.*

*A review of our records since the introduction of Adynovate shows that the change control process has been followed for the introduction of all new plasma protein products and that change assessments and implementation plans have been completed in all cases.*

**C.02.006 - Personnel**

**3. Deficiencies were noted with regards to the training program.**
- **a. There was no procedural requirement to conduct periodic GMP training.**

*Starting April 1, 2020, all staff will be required to complete a good manufacturing practices refresher course annually. This requirement will be incorporated into the applicable management process procedure.*

**b. A training matrix identifying training requirements for Supervisor, Logistics Coordination Center was not available.**

*It is our understanding that the training matrix was available but not up to date. It has been corrected and any outstanding training will be completed by 2020-02-28.*

*The staff member responsible for updating the training matrix for the Logistics group was retrained on procedure 08 551 v4, Identify Training Requirements.*

**c. Records of training on the following SOPs were not available for warehouse receiver and shipper:**
- **i. SOP 12-304 Picking and Shipping for SAP Inventory, version 11.**
- **ii. SOP 08-851 Manual of Good Documentation Practices, version 7.**

*Training to SOP 12 304 and 08 851 has been completed and training files for the respective employees updated accordingly.*



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*Going forward, Supervisor- Logistics Coordination Centre will receive notification of new or revised documents requiring training and will follow-up regularly to ensure all training is completed prior to implementation and supported by confirmation of employee training records.*

**C.02.015 - Quality control department**

4. **SOP 12-022 "Inspection of Plasma Protein Products Received at a Site" did not include how long the product could be staged in the receiving area prior to being put into proper storage locations.**

*Work instruction 12 022 will be revised by 2020-06-30 to clarify requirements for exposure to temperatures outside of storage ranges. In addition, the training material will be revised to provide the rationale for such requirements.*

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.

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Vice-President
Quality & Regulatory Affairs
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