Questions and Answers for the Industry Training Workshop on Product Defect Reporting and Recall Procedures for Therapeutic Products and Cells, Tissue and Gene Therapy Products

This document aims to address the questions that were received during the HSA Industry Training Workshop on Product Defect Reporting and Recall Procedures for Therapeutic Products and Cells, Tissue and Gene Therapy Products held on 29 October 2024.

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Product Defect Reporting

1. **In a scenario where a temperature excursion occurs, and the company has stability study data confirming that the product quality remains unaffected by the excursion duration, and the batch is released, is defect reporting still required?**

   Product defect reporting is not required if the company's Quality Assurance (QA) team has evaluated the temperature excursion and determined, based on stability data, that the product quality has not been compromised, leading to the batch's release.

2. **Should company report product defects related to batches that have not been imported into Singapore, given that the local importing company may not have immediate access to information about global product defects or recall cases? Specifically, what are the reporting obligations when the local market is not directly impacted, and how might HSA consider the challenges in obtaining timely investigation reports from global affiliates under these circumstances?**

   If the root cause of the defect is a systemic issue rather than batch-specific, even if the affected batch has not been imported into Singapore, the product defect must still be reported as the issue would need to be addressed before future batches of the product is imported. Once the local product registrant becomes aware of the defect, the company is required to submit the report in accordance with regulatory timelines.

   The necessary information should be provided within the stipulated deadlines. If more time is required to obtain the information, companies should inform HSA and propose the timeline for provision of the information with the justifications for HSA's consideration.

   It is also important for companies to consider whether the corrective/preventive action needed to address the defect requires a variation application to be submitted and

approved by HSA. In such cases, companies would need to cater for the required time to prevent interruptions in importation and supply of the product.

3. Is an out-of-specification (OOS) result from stability batches (provided as part of a stability commitment in a previous application to HSA) considered non-reportable if the root cause does not affect subsequent batches?

All OOS events are considered reportable product defects, including those involving stability commitment batches from previous applications. Even if the OOS result from historical batches does not impact future batches, these historical batches may still be on the market and could be affected by the findings. Therefore, companies are required to report these OOS findings as product defects for review, allowing HSA to assess the potential impact on any remaining historical batches.

4. How should counterfeit products be reported, and what are the responsibilities of importers and wholesalers? Additionally, are importers and wholesalers liable for adverse events that occur when a user fits a counterfeit part into a registered medical device imported and sold by a local distributor?

If your company identifies a counterfeit version of its product, it is advisable to issue proactive communications to educate consumers on how to distinguish the counterfeit product from your legitimate one.

Counterfeit therapeutic products should be reported to the HSA's Enforcement Branch, while counterfeit medical devices should be reported to HSA's Medical Device Cluster.

Regarding adverse events, while importers and wholesalers are responsible for ensuring the safety and quality of the products they distribute, liability for adverse events related to counterfeit parts would generally depend on the circumstances. If the counterfeit part was fitted into a registered medical device, the company may have a responsibility to report the event, but the liability for any harm caused could be more complex, involving

factors such as knowledge of the counterfeit nature of the product and its sale in the market.

5. What is considered "Day Zero"? If a company becomes aware of an issue (e.g., receives a complaint), but the risk can only be identified after further investigation, can the company report to HSA after completing the investigation and assessing the risk?

"Day Zero" is the day the local company becomes aware of the issue. If the issue appears to be an isolated incident that is not likely to be due to manufacturing deviation, the company should first investigate and consult with HSA. However, if the issue seems to be systemic or widespread, it must be reported to HSA within the required reporting timelines. Companies are advised to file the report with HSA as soon as they become aware of the issue. If the investigation later reveals that the issue is isolated or does not qualify as a defect, HSA will review the findings and may close the matter.

6. A recall occurred in another country, but the affected batch was not imported to Singapore. The manufacturer has implemented CAPA, and future batches will not be affected. A medical risk assessment indicates no impact on patient safety, and the product remains safe and effective. Does the company need to report this to HSA?

If the cause of the recall is a systemic issue (e.g., manufacturing-related or non-batch-specific out-of-specification results), the incident must be reported to HSA, even if:

- The affected batch was not imported into Singapore;
- CAPA has been implemented; and/or
- The medical risk assessment shows no risk to patient safety.

This is to allow for review of the CAPA and supporting documentation to confirm that the root cause has been adequately addressed.

Product Recall

7. Does the company need to provide HSA with a 24-hour notification for voluntary recalls, even if the recall may or may not impact patient health?

Yes, this requirement applies to all recalls. Under Regulation 35 of the Health Products (Therapeutic Products) Regulations 2016, HSA must be notified at least 24 hours before the initiation of any recall. This is regardless of whether the recall involves potential impact on patient health.

8. Is HSA's approval required before a recalled product can be destroyed?

Following completion of a product recall, the Product Recall Completion Form needs to be submitted to HSA, which includes an update on the follow-up actions that will be taken for the recalled products. If the products are to be destroyed locally, the company should submit the certificate of destruction to HSA within 3 months from the completion of recall, unless otherwise justified. The company is not required to seek prior approval from HSA for the destruction.

9. It has been mentioned that a 1-for-1 exchange of a defective product is considered a recall. Complaints are often reported to companies, and we perform a 1-for-1 exchange as an immediate action. Is this action reportable to HSA?

It will not be considered a recall if the 1-for-1 exchange is for retrieval of the defective product for investigation purpose. Any 1-for-1 exchange involving multiple units of the product, whether from one or more purchasers, is deemed a recall and must be reported to HSA. If the issue recurs or many units are affected, it may indicate a widespread quality issue, further supporting the need for a recall.

10. At the time of exchange, the company has not completed the assessment. After the assessment, the complaint is determined to be due to user mishandling. Will this be considered a recall?

It will not be considered a recall if the 1-for-1 exchange is for retrieval of the defective product for investigation purpose. Based on the severity of the defect, your company may need to report the issue to HSA (e.g., contamination of injectables). Subsequently, if investigations have identified this to be an isolated incident of user mishandling, the case will be closed, and it will not be treated as a recall.

However, if more exchanges are carried out involving multiple units of the same defective product, whether from one or more purchasers, it will be deemed a recall and HSA must be informed. If the issue recurs or many units are affected, it may indicate a widespread quality issue, further supporting the need for a recall.

11. If a product is taken back for investigation following a product complaint, but no replacement is given to the customer, is this still considered a recall?

Retrieving the initial defective unit(s) for investigation, by itself, is not considered a recall. If only the affected unit is taken back for root cause investigation, it is considered part of the investigation process. However, if additional units with the same defect are identified, the company will need to assess whether a recall is necessary for the entire affected batch or batches.

12. When does HSA consider a recall case as closed? Is it after the product recall and reconciliation are completed, or only after the Certificate of Destruction (COD) is submitted to HSA?

A recall is considered completed after the COD is submitted to HSA.

13. How is the 12-month timeframe for performing a recall simulation calculated? Is it based on the date the recall is closed or the date the recall execution begins?

The 12-month timeframe for performing a recall simulation serves as a guideline, and the company can determine the appropriate timing for the simulation.

14. What are the key considerations when conducting a mock recall?

A mock recall should closely simulate a real recall scenario in line with the company's Standard Operating Procedures (SOP), considering the products, suppliers, and purchasers involved. Since each company’s operations may differ, it is essential for companies to review their specific processes and establish procedures tailored to conducting a mock recall. Additionally, companies should ensure they maintain an up-to-date contact list of customers to facilitate the swift dissemination of recall information if needed.