THIOMERSAL RELATED AUDIT SITUATIONS & FINDINGS – CASE STUDY

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dcvmn
Developing Countries Vaccine Manufacturers Network

Introduction

Thiomersal is widely used preservative for vaccines. As Thiomersal is absorbed by stoppers and plungers, they are soaked in Thiomersal solution (with WFI) to saturate them before sterilization and filling.

Case 1

During the walkthrough as part of your audit, auditors observed white spots on the stoppers, and several interventions during the aseptic fill to dislodge stoppers which were sticking to the chute of stoppering station (e.g. hitting and shaking the hopper). Customer complaints had also been received related to white spots on stoppers.

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Case 2

Review the stability study provided.

Case 3

Complaints were received related to contamination which appeared after severa
days in opened containers of a multidose vaccine with Thiomersal as preservati
Review stability studies provided

Case 4

Complaints were received related to contamination of unopened vials of a multidose vaccine with Thiomersal as preservative. Review stability studies provided.

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Instructions to the group

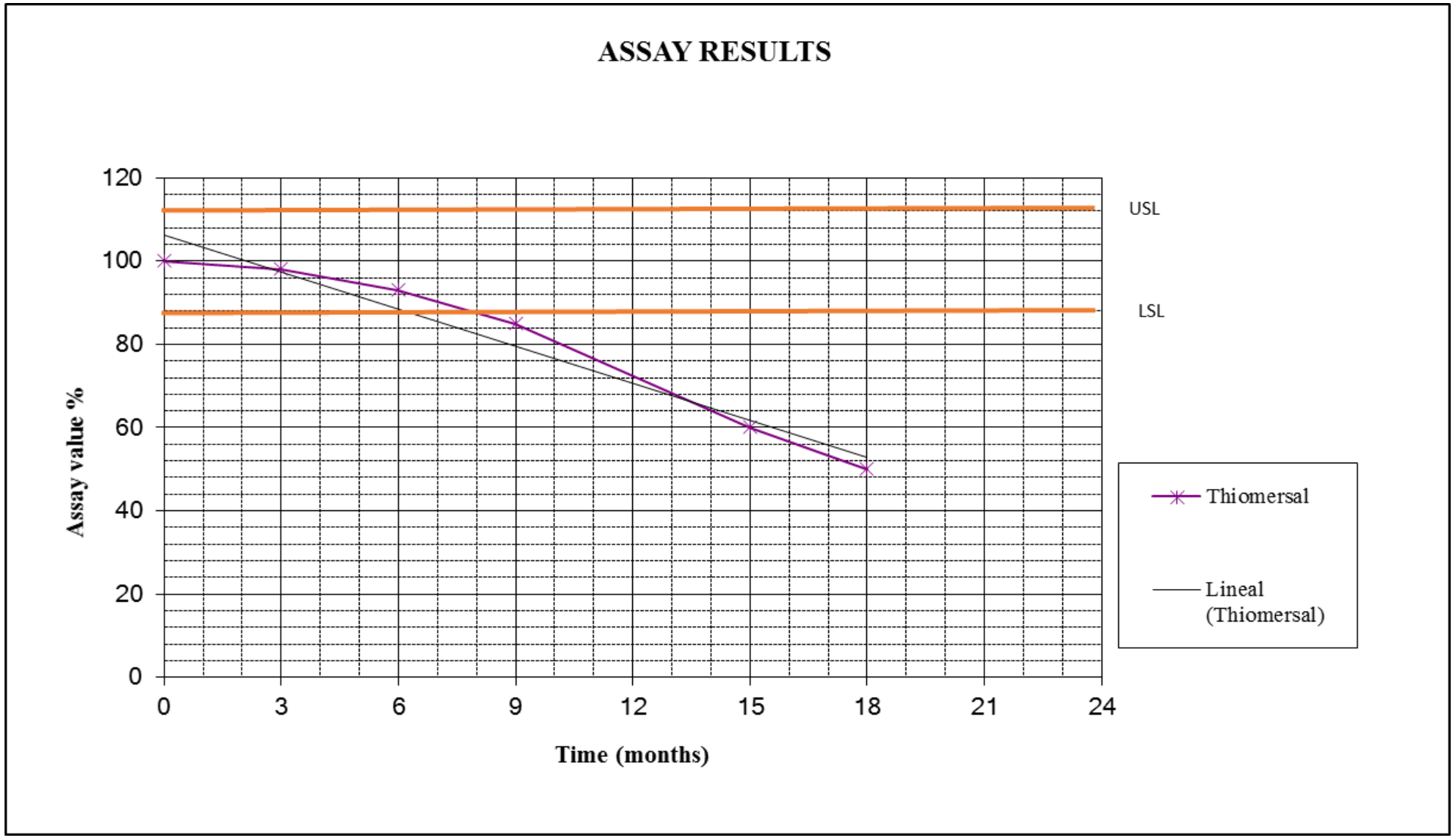
1. As auditors, briefly discuss and prepare an audit checklist and the associated documentation. Draw conclusions and identify the probable cause!

2. Briefly, write in bullet-point format in your flipchart.

3. Make a brief presentation to the class justifying the points to be audited.

(Reference: WHO Policy Statement: Multi-dose Vial Policy – MDVP; ICH Q 5 C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products).

THIOMERSAL RELATED AUDIT SITUATIONS & FINDINGS – **CASE STUDY 2**



THIOMERSAL RELATED AUDIT SITUATIONS & FINDINGS – CASE STUDY

Summary/Justification

Case 1: Sticky stoppers with white spots.

- If Thiomersal concentration is too high, rubber stoppers or plungers may become sticky after steam sterilization, and product residue will appear on stopper surface after drying, in the form of white spots. Extended exposure of stoppers to the right Thiomersal concentration will also produce same effects.
- Sticky plugs / stoppers may get stuck in the rubber stopper hopper and chute Hence, operators need to frequently do “topping” intervention for a free stoppers (i.e. by hitting or shaking of the stopper hopper).
- Thiomersal: 0.003 to 0.005 %. Normally prepared 1 day before filling.

THIOMERSAL RELATED AUDIT SITUATIONS & FINDINGS – CASE STUDY

Summary/Justification

Case 1: Sticky stoppers with white spots.

- Industry standard: rubber stoppers & plungers should not be excessively soaked in Thiomersal solution (validated hold time to check bio burden and endotoxins, and Thiomersal content through time --stability).
- Avoid loading sterilization pouch too much with stoppers to avoid sticking.
- Plug drying cycle should be sufficient (e.g., 120 minutes).
- Most probable cause for white spots in stoppers is excessive concentration of Thiomersal solution, or excessive soaking time.

Case 2: Decrease of Thiomersal.

- Stability study reveals decrease of Thiomersal
- If stopper / plunger Thiomersal treatment is not effective (i.e. insufficient soaking) and not validated, a decrease in Thiomersal may be observed.

Case 3: Contamination in opened containers of multidose vaccine

- Stability protocol did not include stability of opened vial as required by WHO 28 days with testing at 0, 7, 14 and 28 days, simulating multiple injections according an estimated frequency of use or instructions included in the inser
- Contamination due to Thiomersal decrease should be ruled out by means of stability study.

Case 3: Contamination in opened containers of multidose vaccine

- ICH Q5C - 6.5 Container/Closure.

"Changes in the quality of the product may occur due to the interactions betwee the formulated biotechnological/biological product and container/closure.

Where the lack of interactions cannot be excluded in liquid products (other than sealed ampoules), stability studies should include samples maintained in the inverted or horizontal position (i.e., in contact with the closure), as well as in the upright position, to determine the effects of the closure on product quality".

Case 4: Contamination in unopened containers of multidose vaccine

- The vaccine instructions for use did not specify the orientation of the container during storage. Stability studies were performed with the containers placed in upright position only, with no product-stopper contact. Users may not store the product in an upright position. In this case, stability studies need to be performed with the container in upright position and in upside down position.

- Validation of right concentration and soaking time should be verified.

Case 4: Contamination in unopened containers of multidose vaccine

ICH Q5C - 6.5 Container/Closure.

‘Data should be supplied for all different container/closure combinations that will
marketed. In addition to the standard data necessary for a conventional single-u
vial, the applicant should demonstrate that the closure used with a multiple-dose
vial is capable of withstanding the conditions of repeated insertions and
withdrawals so that the product retains its full potency, purity, and quality for the
maximum period specified in the instructions-for-use on containers, packages, a
or package inserts. Such labelling should be in accordance with relevant nationa
regional requirements”.

THIOMERSAL RELATED AUDIT SITUATIONS & FINDINGS – CASE STUDY

Summary/Justification

WHO Policy Statement: Multi-dose Vial Policy – MDVP

"To determine safety, WHO reviews the preservative efficacy of the vaccine to determine whether the opened vaccine vial can be kept and re-used safely for a period of up to 28 days. Injectable vaccines that can be kept for this length of ti contain sufficient levels of preservative (traditionally thiomersal) to prevent grow of bacterial contamination. If the contents of the vial become contaminated, the action of the preservative prevents any increase in bacterial or fungal growth ov time, and actually decreases the level of contamination".