THIOMERSAL RELATED AUDIT SITUATIONS & FINDINGS – CASE STUDY

DCVMN, Hyderabad – INDIA

Victor G. Maqueda (with contribution of Prof. Jose Luis Monteagudo) - Argentina – April 2017
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.
Case 2
Review the stability study provided.

Case 3
Complaints were received related to contamination which appeared after several days in opened containers of a multidose vaccine with Thiomersal as preservative. 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.
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.

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.
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 insert.

- Contamination due to Thiomersal decrease should be ruled out by means of a 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 between 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 be marketed. In addition to the standard data necessary for a conventional single-use 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, and/or package inserts. Such labelling should be in accordance with relevant national/regional requirements”.

Victor G. Maqueda – Jose Luis Monteagudo - DCVMN, April 2017
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 time contain sufficient levels of preservative (traditionally thiomersal) to prevent growth of bacterial contamination. If the contents of the vial become contaminated, the action of the preservative prevents any increase in bacterial or fungal growth over time, and actually decreases the level of contamination”.

Victor G. Maqueda – Jose Luis Monteagudo - DCVMN, April 2017