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Assessment Report for particles on silicone tubing of Diphtheria and Tetanus toxoid (DT) and Diphtheria/Tetanus toxoid/Pertussis (DTwP) antigen bulk containers

Review under Article 5(3) of **Regulation (EC) No 726/2004**

Procedure no: EMEA/H/A-5(3)/1307

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Referral of the matter to the CHMP

On 11 April 2011, the EU National Competent Authorities and the European Medicines Agency were informed that particles had been found on the silicone tubing of some of the bulk containers for antigens manufactured by Novartis Vaccines in Marburg, Germany. This manufacturing plant is responsible for the production of bulk antigen used in the manufacturing of several vaccines.

While the investigation was ongoing and corrective/preventive actions were being implemented, manufacturing continued but batch release of products potentially affected by the presence of particles was stopped. The fact that batch release of potentially affected lots had been suspended in the European Union was likely to originate shortage of vaccines in some Member States.

On 17 May 2011, Germany referred the issue to the European Medicines Agency's Committee for Medicinal products for Human Use (CHMP). The Paul Ehrlich Institut requested the Committee to draw up an opinion under Article 5(3) of Regulation No 726/2004 as amended on:

- The possible risks associated with DT and DTwP antigen bulks filled and stored in glass containers using silicone tubes containing metal particles;
- How best to balance the possible risks of contaminant particles against the public health risks linked to out-of-stock situations that would result from discarding the affected bulks.
- How best to communicate out-of stock situations or interruptions in the supply chain resulting from the detection of this manufacturing deviation.

2. Scientific discussion

2.1. Introduction

The presence of small particles (typically $\leq$200 μm) in the manufacturing process of some vaccines was identified in February and March 2011 during routine visual inspection. The analysis of these particles revealed that they are composed of several elements consistent with product elements such as aluminium (Al), chloride (Cl), sulphur (S), mercury (Hg – present in DTwP concentrate only) and include additional elements like nickel (Ni), zinc (Zn), chromium (Cr), iron (Fe), tin (Sn) and copper (Cu).

During the investigation it was concluded that the most likely root cause for the presence of the particles was the silicon tubing used during the production, which was found not to be particle free and is not subject to any further processing step that would allow removal of the particles. This type of silicone tubing is routinely used during vaccine production to allow filling or sampling. The currently used silicon tubing was introduced following a change of supplier in September 2007, and in August 2008 (DT) and January 2009 (DTwP) the manufacturing process itself was changed to introduce the tube in 20 L bottles for sampling purposes.

The particles were found to be adhered to the silicone tubing and did not seem to be released into the bulk container. Accordingly they have not been found in the bulk or the final product. While the particles are in contact with concentrates that will be used in the production of several types of vaccines, in most cases subsequent manufacturing steps are sufficient to ensure removal of any particles. In the case of the DT and DTwP vaccines, however, the presence of adjuvant does not allow a sterile filtration to be performed. Therefore products manufactured using DT and DTwP bulks represent the worst case scenario in terms of contact with the particles.

The bulk DT and DTwP antigens produced in the Marburg Novartis manufacturing plant are both used in Novartis' own vaccines and sold for the production of other vaccines marketed by GlaxoSmithKline (GSK).

A review of product complaints received by the MAHs did not reveal any increase of complaints on foreign particulate matter. Post-marketing safety data also did not reveal any safety concern or higher-than-expected reporting of adverse events related to this possible contamination. It is estimated that even if all the particles observed in the tubing were to enter the bulk, the worst case estimated amounts in a vaccine dose would be below established or calculated thresholds associated with toxicity.

The manufacturing process of the antigen bulks includes numerous steps and usually requires several months. Discarding the already available bulks could therefore result in a long-term supply issue.

2.2. Discussion

The following products were identified as potentially having been in contact with the particles detected in the silicon tubing at some stage of the manufacturing process. Other products have been in contact with the same type of silicon tubing, but as subsequent filtration steps are applied no concerns are raised for these products.

GlaxoSmithKline	**Novartis**
Tedivax/Ditanrix	Tetanol Pur*
Infanrix (DTPa)	Td-pur*
Infanrix + Hib (DTPa+Hib)	Diphtheria Adsorbat Impfstoff*
Infanrix IPV (DTPa-IPV)	
Infanrix IPV + Hib (DTPa-IPV+Hib)	
Infanrix hexa (DTPa-HB-IPV+Hib)	
Infanrix penta (DTPa-HB-IPV)	
Tritanrix HB (DTwP-HB)	
Boostrix (dTpa)	
Boostrix IPV (dTpa-IPV)	
Hiberix (Hib)	

Possible risks associated with DT and DTwP antigens filled and stored in glass containers using silicon tubes containing metal particles

The presence of particles on the silicon tubing was first detected by GlaxoSmithKline Biologicals during a visual inspection process at the formulation step. All lots potentially impacted by this quality defect were put on quarantine by the manufacturer and not further released. This precautionary measure ensured that products that at some stage of the manufacturing process are known to have been in contact with particles were not released to the market. Following the detection of this quality defect, visual controls for detection of particles were strengthened.

During the investigation, both particles and spots were observed on the silicone tubing. The visual appearance and the composition of the two are not exactly the same, although they share common elements.

Particles/spots were found to adhere firmly to the silicone tubing and could not be dislodged during agitation studies over a 22-hour period at 50 rpm and room temperature or when subject to an ultrasonic bath for an extended timeframe. As no particles were detected in any of the final products, it is unlikely that particles were ever present in the final product.

Toxicological Evaluation

Taking a conservative approach, the following theoretical exposure scenarios have been considered in the toxicological evaluation:

- a first scenario, in which particles/spots detach from the tubing, are suspended in the volume of the bulk storage bottle, and the elemental content from an entire particle/spot is present or dissolves in a 0.5 mL vaccine dose;

* The bulk is not in direct contact with the silicon tubing, but the individual toxoids are.

- a second scenario where all particles/spots dissolve into the volume of the bulk storage bottle, after which the dissolved elements are distributed evenly throughout the vaccine doses, with no further dilution,

The particles detected on the silicone tubing were analysed by Energy-Dispersive X-ray spectroscopy and shown to contain copper, zinc, iron, chromium, nickel, and lead.

The mass of each of these metals in the different scenarios is summarized in the table below:

Elements	μg/particle	μg/26 particles (worst case)	μg from one particle in 0,5 ml dose (scenario 1)	μg from 26 particles distributed evenly into 0,5 ml doses (scenario 2)
Copper	38.1	990.6	38.1	0.025
Zinc	90.9	2363.4	90.9	0.059
Iron	5.2	135.2	5.2	0.0034
Chromium	1.0	26.0	1.0	0.0006
Nickel	15.3	397.8	15.3	0.0099
Lead	20.3	527.8	20.3	0.013

Even in the worst case scenario, calculated levels of Zn, Fe and Cr are lower than the permitted daily parenteral exposure (PDE) set in the relevant European guideline[1].

For lead (Pb), no limit exists in the above mentioned guideline. Based on a WHO and FDA document[2], a parenteral permissible chronic daily intake (PPDI) of 3 μg/day for a 5 kg infant is a reasonable calculation. Although the theoretical exposure to Pb in the worst case scenario is approximately 7 times higher than the conservatively calculated PPDI, no systemic toxicity would be predicted from this amount of lead in a vaccine dose, because the PPDI supports continuous daily chronic dosing and does not reflect a single day exposure.

Similarly, the worst case assumptions for Cu and Ni indicate that the amounts that may be theoretically present in one vaccine dose exceed the levels set in the guideline (for Ni 6-times and for Cu 1.5-times above the level). Although this theoretical amount is higher than the infant parenteral PDE, no risk to human safety is predicted because the PDE reflects daily chronic dosing, and an occasional exposure to doses above the PDE with vaccination would not increase the body burden significantly and would not be expected to produce clinically relevant toxicity.

Energy-Dispersive X-ray spectroscopy analysis of the spots detected on the tubing demonstrates that they contain copper, nickel, zinc, and mercury.

The mass of each of these metals in the worst-case scenario is summarized in the table below:

Elements	μg/spot
Copper	55.4
Zinc	0.3
Nickel	1.9
Mercury	63.5

The worst-case estimated levels of each of the metals were evaluated in the context of the permissible daily exposures (PDE) presented in the EMEA/CHMP/SWP/4446/2000 guideline (for Cu, Zn, Ni) or toxicologically acceptable limits available from the scientific literature and/or public regulations (for Hg).

For spots, the calculated levels of Zn, and Ni were lower than the applicable permitted daily parenteral exposure (PDE) levels set in the guideline.

The worst case assumptions for Cu indicate that the amount that may be theoretically present in one vaccine dose exceeds the levels set in the guideline (Cu 2.2 times above the level). Although this

[1] Guideline on the specification limits for residues of metal catalysts or metal reagents (EMEA/CHMP/SWP/4446/2000).
[2] FAO/WHO, 1993; http://www.inchem.org/documents/ehc/ehc/ehc165.htm#PartNumber:10

theoretical amount is higher than the infant parenteral PDE, no risk to human safety is predicted because the PDE reflects daily chronic dosing, and an occasional exposure to doses above the PDE with vaccination would not increase the body burden significantly and would not be expected to produce clinically relevant toxicity.

As there is no oral or parenteral PDE for mercury in the EMEA/CHMP/SWP/4446/2000 guideline, reference is made to a toxicological evaluation of elemental mercury and inorganic mercury published by WHO[3]. The limit set for tolerable daily intake (TDI) for Hg was calculated to be 0.8 µg/kg/day (for parenteral application), based on the Hg limit set for oral uptake assuming 40% bioavailability which is again considered a conservative approach as bioavailability reported in literature ranges from 1%-38%. Applying the 0,8 µg/kg/day parenteral limit (4 µg/day for a 5 kg infant), the 63,5 µg of Hg representing a worst case estimate of the mass present in a single vaccine dose is approximately 16-fold higher. Again it is important to highlight that the limit is calculated for regular daily parenteral intake tolerable for infants, not a single exposure.

It should also be noted that in the past pediatric vaccines containing thiomersal as a preservative were formulated with around 50 µg thiomersal/dose corresponding to about 25 µg of Hg. This concentration is about 2.5 times below and therefore quite close to the worst case estimate in this evaluation.

Extraction studies

Extraction studies with silicone tubing (using WFI, isopropanol and dichloromethane) demonstrate that none of the extracted substances is present at above the Threshold of Toxicological Concern (TTC) of 1,5 µg/dose[4]. It can therefore be agreed that extractable substances are not considered to be of toxicological concern.

Post authorisation safety monitoring

A review of product complaints received by the MAHs did not reveal any increase of complaints on foreign particulate matter. Post-marketing safety data also did not reveal any safety concern or higher-than-expected reporting of adverse events.

Conclusion

The root cause for the manufacturing deviation has been identified and the investigation completed. Based on:

- Low probability that particles can be found in the final products
- Even if particles were found in the final products, their potential for toxicity is low
- Extraction studies showing no toxicological concern
- The absence of a safety signal identified during post-authorisation monitoring

It can be concluded that the presence of particles or spots on the silicon tubing used during the manufacturing process does not have a negative impact on the quality, safety or efficacy of the vaccines concerned.

How best to balance the possible risks of contaminant particles against the public health risks linked to out-of-stock situations that would result from discarding the affected bulks

Novartis will not further process any bulks where the presence of particles or spots on the silicone tubing was identified, unless validated and approved reprocessing steps can be applied to remove potential particles and a further assessment of the resulting material for any potential impact is done. GSK has committed not to use any bulks showing particles or spots on the silicone tubing for the manufacture of the vaccines.

Based on information provided by the MAHs, even if all the bulks affected by the findings are discarded, no long term supply shortage is expected to occur, as corrective measures have been implemented and manufacturing has already been resumed.

[3] Concise International Chemical Assessment Document (CICAD) 50. WHO, 2003

[4] Defined in the EMA guideline on limits of genotoxic impurities (EMEA/CHMP/QWP/251/344/2006), according to which contaminants below this dose are not subject to further toxicological evaluation

However, because batch release was discontinued during the investigation, in the short term situations of supply shortage are likely to occur for some products. In the absence of safety concerns, production, testing and release of vaccine batches should be expedited to ensure that situations of supply shortage are avoided or minimised.

How best to communicate the out-of stock situations or interruptions in the supply chain resulting from the detection of this manufacturing deviation

As mentioned above, information provided by the MAHs indicates that long term effects on the supply chain are not foreseen.

3. Overall conclusion

The CHMP considered the procedure under Article 5(3) of Regulation (EC) No 726/2004 on the risk of particle matter on Diphtheria and Tetanus toxoid (DT) and Diphtheria/Tetanus toxoid/Pertussis (DTwP) antigen-bulks.

Based on the overall quality and safety data available, the Committee considered that
- There is low probability that particles can be found in the final products
- Even if particles were found in the final products, their potential for toxicity is low
- Extraction studies show no toxicological concern
- No safety signal was identified from post-authorisation monitoring

The Committee therefore concluded that the presence of particles or spots in the silicon tubing used during the manufacturing process does not have a negative impact on the quality, safety or efficacy of the vaccines concerned.