Manufacturer perspectives on alternatives to thiomersal

The views of 3 Manufacturers

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Objectives of the presentation

- Present the common position of three developed countries manufacturers
- Contribute to the discussion by highlighting our view on the potential alternatives to thiomersal

Agenda

1. Background information
2. Potential alternative scenarios
3. Need for evidence-based policies
4. Conclusion

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Thiomersal in vaccines

- Thiomersal is an antimicrobial compound used to control contamination with bacteria and fungi during production, storage and use of some vaccines.

- It is used since the 1930's in the manufacture of some inactivated vaccines (D,T, P, Hib, Flu, Hep B,….)
  - As an inactivation agent
    - e.g. whole cell Pertussis
  - as a preservative for multi-dose presentations.
    - Without appropriate preservation, there are important quality and safety risks.
    - In a number of developing countries, currently insufficient infrastructure (cold chain, storage space) limits the delivery of only single dose preservative free vaccines.
    - Multi dose vaccines are used worldwide during mass vaccination campaigns (ex. Pandemic influenza)

- Every year, several hundred Mdoses of thiomersal containing vaccines are supplied to serve global public health needs by preventing disease and thereby reducing morbidity and mortality worldwide.

Regulatory requirements

- The use of a preservative in multidose presentations is required by regulations
  - **WHO:** Programmatic Suitability for Pre-Qualification
    - « Ready to use multi-dose vaccines must demonstrate adequate preservation, defined by: having either the standard thiomersal concentration (i.e., thiomersal concentration is >50 µg per ml for monovalent HBV vaccine and >100 µg per ml for other vaccines) or the preservative having demonstrated its anti-microbial efficacy to control contamination for 28 days using a multi-challenge test. "
  - **US**: 21 CFR 610.15(a)
    - « Products in multi-dose containers shall contain a preservative …"
  - **EU:** European Pharmacopoeia – Dosage form – Parenteral (0520) Injections
    - « Multidose aqueous injections contain a suitable antimicrobial preservative at an appropriate concentration …"

Regulatory authorities in industrialised countries encourage thiomersal free formulations

- Notwithstanding the current use of mercury-containing preservatives in multi-dose vaccine vial presentations in many different country settings, regulatory authorities (e.g. US FDA, EMEA, Swissmedic, KFDA) have for a number of years been encouraging the manufacturers to develop and implement thiomersal-free vaccine formulations.
  - EMA and Swissmedic have not registered a thiomersal-containing vaccine since 1999-2000 (EMA Position Statement, 29 June 2000), except for pandemic setting (H1N1 flu)
  - EMA in 2007 reiterated that "in line with the global goal of reducing exposure to mercury, the development of vaccines without thiomersal or with the lowest possible levels of thiomersal and other mercury containing preservatives should continue to be promoted" (CHMP Position Paper, 11 January 2007).

Quantity of thiomersal used in vaccines

- Estimated quantities used in the Industries (/ year):
  - All Industries (incl. vaccines) use about 3,600-3,700 tons of Mercury, including 300 tons in EU
  - Thiomersal is ~ 50% mercury by weight
  - European Vaccine Industry (EVM): 0.25 tons of Thiomersal i.e. <0.125 tons of Mercury*

- **Very low** quantities in vaccines:
  - As a preservative, usually not more than 50 µg/dose
  - As inactivating agent, residual amount in finished product

EU Vaccine Industry represents 0.003% of total Mercury demand

** EVM position "Thiomersal and vaccines", 2008*

Safety

- Safety questions raised in infants who receive a multiple number of vaccine injections which may contain thiomersal. Suspicion of a risk of accumulation of mercury.
- Methyl / Ethyl mercury
  - Mercury toxicity clearly associated with methyl mercury
  - Thiomersal degradation after administration results in ethyl mercury with a much safer toxicity profile than methyl mercury and a rapid excretion by infants
- Consensus in the scientific community: the licensed thiomersal containing vaccines are safe
  - Epidemiological studies performed
  - 2003: GACVS and 2004**:** EMA Public statement: « *No evidence of an association between autism / neurodevelopmental disorders and thiomersal-containing vaccines* »

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Potential alternative scenarios

1. Replacement with other preservatives
2. Elimination of Thiomersal
3. Reduction of Thiomersal content

1. Replacement of Thiomersal

- **Potential alternatives (when preservative)**
  - By agents already used as preservatives in some vaccines: 2 phenoxy-ethanol and phenol. Their anti-microbial effectiveness is not consistently equivalent to thiomersal and therefore not applicable to all vaccines.
  - By other agents to be identified, taking into account their compatibility with Ag/excipients and their own intrinsic potential toxicity (No long-term safety assessment exists). No solution is currently available**.**

- **Potential implications**
  - A suitable alternative may never be found
  - Substantial financial investment for research and development
  - Substantial development and validation work to demonstrate the equivalence to the original product on Quality /Safety /Efficacy (see next slide)
  - Investments will need to be recovered

7-10 y

Development and validation

- Potential significant changes to the manufacturing process
- Substantial development and validation work to demonstrate the equivalence to the original product on Quality /Safety / Efficacy inclusive of
  - Preservative/inactivating effectiveness studies
  - Characterization of Drug Substance/Drug Product,
  - Possible development of new analytical methods due to interference of new preservative/inactivating agent (matrix changes)
  - Equivalence in Quality Control testing,
  - Equivalence in Stability,
  - Pre-clinical & clinical data: bridging studies & safety data (especially if case of a new agent)
- High regulatory impacts (in all countries where the products is registered) for approval of a new preservative or inactivating agent

2. Elimination of Thiomersal

- **Potential alternative**
  - Not possible when thiomersal is used as an inactivating agent (only replacement can be envisaged)
  - Switch to single dose presentation or low-multi dose (2 dose w/o preservative if WHO approved)

- **Potential implications**
  - May reduce available manufacturing capacity (switch from 10D to 1D triggers 9-10 fold reduction) until investments to ramp up filling & finishing are approved and increase in capacity implemented
  - Comparable substantial development (as when thiomersal is replaced) to demonstrate the equivalence to the original product on Quality /Safety /Efficacy

4-5 y

  - High regulatory impact
  - May require substantial investment in time and financial resources for developing the new formulations
  - Investments will need to be recovered

3. Reduction of Thiomersal content

- **Potential implications**

3-5 y

- Also requires demonstration of comparability and thus substantial investment in time and financial resources for developing the new formulation
- High regulatory impact
- Still **may not meet the current WHO specifications**
- Investments will need to be recovered

All potential alternatives

Shared implications

- Additional investments
- Long implementation time (development, validation and regulatory steps)

Shared impacts

- Need to recover investments
- Potential risks on supply side

The current market environment raises challenges towards such investments, especially in case of an immediate mercury ban.

Risk that some manufacturers discontinue some vaccine production.

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Evidence-based Policies

- Global decisions and policies should
  - be **based on science** and
  - consider **periodic scientific review of evidences**.

- It is important
  - to ensure that **the entire health stakeholders community is represented** and involved in the discussions, considering that an immediate ban of thiomersal containing vaccines will have a possible negative impact on public health.
  - **to measure and to transparently communicate** to decision makers **the impact on all stakeholders**
  - to provide **a consistent and long term policy direction** for future vaccine presentations

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General principles

In our view the following principles should apply to the decision

- Focus should be on the **major exposure to / source of** environmental release of mercury.
- Respect of the autonomy and responsibility of national/regional **regulatory authorities to assess the benefit/risk** of each vaccine
  - E.g.: the decision to withdraw a vaccine is made with an appropriate timing for action which takes into account the public health impact.
- Respect for member states **decision making process**
  - E.g.: the choice of single or multi-dose presentation should be made by countries themselves (healthcare infrastructure, public health needs)
- Consider **the broader impact** to switch to thiomersal free vaccines
  - Environemental (negative) impact: by increasing the worldwide energy required for transportation, storage and also increasing the waste treatment
  - Programmatic (positive) impact: by decreasing the wastage (vaccine doses and antigens) and by improving HCW-friendliness and vaccination acceptance

Conclusions

- Safety
  - Based on the results of population-based epidemiological studies, there is **no evidence of association** with thiomersal containing vaccines and specific neurodevelopmental disorders. **The benefit of vaccination far outweighs the risk, if any, of exposure to thiomersal-containing vaccines.**

- Access
  - A complete immediate ban of thiomersal containing vaccines may negatively impact **the availability** and **the use** of life-saving vaccines, especially in developing countries.

Recommendations

- Short term
  - Considering that an immediate and complete removal of thiomersal containing vaccines from the market is not scientifically justified, and has a significant public health impact, **we recommend WHO to support the exclusion of vaccines from the UNEP Mercury Treaty (and allows the availability of raw material).**

- Long term
  - Continuous evidence-based assessment of the health and environmental impact of use of Thiomersal and **country demand** should inform WHO policy-making on thiomersal use in vaccines.
  - **We recommend a long term WHO Policy on thiomersal use which defines a realistic timing for future request of switching.**

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Thank you