Substituting Thimerosal Preservative used in Vaccines: FDA perspective

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Objectives

- Requirement for preservative in multi-dose vaccine formulations
- Food & Drug Modernization Act of 1997 (FDAMA 1997)
- Data review
- US licensed childhood vaccines
- Preservative used in US licensed vaccines
- Substituting Thimerosal preservative in US licensed vaccines

Use of Preservative in Vaccines

- Preservatives are compounds that kill or prevent the growth of microorganisms, particularly bacteria and fungi
- Used in vaccines to prevent microbial growth in the event that the vaccine is accidentally contaminated, as might occur with repeated puncture of multi-dose vials
- In some cases, preservatives are added during manufacture to prevent microbial growth

Use of Preservative in Vaccines

- United States Code of Federal Regulations (the CFR) requires, in general, the addition of a preservative to multi-dose vials of vaccines; [21 CFR 610.15(a)]
- Thimerosal
  - An organic mercury-containing preservative used in US-licensed vaccines since the 1930s
  - Primary purpose is to prevent microbial growth during storage and use
  - Used in manufacturing process for some vaccines (e.g., inactivation of vaccine antigens in whole-cell pertussis vaccine)
  - Long record of safe and effective use preventing bacterial and fungal contamination of vaccines

Examples of US Licensed Pediatric Vaccines

Vaccine	Tradename	Hg Concentration	Thimerosal as a preservative
DTaP	Infanrix	Free	no
	Daptacel	Free	no
DTaP-HepB-IPV	Pediarix	<0.0125 µg Hg/0.5mL	no
Pneumococcal conjugate	Prevnar 13	Free	no
Inactivated Poliovirus	IPOL	Free	no
Varicella (chicken pox)	Varivax	Free	no
Rotavirus	Rotateq/Rotarix	Free	no
Mumps, measles, rubella	M-M-R-II	Free	no
Hepatitis B	Recombivax HB	Free	no
	Engerix B	Free	no
Haemophilus influenzae type b conjugate (Hib)	ActHIB	Free	no
	PedvaxHIB	Free	no
Hib/Hepatitis B comb.	Comvax (M)	Free	no
Influenza	Fluzone	12.5 µg/0.25 mL dose 25 µg/0.5 mL dose	yes
	Fluzone	Free	no
	Fluvirin	25 µg/0.5 mL dose	yes
	Fluvirin	<1ug Hg/0.5mL dose	no
Influenza, live	FluMist	Free	no

Preservatives used in US licensed vaccine

Preservative	Vaccines
Phenol	Typhoid Vi Polysaccharide (Typhim Vi; Sanofi Pasteur, SA) Pneumococcal Polysaccharide (Pneumovax 23; Merck & Co, Inc)
Benzethonium chloride	Anthrax (Biothrax; Emergent BioDefense Operations Lansing Inc.)
2-phenoxyethanol	Inactivated Polio Virus vaccine (IPOL; Sanofi Pasteur, SA)
Thimerosal	Tetanus Toxoid Influenza Multi-Dose presentations

Alternatives to Thimerosal Preservative

- Some have suggested the use of 2-phenoxy ethanol (2-PE) as an alternative to thimerosal-preservative
- Presence of 2-PE in US licensed vaccines:
  - There is 1 US licensed vaccine, IPV, in which 2-PE is used as a preservative (Sanofi Pasteur)
  - Daptacel contains 2-PE as a vaccine ingredient, **not** as a preservative
  - INFANRIX does **no longer** contain 2-PE as preservative or an ingredient

Alternative to Thimerosal preservative (cont.)

- Several studies published in the literature compared the preservative effectiveness of 2-PE to thimerosal used in vaccines, e.g.,
  - Komatsu et al showed that 2-PE has weaker antimicrobial activity than thimerosal against yeast and fungi in DPT vaccine
    - J. Health Science, 48(1): 89-92 (2002)
  - Khandke et al showed that 2-PE provided a superior antimicobial effectiveness over thimerosal for a multi-dose Prevenar13 formulation
    - Vaccine, 29 (41):7144-7153 (2011)
  - Unpublished data conducted during clinical development show that 2-PE did not pass the preservative effectiveness test when used with some childhood vaccines
- Data available are limited and inconclusive
- Preservative effectiveness evaluated using different compendial methods (US, Japanese, and European)

Alternative to Thimerosal Preservative (cont.)

- Thimerosal preservative containing vaccines have been proven safe under the applicable statutory and regulatory requirements
- Substituting thimerosal preservative in currently licensed vaccines has the potential to modify the stability, safety and effectiveness of these vaccines

Alternative to Thimerosal Preservative (cont.)

- 21 CFR Section 610.15(a) provides:
  - All ingredients used in a licensed product, …, shall meet generally accepted standards of purity and quality. Any preservative used shall be sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient. . .
- FDA evaluates whether a preservative contained in a biological product is at such levels that the finished product itself, when used at the recommended dose, is not toxic to the recipient
- Preservatives are not examined in isolation, rather, 21 CFR 610.15(a) specifically directs that preservatives be examined in the context of the overall product and the recommended dose

Alternative to Thimerosal Preservative (cont.)

- Substituting thimerosal preservative in a vaccine would require a manufacturer to establish, through carefully controlled nonclinical and clinical trials and other data, that the vaccine, when formulated with the substitute preservative is safe and effective for each of its intended uses.
- Studies may include
  - Immunogenicty evaluations
  - Pre-licensure safety studies
  - Post-licensure safety studies

Alternative to Thimerosal Preservative (cont.)

- If alternatives to thimerosal preservative are pursued manufacturers will need to supplement their BLA with the following information
  - Data from preservative effectiveness testing
  - Data from preclinical studies demonstrating the safety and effectiveness of the substitute preservative when tested with the vaccine
  - Data from clinical studies demonstrating that that the substitute preservative does not adversely effect the safety and effectiveness of the vaccine product

Summary

- In the US only a small number of licensed and approved products still contain thimerosal preservative
- Data from epidemiological studies indicate that there is no relationship between thimerosal-preservative containing vaccines and autism or other developmental disorders
- Available evidence supports FDA's conclusion that all currently licensed vaccines containing thimerosal preservatives have been proven safe under the applicable statutory and regulatory requirements.
- Comprehensive development program needed to establish the safety and effectiveness of vaccines if thimerosal preservative is substituted with alternate preservatives