



International Alliance for Biological Standardization

# Experience with Alternatives to Thiomersal from other Fields

## A Survey amongst IABS Members

Presented by Johannes Löwer

WHO Informal Consultation to develop further  
guidance on vaccines for INC4

Geneva, April 3 and 4, 2012



International Alliance for Biological Standardization

## IABS

The International Alliance for Biological Standardization (IABS) is a non-profit association located in Geneva, Switzerland.

IABS mission is to contribute to the scientific and medical advancement of biologicals by facilitating the communication among those who develop, produce and regulate biological products for human and animal health.



## Survey amongst IABS Members

Responses from:

Belgium

Denmark

France

Germany

The Netherlands

Argentina

Australia

Canada

China

India

Peru

Response rate: 10%



## Questionnaire 1

1. In the examples you are familiar with, what is or was the use of thiomersal?
2. In which cases could thiomersal be replaced and by what means?
3. In which cases could thiomersal not be replaced although attempted and for what reason?
4. In which cases was a replacement of thiomersal not attempted and for what reasons?



## Questionnaire 2

5. What is the role of antimicrobial effectiveness (AME) testing as requested by US and European Pharmacopoeias?
6. Does the AME testing reflect the practical need?



## Question 1

In the examples you are familiar with, what is or was the use of thiomersal?

Thiomersal is most often used as preservative in multi-dose vials of the final product, but it might also be used in intermediates or during production.



## Response to Question 1

- Human vaccines
  - Thiomersal used to protect against microbial growth after opening of multi-dose vials (DTP, HBV, HIB, JE)
  - Thiomersal used in trace amounts during the production process (e.g. D and T toxoids)
  - Thiomersal as inactivating agent for pertussis vaccine (together with heat)
- Veterinary vaccines
  - Thiomersal used to protect against microbial growth, prior to use, in many veterinary vaccines
  - Thiomersal is generally not used for intermediates



## Response to Question 1

- Sera (Anti-venoms)
  - Thiomersal as preservative in the equine hyperimmune serum used in the production of anti-venoms
- Biotherapeutics?
  - “By the time that biotherapeutics came along, it was widely acknowledged that thimerosal had many disadvantages, and was completely unacceptable in Japan. So when a preservative was required for a multidose biotherapeutic, it was typical to utilize other more acceptable preservatives such as methyparabenz or most commonly metacresol. I do not know of a single biotherapeutic which contains thimerosal.”



## Question 2

In which cases could thiomersal be replaced and by what means?

Please describe your experience where thiomersal could be replaced.

Response:

Replacement of multi-dose vials by single-dose vials (human vaccines).

Strict adherence to Good Manufacturing Practice.

Replacement of thiomersal.



## Examples for Replacements

Early 1990ies: replacement of thiomersal by 2-phenoxyethanol in DTaP vaccine

Phenol in anti-venoms

<b>Preservative</b>	<b>Marketed Vaccines</b>
<u>Phenol</u>	Typhoid Vi Polysaccharide (Typhim Vi; Sanofi Pasteur, SA) Pneumococcal Polysaccharide (Pneumovax 23; Merck & Co, Inc)
Benzethonium chloride (Phemerol)	Anthrax (Biothrax, Emergent biodefense Operations Lansing Inc)
2-Phenoxyethanol	IPV (IPOL, Sanofi Pasteur, SA).



## Question 3

In which cases could thiomersal not be replaced although attempted and for what reason?

Please describe your experience where thiomersal could not be replaced.



## Required Properties for a Preservative

- Antimicrobial activity (as demonstrated according to pharmacopoeias)
- Compatibility with formulation (aqueous, adjuvant etc.)
- No negative effect on antigen integrity



## Impact of Thiomersal on Antigen Integrity

- IPV: => 2-phenoxyethanol
- FMD: => antibiotic (as a preservative is requested by the local pharmacopoeia)



## Question 4

In which cases was a replacement of thiomersal not attempted and for what reasons?

- Technical constraints (see above)
- No market pressure (vet. vaccines except for pet vaccines)
- Regulatory consequences (high costs for the activities needed to obtain approval/registration, loss of minor use, minor species (MUMS) vaccines)



## Questions 5 and 6

What is the role of antimicrobial effectiveness (AME) testing as requested by US and European Pharmacopoeias?

Does the AME testing reflect the practical need?

„Generally most preservatives used seem to have an effect in the field. We don't really have information on how the AME requirements are related to usefulness in the field, but it is clear that sometimes they are prohibitive on the choice of preservatives that can be used for a certain composition.”



## EP: 5.1.3. EFFICACY OF ANTIMICROBIAL PRESERVATION

Table 5.1.3.-1. - Parenteral ► preparations, eye preparations, intrauterine preparations and intramammary preparations ◀

		Log reduction				
		6 h	24 h	7 d	14 d	28 d
Bacteria	A	2	3	-	-	NR
	B	-	1	3	-	NI
Fungi	A	-	-	2	-	NI
	B	-	-	-	1	NI
NR: no recovery. NI: no increase ► in number of viable micro-organisms compared to the previous reading. ◀						

The A criteria express the recommended efficacy to be achieved. In justified cases where the A criteria cannot be attained, for example for reasons of an increased risk of adverse reactions, the B criteria must be satisfied.



## EP: VACCINES FOR HUMAN USE

The efficacy of the antimicrobial preservative is evaluated as described in chapter 5.1.3. If neither the A criteria nor the B criteria can be met, then in justified cases the following criteria are applied to vaccines for human use: bacteria, no increase at 24 h and 7 days, 3 log reduction at 14 days, no increase at 28 days; fungi, no increase at 14 days and 28 days.

# EP: Summary

		Log reduction				
		6 h	24 h	7 d	14 d	28 d
Bacteria	A	2	3	-	-	NR
	B	-	1	3	-	NI
	Vaccines	-	NI	NI	3	NI
Fungi	A	-	-	2	-	NI
	B	-	-	-	1	NI
	Vaccines	-	-	-	NI	NI
NR: no recovery NI: no increase						



International Alliance for Biological Standardization

## Veterinary Vaccines

In some countries no request for AME testing, instead only

stability testing



International Alliance for Biological Standardization

Thanks

to the responding IABS members