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Meeting report

Thiomersal in vaccines: a regulatory perspective

WHO Consultation, Geneva, 15-16 April 2002

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1. Introduction

Over the past decade, safety concerns have been raised over the use of the organo-mercurial preservative ethyl mercury, often called thiomersal, in vaccines. Although these safety concerns are theoretical, the perception of risk remains and has led to initiatives in some countries to eliminate, reduce or replace thiomersal in all monodose and multidose vaccine presentations.

The question arises as to whether there is compelling scientific or medical evidence for removing thiomersal from vaccines [1,2,3,4,5,6]. Also, what evidence is needed to ensure that vaccines from which thiomersal has been removed are as safe and efficacious as those products already licensed. The strategy for the elimination, reduction or replacement of thiomersal in vaccines therefore raises issues relating not only to the toxicity of ethyl mercury and the efficacy of preservatives in vaccines, but also to the effects of thiomersal on the quality, safety and efficacy of the vaccines themselves. Thiomersal is used in vaccines not only as a preservative but also sometimes as an inactivating agent during production.

WHO policy [7] on the use of thiomersal is clear. The Organization continues to recommend the use of vaccines containing thiomersal for global immunization programmes since the benefits of using such products far outweigh any theoretical risk of toxicity [8,9]. However, since some countries were considering removing thiomersal from both monodose and multidose vaccine presentations, it was important to better understand some of these complex issues before taking this step. A consultation, organized by the WHO Quality Assurance and Safety of Biologicals

Team, was therefore held in Geneva, 15-16 April 2002, to review experiences with the removal of thiomersal from vaccines and to discuss related regulatory implications. It was attended by representatives from National Regulatory Authorities (NRAs) and the vaccine industry (list of participants in Annex) and chaired by Dr Franz Reigel (Switzerland); Dr Roland Dobbelaer (Belgium) served as a rapporteur. The meeting was not an isolated event, but part of a co-ordinated programme of work on the issue of thiomersal undertaken by the whole WHO Department of Vaccines and Biologicals.

The objective of the Consultation was to review, in a global forum, the experience of eliminating, reducing and/ or replacing thiomersal in vaccines and to discuss the potential impact of these changes on the quality, safety and efficacy of vaccines. The review involved NRAs and vaccine manufacturers from developing and industrialized countries and the focus was on vaccines already licensed with thiomersal.

The main issues considered were:

- Understanding the function of thiomersal in vaccines (past and current view)
- General and specific consequences of eliminating, reducing and/or replacing thiomersal in vaccines already licensed with thiomersal
- Regulatory requirements and their implications
- Relevance of existing data regarding production and control, pre-clinical testing, clinical trials and post-marketing surveillance generated using

thiomersal-containing formulations. Not all data may be relevant when the formulation is changed.

- How much data will be required to demonstrate that a new product is at least of the same quality as the previous one containing thiomersal, including product stability, safety and efficacy.

It was not the primary intention of this meeting to discuss the policy of using or not using thiomersal, nor to discuss the effectiveness of reduced levels of thiomersal, or a new preservative, in preventing microbial contamination.

2. Lessons learned from recent experience

1.0. Elimination of thiomersal from Tick Borne Encephalitis (TBE) vaccine: NRA experience

It was reported by the Paul Ehrlich Institut, Germany, that thiomersal was eliminated from a Tick Borne Encephalitis vaccine (TBE), produced by one manufacturer, in 1999. A new TBE vaccine that did not contain thiomersal nor human serum albumin was approved and used in 2000. Since that time, increased reactogenicity of TBE vaccine had been reported in Germany. Data from the spontaneous reporting system showed a significant increase in all fever reports as well as an increase of serious adverse events. All lots that caused fever reactions were found to pass the Limulus-Amebocyte-Lysate (LAL) test and also the rabbit pyrogen assay. In this particular case, the problem was shown to be product-related and not a lot related issue.

Investigations at the Paul Ehrlich Institut, focused on the comparison of the induction of fever-related cytokines by vaccines containing thiomersal and vaccines without thiomersal using an *in vitro* system. A new test for pyrogens based on cytokine production after exposure of whole blood to a pyrogen was described at the meeting. It is likely that this test may detect pyrogens that are undetected by the established models. Results showed an inhibition of IL-1, IL-6, and TNF α synthesis by thiomersal and that this was independent of the pyrogenic substance used. There are species differences in susceptibility to non-endotoxin pyrogens. The mechanism of monocyte modulation by thiomersal is unknown (e.g., monocytes can serve as direct or indirect targets). TBE vaccine without thiomersal was shown to be reactive in the model and restoring the thiomersal content could abolish reactivity.

Further research is needed to understand and define the mechanism of this model and its relevance to the pyrogenicity found in humans following immunizations with TBE vaccine where both thiomersal and human albumin had been removed.

2.2. Thiomersal in vaccines - industry experience

2.2.1. Experience in industrialized countries

The current approach of industry to new vaccines is to develop thiomersal-free products in mono-dose presentations. If a preservative is needed, an alternative to thiomersal such as 2-phenoxy-ethanol (2-PE) is preferred.

The following vaccines were discussed as recent examples where thiomersal had been eliminated, reduced and/or replaced. These vaccines produced by different manufacturers had already been licensed as thiomersal-containing products and were in use as multi-dose or mono-dose presentations.

1. In the case of rDNA hepatitis B vaccine (Hep B vaccine) from one manufacturer, the omission of thiomersal as a preservative resulted in a formulation containing only residual amounts of thiomersal (a reduction from 50µg/mL to 1-2µg/mL in the final product). The trace amounts of thiomersal remaining in the product is due to its use during early production stages. In this case there was a trend towards a higher measured HBsAg content both at release and over time. A higher activity in the mouse immunogenicity assay was also observed. The combination of residual thiomersal with 2-phenoxy-ethanol showed adequate antimicrobial effectiveness when tested according to the assays demanded by European Pharmacopoeia for the effectiveness of preservatives * (Ph.Eur test). For the two rDNA hepatitis B vaccines currently on the market in the European Union (one thiomersal-reduced and one thiomersal-free), post-marketing clinical safety and immunogenicity studies have been requested by the Committee for Proprietary Medicinal Products (CPMP) of the European Medicines Evaluation Agency.

2. When the thiomersal content of Diphtheria, Tetanus and whole cell Pertussis vaccine in combination with Hepatitis B vaccine (DTwP - HepB vaccine) from one manufacturer was reduced from 50µg/mL to 15µg/ml, no differences were observed between quality control data of the original vaccine and that with reduced thiomersal levels at release, or in preliminary stability data, including accelerated stability data. It

was reported that the residual formaldehyde in DTwP-HepB vaccine, in combination with the reduced levels of thiomersal, provided adequate antimicrobial coverage.

3. The complexity of removing thiomersal from single dose presentation of influenza and DTaP vaccines was highlighted. In the case of influenza vaccine, the use of different strains, sites of manufacturing and presentations (ampoules, syringes), as well as the introduction of changes at different levels of the manufacturing process (monovalent bulk/ final bulk) had made the process of thiomersal removal complex. For influenza and DTaP vaccines alike, a huge amount of quality control testing had been carried out on numerous lots. Changes in the bulk manufacturing process has required extensive process validation and additional quality control tests and was considered as a type II variation according to EU regulation [11]. Stability tests on several batches, at different levels (bulk and final lot) and at different temperatures (+5°C and +25°C) were performed in parallel with thiomersal containing batches of the same product. No differences were observed in quality control test results. Generally, changes to the thiomersal content of these vaccines required more than 2 years of technically complex work, financial investment, well-trained staff and regulatory approval.

2.2.2. Experience in developing countries

In the case of the DTwP group of vaccines, including DTwP-Hep vaccine, thiomersal is not only used as a preservative but also frequently as an inactivating agent for the whole cell pertussis component, hence making its complete removal from the product difficult. Furthermore, the requirements of at least one National Pharmacopoeia demand that all DTwP vaccines and Hepatitis B vaccines contain a

preservative; such vaccines have thiomersal concentrations in a range from 0.005 to 0.02%. If a decision is taken by an NRA to reduce or to replace thiomersal by another preservative, then such a product would have to be exhaustively studied, including a clinical trial, to prove the efficacy of the product. Such changes would also call for changes in the Pharmacopoeial requirements. In any case, the removal or reduction of thiomersal will be possible only in the case of single dose presentations. For multi-dose presentations used by national immunization programmes and UN procurement agencies (such as UNICEF and PAHO), it will be very difficult to change. Thiomersal has proved to be a very effective preservative for this group of vaccines.

A study of the antimicrobial effectiveness of reduced concentrations of thiomersal (reduced to 0.001-0.01% from 0.005-0.02% or 50-200µg/dose) was presented. The need to make the Ph.Eur test more relevant to use in field conditions was discussed. It was proposed that further information be collected on the rationale for the Ph.Eur test parameters, in particular the choice of challenge dose and strains.

2.2.3. Conclusions from the vaccine industry

- The decision has already been taken by companies in many industrialized countries to eliminate, reduce and/ or replace thiomersal in monodose presentations of vaccines.
- Elimination, reduction or replacement of thiomersal in vaccines in developing countries is under consideration but a final decision has not yet been taken.

- It should be recognized that the process of elimination, reduction and/ or replacement of thiomersal in vaccines is more complex than initially foreseen due to the following considerations:

- Requirements by NRAs regarding changes in the thiomersal content are highly variable.

- Lengthy and costly clinical trials may be needed.

- There is no guarantee of obtaining a vaccine of equivalent quality, safety and efficacy following reduction and /or removal of thiomersal from an existing product.

- Preservative in the final bulk formulation is fairly easily eliminated. However where existing products involved the use of mercurial compounds in the intermediate production stages, it may be essential to continue use of thiomersal at these stages of manufacture, resulting in the presence of mercury traces in the final product.

- An improvement in aseptic production technology might be required if thiomersal is eliminated from the production process.

Multi-dose presentations raise additional concerns:

- A real risk of contamination during field use. The efficacy of the preservative in the new final formulations with reduced thiomersal and/ or alternative preservative in multidose presentation may be insufficient to ensure continued sterility of vaccines under currently used field conditions.
- The potential impact on immunization practice, in particular, the operation of the multi-dose open vial policy remains open?

3. Review of the positions of the National Regulatory Authorities worldwide

3.1. European position

The CPMP recommendations [10] were presented. The reduction, elimination or substitution of thiomersal in vaccines requires an extensive and detailed research and development programme to ensure appropriate quality, safety and efficacy of the new products. This may take considerable time to complete.

The CPMP has concluded that although there is no evidence of harm caused by the level of exposure from vaccines, it would be prudent to promote the general use of vaccines without thiomersal and other mercury-containing preservatives, particularly for single dose vaccines. However, in some countries requirements may be more strict. In Italy, for example, manufacturers have been instructed to apply for a type II variation [11] to remove thiomersal from single dose vaccine preparations before 31

December 2002. All batches containing thiomersal or any other mercury containing preservative will be withdrawn from the market before June 2003 [12].

While there was a general consensus in Europe that all vaccines presented in multidose containers should contain a preservative, it is possible that even for multidose containers, the regulations on use may change so that once a vial is opened, its contents should be dispensed within a limited period of a few hours. In such instances there may be no need for a preservative.

For any given situation, the potential impact on quality, safety and efficacy would need to be evaluated. It may be necessary in some cases to conduct clinical studies to address the impact of a change on safety and efficacy, but this would be decided upon on a case by case basis.

If procedures are introduced to remove mercury compounds from a vaccine following their use during production, then these should be described in detail and their capacity for removing thiomersal should be demonstrated and validated on at least three batches. A specification for the residual concentration in the finished product should be set.

Where thiomersal is the approved inactivating agent used during the production process, and a new agent is being considered, then a validation study with the new inactivating agent is required to demonstrate that its inactivating capacity is at least equivalent to that of the approved agent on at least three independent inactivation runs.

3.2. Thiomersal in vaccines licenced in United States (USA)

There are no guidelines by Center for Biological Evaluation and Research, Food and Drug Administration (CBER, FDA) regarding the thiomersal elimination. FDA letters to manufacturers did not consider data that need to be submitted in the case of thiomersal elimination, reduction and replacement in vaccines. The issues were discussed with the vaccine industry on a case-by-case basis. The goals, in order of priority, are to reduce or remove thiomersal from all routinely recommended pediatric vaccines, influenza virus vaccines (pregnant women and selected infants/children) and finally all vaccines. The approaches are to convert to single-dose vials or pre-filled syringes where a preservative is not required and to develop new formulations with alternative preservatives, what is to be considered as more difficult.

Generally, vaccines for the US market need to be free of organo-mercurial preservatives, although some traces of thiomersal as a residual component from a production process are acceptable (e.g. less than 1 microgram per dose). In the case of elimination of thiomersal, issues that need to be considered are changes in potency or stability, reversion to toxicity, and sterility of these products. Clinical data may be necessary for formulation changes.

Recent experience in USA has not revealed any problem regarding the quality, safety and efficacy of vaccines with the changes of thiomersal content.

3.3. Thiomersal in vaccines - an Indian Perspective

In India, thiomersal is present in most of the vaccines. Licensed vaccines on the Indian market can be either manufactured locally or imported. Most, but not all, of these vaccines contain thiomersal as a preservative at a concentration of 0.01%. Some contain other preservatives, like phenol and 2-phenoxyethanol. The majority of these vaccines are being filled in multi-dose vials, and therefore need to contain a preservative.

However, single dose presentations of some of these vaccines are formulated without preservatives. Most of these single dose preparations are either ready to use pre-filled syringes or are lyophilized products.

In India, any deviation from the master formula requires regulatory intervention. Such products must be treated as new drugs and have to undergo the usual licensing process, as for new drugs [13]. In such cases, stability and toxicity data have to be generated and the products have to undergo clinical trials. However, some of the requirements of the licensing process are considered on a case-by-case basis for pre-established products.

Should lower limits of thiomersal be considered, then extensive data need to be generated on the efficacy of use of lower concentrations of thiomersal as a preservative in multi dose vials. This will help to reduce the total intake of thiomersal by the vaccinees. Lower concentrations of thiomersal, if found effective, will require minimum regulatory intervention for its use in the vaccine.

3.4. Experience with thiomersal elimination in hepatitis B vaccine in Cuba

The Cuban NRA had experience relating to the elimination of thiomersal from the recombinant DNA derived hepatitis B vaccine. The formulation with thiomersal was first licensed in Cuba in 1990. Thiomersal-free hepatitis B vaccine was then licensed in 2001. The manufacturer performed real time, real conditions and accelerated storage conditions studies, at two stages of vaccine production (bulk and final product). Stability studies were performed over a 12 month period for 3 batches of thiomersal-free vaccine in parallel with 3 batches of thiomersal-containing vaccine. Characteristics evaluated were potency, pH, sterility and percent of adsorption and antigen quantification. In addition, pyrogenicity, aluminium concentration and nonspecific toxicity were performed. Clinical trials were not required.

3.5. Experience with thiomersal elimination in vaccines in Indonesia

The Indonesian NRA had already been involved in the evaluation and licensing approval of thiomersal-free hepatitis B vaccine, in monodose presentation and a DTaP produced by a manufacturer from the developed country. Within the Indonesian regulatory framework such vaccines are regarded as a new product, and therefore a clinical trial is needed for the immunogenicity aspect. Evaluation was performed on the consistency of 3 consecutive batches with respect to stability, sterility and other physico-chemical characteristics. Data on immunogenicity and safety were also required and evaluated.

A one year study by Biofarma, a vaccine manufacturer in Indonesia, aimed at assessing the stability of thiomersal-free hepatitis B vaccine in uniject presentation, is currently underway.

3.6. Experience with thiomersal elimination from vaccines in Switzerland

In general, Switzerland follows the EU recommendations [10]. Most of the vaccines in Switzerland, especially those recommended for routine infant vaccination are available in thiomersal-free or thiomersal-reduced presentations.

In the past, the Swiss NRA requested that manufacturers submit the following data for products where thiomersal had been reduced or eliminated:

- Data from a clinical trial with a reduced number of participants (immunogenicity data). In some cases, safety data were requested.
- The establishment of a proactive post licensure surveillance programme with the submission of periodic safety reports (every 6 months for two years, once a year for the following three years).
- Stability data

In addition to the experience presented, there were also considerations regarding the regulatory expectations of the Brazilian NRA.

4. Conclusions

The main conclusions of the meeting were as follows:

- Recommendations for the removal of thiomersal developed by health authorities in some countries are mainly driven by public perception of risk and not by any scientific evidence of toxicity.
- Limits for chronic exposure to methyl mercury derivatives from food should not be used to set limits for acute exposure to ethyl mercury derivatives (e.g., thiomersal) that can occur through vaccination.
- From a regulatory point of view, no additional substance such as a preservative should be added to vaccine formulations if there is no clear need for doing so.
- Making changes to the thiomersal content of vaccines already licensed with thiomersal is a complex issue that requires careful consideration. The need for new data regarding the quality, safety and efficacy of these products will have to be taken into account before the decision to remove thiomersal is made. Any decision regarding the removal of thiomersal in vaccines should be science-based.
 - There should be a clear rationale for any change in the formulation taking into account different implications of reducing or removing thiomersal from the production steps and/ or from the final stage of production.

- Any change in the formulation could have a serious impact on the quality, safety and efficacy of vaccines and should be considered on a case-by-case basis. Generally, these products are considered as new products and in some cases may require clinical trials.

- The use of thiomersal during production may cause some chemical changes to the antigen(s) that would require full characterization of the new product if thiomersal were it to be completely removed (hepatitis B, whole cell pertussis vaccines).

- When viewed from a regulatory perspective, reducing thiomersal is simpler and has less consequences than eliminating and replacing thiomersal altogether.

A number of issues were addressed for further considerations:

- There should be additional investigations of thiomersal in vaccines apart from a role as a preservative including:
 - its anti-pyrogenic effect (inhibition of monocyte activation) *in vitro*
 - the mechanism of this model and its relevance to pyrogenicity in humans
- The efficacy of its preservative properties under the field conditions should be established
- The potential implications for immunization practice should be evaluated

Following this Consultation, WHO guidelines on regulatory expectations related to the elimination, reduction and replacement of thiomersal in vaccines were developed and adopted by the Expert Committee on Biological Standardization at its 52nd meeting, in February 2003. These guidelines are available in electronic form on the WHO Biologicals Website (www.who.int/biologicals) and will be also printed as an Annex in the Report of the 52nd meeting of the ECBS (2003).

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Appendix I

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** The efficacy of the antimicrobial preservative is evaluated as described in
chapter 5.1.3 of the Ph.Eur. If neither the A criteria nor the B criteria can be met then
in justified cases at least the criteria stated in the general monograph Vaccines for
Human Use (Monograph No. 0153) have to be met.*