

Technical Report Series No.

WHO Guidelines on regulatory expectations related to the elimination, reduction or replacement of thiomersal in vaccines

INTRODUCTION

Thiomersal (also known as thimerosal, merthiolate) is an organo mercurial derivative of ethyl mercury which has been used very widely, and for a very long time, as a preservative in vaccines in their final bulk formulations. Its primary purpose has been to prevent microbial growth in the product during storage and use. It has also been used during vaccine production both to inactivate certain organisms and toxins and to maintain a sterile production line. In recent years safety concerns have been raised over its use in vaccines, especially those given to infants. These concerns have been based primarily on data regarding the toxicity of a related substance, methyl mercury, and from data on chronic exposure to mercury via the food chain.

Such safety concerns have, however, led to initiatives in some countries to eliminate, reduce or replace thiomersal in vaccines, both in monodose and multidose presentations. Immune-mediated reactions to products containing mercury (mainly contact allergy as a manifestation of delayed-type hypersensitivity) can occur in some humans (1). Although this contributed to concerns about vaccine safety, it was not a major force leading to the subsequent recommendation by the authorities in some countries for the elimination of thiomersal from vaccines. It is important to note that concerns about the toxicity of thiomersal are theoretical and there is no compelling scientific evidence of a safety problem with its use in vaccines, although public

perception of risk remains in some countries (2,3,4,5,6,7). WHO policy is clear on this issue, and 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).

The primary role of thiomersal in vaccines has been considered to be that of a preservative, but data indicate that there are other effects of this additive on vaccine antigens which need to be taken into account if consideration is being given to its elimination, reduction or replacement. Indeed, in some production processes thiomersal is used in the inactivation of vaccine antigen along with heat, for example in the case of whole cell pertussis vaccine. Should a national health authority or a manufacturer decide to eliminate, reduce, remove or replace thiomersal in vaccines, then the strategy chosen may affect not only the subsequent ability of microbial contaminants to grow in vaccine preparations, but also vaccine quality, safety and efficacy. The question therefore arises as to what evidence is needed to ensure that a vaccine where the thiomersal content has been altered will be as safe and efficacious as the already licensed product.

A consultation was held in Geneva, 15-16 April 2002, to review experiences with the removal of thiomersal in vaccines and to discuss related regulatory implications. It was attended by representatives from national regulatory authorities and the vaccine industry from both industrialized and developing countries. The objective of the consultation was to review, in a global forum, experiences 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 the products as

well as to consider regulatory requirements and their implications. A report of the meeting is available and could be found on the following web site www.who.int/biologicals. The focus was on vaccines already licensed with thiomersal when used as an inactivating agent and/ or as a preservative.

Making changes to the thiomersal content of vaccines already licensed with this preservative is a complex issue that requires careful consideration. It should be borne in mind that any change in the formulation may have an important impact on the quality, safety and efficacy of vaccines. Experience shows that eliminating or reducing thiomersal from an existing product can have some unexpected effects on vaccine quality, safety and efficacy. Effects on vaccine stability might also be expected. The amount of additional data required to demonstrate that a product with an altered thiomersal content is at least of the same quality as the previous licensed one containing thiomersal, including product stability, safety and efficacy, will need to be evaluated on a case by case basis. Any decision regarding the elimination or reduction of thiomersal in vaccines should be science-based. There should be a clear rationale for any change in the formulation taking into account the different implications of reducing or eliminating thiomersal from the production steps and/ or from the final stage of production. In some cases the resulting products should be considered as new vaccines and may require further clinical trials.

SCOPE

In this guidance document, the general principles of evaluating a vaccine following the elimination, reduction, removal or replacement of thiomersal from an

already licensed vaccine are discussed with particular attention being given to the regulatory expectations for each of the above possibilities. It is not the intention of this guidelines 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. Useful guidance on the reduction, elimination or substitution of thiomersal in vaccines has also been developed by the Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMA), (9).

TERMINOLOGY

The following terminology may be helpful in clarifying different options regarding altering the content of thiomersal in vaccines:

Thiomersal elimination indicates that thiomersal is not used at any stage of production. Such product is considered as a thiomersal - free vaccine.

Reduction of thiomersal means that thiomersal is used at some stage of vaccine production but its amount has been reduced in comparison with the amount in the already licensed vaccine. Reduction of thiomersal, even if significant, results in residual levels of thiomersal and such a product is not considered to be a thiomersal - free vaccine.

Removal of thiomersal means that thiomersal was used during the production of vaccine and then removed at a certain stage of production. This also results in residual traces of thiomersal.

Replacement of thiomersal in vaccines means that thiomersal is not used at all and that another preservative is included instead. In this case, there is no thiomersal in the final product but another preservative is present.

Reduction and replacement of thiomersal in vaccines indicates that the amount of thiomersal used is reduced and another preservative is added. There are several possibilities regarding the stage of vaccine production at which thiomersal could be reduced and replaced. These changes result in traces of thiomersal in the final product.

Residual traces of thiomersal (or mercury) represent a residual amount of these substances in vaccines, which might occur following a significant reduction or removal of thiomersal in the product. Residual traces should be specified, usually with an upper limit, and validated assays to substantiate these claims should be established. In some cases an amount of less than 1 microgram (per dose) is considered as a trace.

REGULATORY EXPECTATIONS

Elimination of thiomersal

Thiomersal could be used as an inactivating agent, and /or as a preservative to protect the production line and/or added as a preservative at the final stage of vaccine production.

a) The elimination of thiomersal from an already licensed vaccine in which thiomersal was used at all stages (as an inactivating agent and/or as a preservative in the production line, and as a true preservative added during the final formulation steps) might be expected to have the maximum consequences on quality, safety and efficacy.

Therefore, the resulting product will need considerable re-evaluation such as: extensive characterization of the active substance and finished product in comparison with the existing product; comparative quality control testing and assessment of in-process controls, for example bioburden and endotoxin; comparative stability studies on intermediates, final bulk and finished product.

b) The elimination of thiomersal used as an inactivating agent and/or as a preservative in the production line will also require considerable re-evaluation, as described above.

c) The elimination of thiomersal added simply as a preservative at the final stage of vaccine formulation may be expected to have less consequences and therefore a more flexible approach might be considered.

Comparative pre-clinical data should also be obtained, focusing on immunogenicity and safety testing using *in vitro* and *in vivo* assays appropriate for the type of product being evaluated.

Reduction of thiomersal

In the case of reduction of thiomersal used as an inactivating agent or to protect the production process, re-validation of inactivation process as well as some additional tests (see elimination) in order to re-characterize the product will be required. Reduction of thiomersal, added as a preservative at the final stage of production, will require justification of the antimicrobial efficacy. Specifications for residual amounts and/or for reduced content of thiomersal as a preservative need to be set and validated assays to substantiate these claims should be established.

Removal of thiomersal

If thiomersal is used in the manufacturing process (e.g., as an inactivating agent or to ensure the sterility of the manufacturing process), its removal will require product characterization similar to that described under elimination. In the case where thiomersal is used as an inactivating agent, there is no need for any revalidation of the inactivation process since thiomersal removal occurs after inactivation. Thiomersal removal will result in residual traces of thiomersal in the final product. The procedure used to remove thiomersal should be fully described and validated. Specifications for the residual amount of thiomersal in the final product should be set and validated assays to substantiate these claims should be established.

Replacement of thiomersal

Replacing thiomersal in an already licensed vaccine, where thiomersal is used as an inactivating agent and/or preservative during the production process and/or in the

final product, will require considerable product characterization as well as preclinical evaluation. In addition, replacement of thiomersal used as an inactivating agent will require validation of the inactivation process. In the case of the replacement of thiomersal used as a preservative at the final stage, the antimicrobial efficacy of the new preservative should be justified. Specification for the new preservative in the final product should be set and validated assays to substantiate these claims should be established. Specific toxicity should be addressed in preclinical testing to demonstrate that an alternative inactivating agent and /or preservative which replaced thiomersal has no toxic effects.

Clinical trials and postmarketing surveillance

The need for clinical trials should be considered on a case by case basis. More extensive clinical trials are likely to be required in the case of elimination and replacement of thiomersal in vaccines compared to its reduction and/or removal.

The design and size of the studies will depend on the vaccine in question, the nature of the changes introduced and the results of product characterization and preclinical testing. The clinical trials should be based on the principles described in WHO guidelines on clinical evaluation of vaccines: Regulatory Expectations (10). In some cases, immunogenicity data may be sufficient for licensure but every effort should be made to continue safety and efficacy evaluation as a part of post-marketing surveillance.

Postmarketing surveillance is of critical importance especially if data obtained from clinical trials are limited. A period of active postmarketing surveillance should be undertaken following the introduction of a product with altered thiomersal content on to the market.

Antimicrobial efficacy

Where thiomersal at a reduced level, or an alternative reagent, is to be used as a preservative in a multidose presentation, the antimicrobial effectiveness should be evaluated and specifications set. The criteria to be met should be discussed with and agreed by the appropriate national regulatory authority on a case by case basis.

Labelling

The information on the label should be clear regarding the presence of thiomersal in the product. The label should follow the guidance given above in the section on Terminology. It is insufficient to indicate that a vaccine is "preservative-free". "Preservative-free" does not necessarily mean a thiomersal - free product. Thiomersal could still be used during production as an inactivating agent, resulting in traces of thiomersal in the final product, which are not intended to have a preservative function.

The label should indicate, as appropriate, the amount of thiomersal in the product or state that the product is thiomersal free.

REFERENCES

Adopted by the 53 rd meeting of the WHO Expert Committee on Biological Standardization, 17-21 February 2003. A definitive version of this document, which will differ from this version in editorial but not scientific detail, will be published in the WHO Technical Report Series.
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Adopted by the 53rd meeting of the WHO Expert Committee on Biological Standardization, 17-21 February 2003. A definitive version of this document, which will differ from this version in editorial but not scientific detail, will be published in the WHO Technical Report Series.

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Acknowledgement are due to the following for their comments and advice: Dr Manfred Haase, Paul Ehrlich Institute, Germany, Dr Bettie Voordouw, Medicine Evaluation Board, Hague, Netherlands, Dr Robert Pless, Population and Public Health Branch, Health Canada and Dr Maria Baca-Estrada, Biologics and Therapies Directorate, Health Canada.