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Annex 4
Guidelines on regulatory expectations related to the elimination, reduction or replacement of thiomersal in vaccines

Introduction

Thiomersal (also known as thimerosal, merthiolate) is an organomercurial derivative of ethylmercury that 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, methylmercury, and from data on chronic exposure to mercury from the food chain.

Such safety concerns have led to initiatives in some countries to eliminate, reduce or replace thiomersal in vaccines, both in single dose 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 reaction has contributed to concerns about vaccine safety, it was not a major force leading to the 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 that there is no compelling scientific evidence of a safety problem related to its use in vaccines, although public perception of risk has been reported in some countries (*2–7*). WHO policy is clear on this issue, and the Organization continues to recommend the use of vaccines containing thiomersal for global immunization programmes because 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 that need to be taken into account when considering its elimination, reduction or replacement. In some

production processes thiomersal is used in the inactivation of vaccine antigen together with heat, for example in the manufacture 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 in which the thiomersal content has been altered will be as safe and efficacious as the already licensed product.

A consultation attended by representatives from national regulatory authorities and the vaccine industry from both industrialized and developing countries was held in Geneva from 15 to 16 April 2002.[1] 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 at www.who.int/biologicals. The focus was on already licensed vaccines that include thiomersal as an inactivating agent and/or as a preservative.

Making changes to the thiomersal content of vaccines containing this preservative that are already licensed 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 a vaccine. Experience shows that eliminating or reducing thiomersal in 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 that takes 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

[1] A summary of the meeting was subsequently published as: Knezevic I, Griffiths E, Reigel F, Dobbelaer R (2004) Thiomersal in vaccines: a regulatory perspective. Vaccine, volume 22, pages 1836–41.

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 paid to the regulatory expectations for each of the above possibilities. It is not within the scope of these guidelines to discuss the policy of using or not using thiomersal, nor to discuss the effectiveness of reducing levels of thiomersal, or using a new preservative, in preventing microbial contamination. Useful guidance on the reduction, elimination or substitution of thiomersal in vaccines has also been produced by the Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMEA) (*9*).

Terminology

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

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

Reduction of thiomersal means that thiomersal is used at some stage of vaccine production, but the amount is smaller than that in the already licensed vaccine. Reduction of thiomersal, even if significant, still leaves residual levels of thiomersal and such a product can not therefore be 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 later stage by a specific production step. This procedure also results in residual traces of thiomersal.

Replacement of thiomersal in vaccines means that thiomersal is not used at all and another preservative is included instead. In this case, there is no thiomersal in the final product, but the replacement 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 as to 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 in vaccines may remain following a significant reduction in or removal of thiomersal from the product. Specifications for residual levels of thiomersal with an upper limit should be set. Validated assays should be established to substantiate these specifications. 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 from contamination and/or added as a preservative at the final stage of vaccine production. A number of scenarios for elimination of thiomersal can be envisaged, each with different regulatory consequences:

- The elimination of thiomersal from an already licensed vaccine in which thiomersal has been 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 greatest consequences on quality, safety and efficacy. The resulting product will therefore need considerable re-evaluation. Re-evaluation should include: extensive characterization of the active substance and finished product and comparison with the existing product; comparative quality control testing and assessment of in-process controls, for example bioburden and endotoxin; and comparative stability studies on intermediates, final bulk and finished product.
- 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.
- The elimination of thiomersal added simply as a preservative at the final stage of vaccine formulation may be expected to have fewer consequences and therefore a more flexible approach to re-evaluation 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 that has been used as an inactivating agent or to protect the production process, re-validation

of the inactivation process together with some additional tests (see those described above for 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 based on evidence that antimicrobial efficacy is retained. Specifications for residual amounts and/or for reduced content of thiomersal as a preservative need to be set, and validated assays to substantiate these specifications should be established.

Removal of thiomersal

If thiomersal is used in the manufacturing process (e.g. as an inactivating agent or to protect the production process), its removal will require product characterization similar to that described under elimination. Where thiomersal is used as an inactivating agent, there is no need for any re-validation of the inactivation process because thiomersal removal occurs after inactivation. Thiomersal removal will leave 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 specifications should be established.

Replacement of thiomersal

Replacing thiomersal in an already licensed vaccine in which thiomersal has been 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 demonstrated. Specifications for the new preservative in the final product should be set and validated assays to substantiate these specifications should be established. Specific toxicity should be addressed in preclinical testing to demonstrate that an alternative inactivating agent and/or preservative which replaces 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 than in the case of 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 the 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 postmarketing surveillance.

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

Antimicrobial efficacy

Where a reduced quantity of thiomersal, 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 clearly indicate 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 product is thiomersal-free. Thiomersal might still have been 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 that the product is thiomersal-free.

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