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POINTS TO CONSIDER ON THE REDUCTION, ELIMINATION OR SUBSTITUTION OF THIOMERSAL IN VACCINES

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Points to Consider have been developed to provide advice on selected areas relevant to the development of medicinal products in specific therapeutic fields.

This document related to thiomersal in vaccines will be revised in accordance with the scientific advances made in this area.

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POINTS TO CONSIDER ON THE REDUCTION, ELIMINATION OR SUBSTITUTION OF THIOMERSAL IN VACCINES

1. INTRODUCTION AND SCOPE

Thiomersal is an antimicrobial preservative included in some vaccines for human use. In addition to its antimicrobial capacity, it may perform other functions affecting antigenicity and stability. Thiomersal and other organo-mercurial compounds may be present in inactivated vaccines because they have been added as a preservative during formulation of the final bulk stage or as a residue from their use as an antimicrobial at an earlier stage of the manufacturing process (e.g. as the inactivating agent or to avoid growth of a bacterial contamination). These compounds are not used in live vaccines due to their interaction with the active substance of these vaccines. Manufacturers and authorities generally have been accepting the use of antimicrobial compounds because the Ph.Eur. methods recommended for the preparation of sterile products with physical means such as heat and/or filtration can, in general, not be applied to the active substances of this class of biologicals.

Organo-mercurial preservatives may be present during the preparation of the active substance(s), of bulk intermediate(s) and of final bulk and finished product (final lot):

Active substance

In some vaccines where thiomersal is used during the manufacturing process of the active substance(s), the organomercurial compound may contribute to the microbiological quality of the antigen: as an example, the complex manipulations involved in the harvesting of influenza vaccine virus from embryonated eggs, warrants the use of an antimicrobial agent at this stage of production. Thiomersal has been shown to be effective for this purpose. Thiomersal may also contribute to the inactivation of an antigen. As an example, it is added as an additive to heat-inactivation of pertussis bacteria.

Bulk intermediates

Owing to their lability, vaccines cannot be terminally sterilised in their final containers. For some bulk components of combined vaccines and final bulks presented as a suspension, the nature of the formulation may preclude them from being sterilised by filtration immediately before blending or filling. The addition of an antimicrobial preservative therefore provides additional assurances by avoiding proliferation of incidental bacterial contamination.

Final bulk and finished product (final lot)

In some production procedures, one final bulk is used to fill both multidose (where the presence of a preservative is mandatory according to the Ph Eur and also part of a WHO policy*1*) and single dose containers (in some cases by different companies). The use of single-dose vaccines is perceived as a fundamentally safer approach as compared to multidose vaccines. For monodose containers of biopharmaceuticals in general it seems that there may be no quality rationale for adding thiomersal, or, indeed, any preservative. Multidose containers may offer advantages in terms of ease of administration and cost when mass vaccination campaigns have to be performed under difficult conditions such as in the developing world. While there is a general consensus that all vaccines presented in multidose containers should contain a preservative, it is conceivable that even for multidose containers, once the vial is opened, its contents should be dispensed within a limited period

[1] World Health Organisation 2000, Department of Vaccines and Biologicals. WHO Policy Statement. The use of opened multi-dose vials of vaccine in subsequent immunization sessions. www.vaccines.who.int/vaccines-documents/

of a few hours and there may be no need for a preservative. However, appropriate use of multidose containers is dependent on scrupulous attention to the care of the rubber inlet and needle and syringe sterility.

Another matter of concern is that vaccines are often turbid and this turbidity could mask growth of a microbial contamination. The presence of a preservative would suppress any microbial growth.

For vaccination in infants and toddlers, 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 organo-mercurial preservatives, particularly for single dose vaccines

There are three options:

- Reduce the amount of thiomersal in finished product (final lot)s.
- Eliminate thiomersal altogether.
- Eliminate thiomersal but substitute it by an alternative preservative.

These three options are not mutually exclusive as, in an initial stage, a manufacturer may apply for a variation to reduce the amount of thiomersal whilst developing a thiomersal-free formulation with or without a substitute preservative, the latter being the favoured option.

Vaccines without organo-mercury containing preservatives may be obtained by omitting these compounds from all the stages of the production where they are used. Vaccines with only residual levels of organo-mercury containing compounds may be obtained by removal of the compounds through physico-chemical means or by omitting these compounds only at the final formulation step. In this case, the residual amount of the organo-mercury containing compound no longer plays the role of an antimicrobial preservative.

Reducing or eliminating thiomersal could have an impact on microbiological quality, solubility, antigenicity, immunogenicity, reactogenicity and stability. Substantial developmental and validation work may therefore be necessary before such modifications can be implemented. Each vaccine would have to be considered on a case by case basis. For each individual situation the potential impact on quality, safety and efficacy would have to be evaluated. After critical analysis, it may be necessary in some cases to conduct clinical studies to address the impact of the change on safety and efficacy. As a result, the whole process is to be considered as a middle and long term effort. This Points to Consider document addresses the quality, safety and efficacy issues arising from such modifications and the nature of the data to be submitted.

2. REDUCING/REMOVING THIOMERSAL FROM VACCINES

While in agreement with the CPMP position, obtaining vaccines without organo-mercury containing preservatives should be the ultimate goal, it is also possible, in a shorter timeframe, to reduce their concentration in the final product to residual levels, using physico-chemical methods to remove the preservative at intermediate production stages or by omitting or reducing their addition at the formulation step.

In the case of removal processes (and in analogy to what is required for other chemicals used during production), the methods used to remove organo-mercury-compounds from the production stages involved should be described and their capacity of removal should be demonstrated and validated on at least three batches.

A specification for the residual concentration in the finished product (final lot) should be set. This can be a specification by calculation if residual levels fall outside the quantification limits of the test method. The presence of residuals should be declared in the SPC as referred to in the NtA Guideline on SPC (December 1999), withthe CPMP Position Paper on Thiomersal: Implementation of the Warning Statement Relating to Sensitisation (CPMP/2612/99) and with CPMP/463/00, Excipients in the Label and Package leaflet of Medicinal Products for human use (March 2000).

3. SUBSTITUTION OF THIOMERSAL BY OTHER ANTIMICROBIALS

While it should be the final goal to prepare single dose presentations without any preservative at all, in the case of multidose containers, the use of an effective preservative is currently required. Organo-mercurial preservatives may have to be replaced by alternative preservatives currently in use in biologicals. The product will have to comply at least with the C criteria for antimicrobial effectiveness of the European Pharmacopoeia. The submitted documentation should include data after storage on at least three batches.

As outlined in the chapters below, substitutions should only be made after carefully examining the risk/benefit balance with regard to anti-microbial efficacy (Ph. Eur), compatibility with the antigen(s), excipients and container and vaccine stability, safety and efficacy.

If organo-mercurial compounds are replaced as an inactivating agent, 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. Such a study should be performed on at least three independent inactivation runs.

General guidance on antimicrobial agents in vaccines is also presented in the CPMP Note for Guidance on Pharmaceutical and Biological Aspects of Combined Vaccines (CPMP/BWP/477/97) and in monographs of the European Pharmacopoeia.

4. THE EFFECT OF REDUCTION, ELIMINATION OR SUBSTITUTION OF THIOMERSAL ON MICROBIOLOGICAL QUALITY

The primary aim of using organo-mercurial preservatives or any other antimicrobial compound is to contribute to the overall assurance of the microbial quality (in particular of the absence of harmful viable micro-organisms) of the vaccine. Therefore, the primary effect of eliminating or replacing an antimicrobial or reducing its concentration, may be on the microbiological quality as represented by parameters such as bioburden, sterility and endotoxin content. Validation of the reduction or elimination (and possibly replacement) of thiomersal will therefore also be based on data on the microbiological quality of the relevant production stages, including all stages downstream of the stage(s) where the antimicrobial has been omitted and where this omission may have an impact.

Data on bioburden and endotoxin levels will include a comparison with (historical) data obtained with the approved production method. Such a comparison should be performed on at least three independent commercial-scale production runs.

Data on the microbiological quality after storage should be presented on at least three batches.

5. THE EFFECT OF REDUCTION, ELIMINATION OR SUBSTITUTION OF THIOMERSAL ON NON-MICROBIOLOGICAL QUALITY ASPECTS

Traces of organo-mercury ions have been reported to have a stabilising effect on the surface antigen of Hepatitis B virus (HbsAg) which is the active substance of rDNA Hepatitis B vaccines. A

stabilising effect of organo-mercury compounds has also been signalled for whole cell Pertussis vaccines. In general, organo-mercurial preservatives may interact with antigens in the vaccine and their reduction, elimination or substitution in some or all of the production stages may have an impact on the quality of the antigen. Therefore, variations aiming at vaccines without organo-mercurial preservatives will have to be supported by appropriate characterisation and stability data, including potency data. On a case-by-case basis, a full set of stability data may not be required at the time of submission and it may be acceptable for the applicant to submit real time stability data on an ongoing basis.

In some cases it may not be sufficient to demonstrate compliance with the approved specifications and more extensive characterisation of the protein structure, impurity profile and biological activity may be needed. All characterisation data should be generated in comparison with the product prepared according to the approved process. In those cases where thiomersal is eliminated or substituted at the formulation stage, it may be difficult to study the effect on antigen quality as the antigen concentration and the presence of excipients, as well as adsorption of the antigen on adjuvants, may prohibit extensive characterisation studies. On the basis of characterisation studies the need for appropriate pre-clinical and clinical data, including a comparison with the thiomersal containing formulation, will have to be considered. The CPMP "Guideline on Comparability of Medicinal Products Containing Biotechnology-derived Proteins as active substance" (CPMP/BWP/3207/00) may be applicable to some products or may contain useful principles.

6. ISSUES CONCERNING SAFETY AND EFFICACY

Although the removal of thiomersal when used as a preservative added at the finished product (final lot) stage is not expected to affect a vaccine's efficacy to a significant extent, it should be shown that the product has biological characteristics equally stable to the original.

Efficacy

When clinical trials are considered necessary, equivalence between the thiomersal-containing and thiomersal-free formulation has to be established, using adequate study designs. It is the responsibility of the applicant to demonstrate that the thiomersal-free vaccine is not inferior to the original thiomersal-containing vaccine. Therapeutic equivalence between the thiomersal-free and thiomersal containing vaccines needs to be established, according to predefined criteria ([2]).

Studies should be adequately powered for equivalence testing. When a vaccine is initially developed as thiomersal-free, it is not necessary to establish therapeutic equivalence with an antigenically similar thiomersal containing vaccine.

Supporting evidence on the immunogenicity of the vaccine antigen in a vaccine without thiomersal can be obtained if the vaccine antigen already constitutes a combined vaccine without thiomersal.

Safety

The safety consequence of removing or limiting thiomersal from the vaccines is an important issue to be addressed. This means that where no negative consequences for efficacy are to be expected a comparative study, adequately powered to address at least the most common adverse events, (or those events for which there is a pharmacological rationale that these may be enhanced by removing thiomersal) may be necessary. For example recently, an abnormally high frequency of fever-related reactions has been associated with the elimination of thiomersal from one viral vaccine. It is the responsibility of the applicant to justify the basis for the power analysis for safety or efficacy.

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[2] CPMP Note for Guidance Clinical Evaluation of New Vaccines (CPMP/EWP/463/97)

The safety of the proposed thiomersal-reduced/-free vaccine containing no alternative preservative cannot however be inferred from the safety of the combined vaccine if that vaccine contained an alternative preservative since the latter may have performed some or all of the functions of thiomersal and in such cases a suitable study might be required.

Supporting evidence on the safety of the vaccine antigen in a vaccine without thiomersal can be obtained if the vaccine antigen already constitutes a combined vaccine without thiomersal.

Substitution of thiomersal by other antimicrobials

With regard to efficacy and safety data indirect evidence of the immunogenicity of the vaccine antigen in the presence of an alternative preservative; for example 2-phenoxyethanol can be obtained from clinical trials where the vaccine antigen was combined with other vaccine antigens in a combined vaccine containing 2-phenoxyethanol. These should be valid only for vaccine antigens from the same manufacturer. However, the same recommendations for establishing the relative efficacy and safety profile after the replacement apply as for the removal of thiomersal (see above).

While the above attempts to give general guidelines for the three proposed changes (i.e., reduction, elimination or substitution of thiomersal), each vaccine will have to be considered on a case-by-case basis.