



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Perspectives on alternatives to thiomersal

WHO Informal Consultation to develop further guidance on vaccines for the UNEP-convened Intergovernmental Negotiating Committee Meeting 4

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Regulatory Guidance for Antimicrobial Preservatives

- CHMP
 - Guideline on Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product (EMA/CHMP/QWP/396951)
 - Excipients in the label and package leaflet of medicinal products for human use
- Ph. Eur. monographs
- WHO
 - Guidelines on regulatory expectations related to the elimination, reduction or replacement of thiomersal in vaccines, TRS No. 926 Annex 4
 - Proposed protocol to test the preservative efficacy of vaccines containing different preservatives in varying concentrations using a multichallenge test, 2005
- USP <51> Antimicrobial effectiveness testing
- JP <19> Preservative effectiveness tests



CHMP Guideline on Excipients in the Dossier for Marketing Authorisation of a Medicinal Product

- Inclusion of preservative needs justification
- Use should be avoided, particularly in paediatric formulations. The concentration should be at the lowest feasible level

3.2.P.5 Control of Drug Product:

- The release specifications should include an identification test and a content determination test with acceptance criteria
- The shelf-life specification should also include limits for preservatives when present



CHMP Guideline on Excipients in the Dossier for Marketing Authorisation of a Medicinal Product

3.2.P.8 Stability:

- The preservative content should be monitored throughout the shelf-life to ensure that preservative levels remain above the level challenged for preservative efficacy and within the specifications
- For non-solid medicinal products in multidose containers that contain preservatives, the efficacy of the preservative under in-use conditions should be established. The tests should be performed under conditions simulating the dosage recommendations, as stated in the Summary of Product Characteristics



CHMP Guideline on Excipients

Annex 2 “antioxidants & antimicrobial preservatives”

- Reason for inclusion and justification of level of inclusion
- Proof of safety* and efficacy**
- Method of control
- Levels on storage of broached and unbroached containers
- Details on the labelling

* Supported by bibliographic and/or experimental data unless well known and generally used at same concentrations and by the same route of administration

** Assessed during product development and at the end of the proposed shelf-life using the method described in the Ph. Eur. chapter 5.1.3



Elimination / replacement of preservative: EU regulatory aspects

- Major type II variation, B.II.a.3.b.3 change in the composition (excipients) of a biological product

→ comparability exercise as per ICH Q5E Note for Guidance on biological products subject to changes in their manufacturing process (EMA/CPMP/BWP/3207/00/Rev1)

- Product Information
- 3.2.P.1 description and composition of the drug product
- 3.2.P.2 pharmaceutical development (choice of excipient, compatibility)
- 3.2.P.3 description of manufacturing process and process controls, batch formula
- 3.2.P.4 control of excipients (specifications, analytical procedures, validation of analytical procedure, justification of specifications)
- 3.2.P.5 control of drug product (specifications, analytical procedures, validation of analytical procedure, batch analysis)
- 3.2.P.8 stability test results
- Pre-clinical / clinical data may be required



Elimination / replacement of preservative: case example

Thiomersal-free manufacturing process for the hepatitis B antigen
and elimination of 2-phenoxyethanol as preservative

(Manufacturer's various hepatitis B combination vaccines)

- Multiple vaccines registered under various regulatory routes
- Complexity of change (extensive characterisation, clinical studies...), subject to regulatory approval in individual countries
- Complexity of implementation (one-time switch, no reversion to previous process)
- Complexity of supply chain management to limit disruption of supply and vaccine lots write-offs



Considerations for veterinary vaccines

- Many important veterinary vaccines for food producing animals on the market contain thiomersal
- Any ban on thiomersal in the absence of a viable alternative would lead to a major negative impact on public and animal health
 - absence of preventive measures against diseases
 - economic losses in the food supply
 - unlimited spread of zoonoses to man



Considerations for veterinary vaccines (cont' d)

- Animals usually receive 2 initial vaccinations followed by a yearly booster
- The lifespan of food producing animals is short
- Given the amount of thiomersal per dose and size of the animals, the amount of thiomersal which could potentially be consumed via food by humans is miniscule



Considerations for human vaccines

- In line with previous EMA position statements (*), there has been a substantial reduction in the use of thiomersal, particularly in single dose vaccines. Efforts to continue this reduction are supported where this is viable.
- It may be possible to substitute thiomersal by other preservatives in multidose presentations; this could however require substantial effort to investigate. The ability of industry to reformulate products is not clear at present.

(*) CHMP Position statement on thiomersal, implementation of the warning statement relating to sensitisation
EMA/CHMP/VWP/19541/2007



Considerations for human vaccines (cont' d)

- A ban on thiomersal in the absence of alternatives may have significant consequences on public health, by impacting on the availability of multidose vaccine preparations and stockpiling of certain necessary injectables.
- The value of thiomersal was seen during the 2009 influenza pandemic. It is considered that preserved multidose presentations are necessary in a pandemic situation to ensure manufacturing capacity of sufficient doses and to facilitate administration in the field.



Conclusions

- EU encourages the development of vaccines without thiomersal, however, its use is supported when adequately justified.
- The feasibility of reformulating existing vaccines containing thiomersal is not clear and requires considerable evaluation.
- Thiomersal plays a valuable role in veterinary vaccines and for certain human vaccines – particularly those used in a crisis, e.g. pandemic influenza scenario, affording substantial Public Health benefits.
- EU supports the position papers developed by WHO outlining the need to use thiomersal in certain medicinal products.



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