NOTICE 1908 OF 2005

Registration of Medicines **General information (Draft 1)**

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

DRAFT GUIDELINES ON SIMULTANEOUS USE OF VACCINES CONTAINING ENDOTOXINS IN INFANTS

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of medicines. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used but these should be scientifically and technically justified. The MCC is committed to ensure that all registered medicines will be of the required quality, safety and efficacy. It is important that applicants adhere to the administrative requirements to avoid delays in the processing and evaluation of applications. This guideline must be read in conjunction with the post registration amendment guideline, guideline on information of package inserts for human medicines (orthodox) and regulation 9 of Act 101. 1965. as amended.

First publication released for comments	October 2005
Deadline for comments	January 2006
Date of finalization/implementation	May 2006

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1. Introduction

Many vaccines contain endotoxins and pyrogenic materials, either as contaminants or as part of the normal constitution of the vaccine. Injected endotoxins cause fever and swelling and may, in larger doses, precipitate endotoxic shock that can be life threatening, particularly in infants. These endotoxins are probably responsible for the majority of adverse reactions seen with whole cell vaccines, such as adsorbed diphtheria, tetanus and pertusis vaccines. Endotoxins have an immunologically enhancing (adjuvant) effect and are important in the efficacy of some vaccine components. The British Pharmacopoeia (BP) and the European Pharmacopoeia (Ph Eur) have set limits for the endotoxin and or pyrogen content of certain vaccines, but not for others. The BP provides a formula for calculation of an Endotoxin Limit concentration per millilitre of any parenteral product. For a vaccine this would be about 15 IU per 0,5 ml dose. An infant may receive DTP, HiB and HepB simultaneously. Inactivated polio may also be given. Thus the cumulative dose should be less than 15 IU.

The requirements

1. All vaccines should be tested using LAL test for endotoxins or pyrogens in rabbits if LAL is inappropriate and a value in IU per dose established.
2. The endotoxin IU per dose must be included on the package insert under "Composition" for all Vaccines.
3. Infant vaccines that contain more that 5 IU per dose will be required to include a warning on the package insert that care must be exercised during simultaneous use or administration of the vaccine with other products containing endotoxins. The statement such as "the use of this vaccine at the same time as other medications that contain endotoxin may provoke a febrile reaction" should be included under the warnings section of the package insert.
4. All new applications for registration and applications to amend registered vaccines will be required to comply with this policy.

All stakeholders are invited to submit written comments within 3 moths from the date of publication of this notice.

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Please submit all written comments for the attention of **Mr S** Phoshoko and addressed to:

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Comments can also be delivered to:
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Room 214

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