The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 25 January 2001
CPMP/BWP/4310/00

CONCEPT PAPER ON THE DEVELOPMENT OF A COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP) POINTS TO CONSIDER ON STABILITY AND TRACEABILITY REQUIREMENTS FOR VACCINE INTERMEDIATES

1. INTRODUCTION

Current trends in vaccine manufacturing are for production of ever more complex monovalent and combination vaccines. The individual active substances are produced in campaigns allowing manufacturers to maintain a high degree of flexibility and the rational use of production facilities. Depending on the number of intermediates *(for definition of the term intermediate see references [1, 2])* within a production process, holding periods for individual active substances of several years are possible before the actual shelf life of the finished product begins. The typical shelf-life of a vaccine is 3 years. The total age of an active substance could exceed 10 years by the end of the shelf life, taking into account the holding periods of the intermediates used to manufacture the vaccine. There is a clear tendency towards even longer holding periods and shelf lives. This has consequences for the traceability of all components that have been used in the manufacturing process and may have consequences for the stability of the product. Variations on the extension of holding periods of intermediates are common. Recent experience in dealing with such requests has revealed some differences of approach between Member States. Therefore the proposed points to consider document is intended to develop a common approach to traceability and stability requirements for vaccine intermediates.

2. PROBLEM STATEMENT

The current ICH guideline[1] on the stability for biological and biotechnology products is focussed on the requirements to define the shelf life of the finished product and does not address adequately traceability issues and stability testing on intermediates. This may apply to many biological products but has recently become of particular importance for mono- and multivalent vaccines.

Traceability issues for intermediates are common to all types of vaccine whilst potential stability problems may be most pronounced with combined vaccines where complex interactions between components may occur. Consistent quality and stability has to be documented for the claimed holding period of each individual vaccine intermediate. The necessity of more comprehensive stability testing programmes has been identified to ensure equal quality and, as a consequence of this, consistent safety and efficacy of the final vaccine regardless of the age of the intermediates used in the manufacturing of the finished product.

In considering the question of traceability issues and stability requirements of intermediates it is recognised that measures such as:

- a fixed maximum age for intermediates
- fixing the maximum age of intermediates to data presented in the clinical data file of a marketing authorisation application
- requesting data from products made with intermediates at the maximum age claimed for storage before the marketing authorisation

may deter manufacturers from future development of new and improved vaccines.

The appropriate extension of the existing regulatory measures as well as pre- and post-authorisation requirements is the focus of this Concept Paper.

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel. (+44-20) 74 18 84 00 Fax: (+44-20-) 74 18 85 45
E_Mail: mail@emea.eudra.org http://www.emea.eu.int/

Existing regulatory measures can not be regarded as entirely sufficient to cover all aspects of vaccines manufactured from multiple intermediates. As a consequence, relevant guidance has to be provided to assist manufacturers in their development programmes taking into account the impact of long-term holding periods of vaccine intermediates.

3. RECOMMENDATION

It is proposed that a Points to Consider paper will be prepared for CPMP giving an EU scientific guidance on these issues.

4 TIMETABLE

The Concept Paper on the stability requirements for vaccine intermediates will be available for submission to the CPMP in December 2000, for adoption and release in January 2001.

References

[1] ICH Topic Q 5 C (CPMP/ICH/138/95 Note for guidance on quality of biotechnological products: Stability testing of biotechnological/biological products; glossary)

[2] PHARMEUROPA Vol. 12, No. 2, April 2000 – Vaccines for Human Use – Revision proposal for the Monograph