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

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CONCEPT PAPER ON THE DEVELOPMENT OF A COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP) POINTS TO CONSIDER ON LIVE ATTENUATED INFLUENZA VACCINES

1. INTRODUCTION

At the CPMP meeting in May 1999, the need for guidance addressing recent scientific developments in the production of influenza vaccines was highlighted following the discussion at the BWP, of live attenuated influenza vaccines. The current *CPMP Note for guidance on the harmonisation of influenza vaccines* covers only the egg-derived influenza vaccines and does not include guidance on more recent, innovative influenza vaccines. The present concept paper summarises the areas of concern relating to live attenuated influenza vaccines including cold-adapted influenza vaccines (CAIV).

2. PROBLEM STATEMENT

Issues concerning live attenuated influenza vaccines are of special significance. It has been reported that CAIV are highly effective in seronegative children with protection rates exceeding 90% after two doses of intranasally administered CAIV vaccine. In contrast, protective efficacy in seropositive individuals, particularly in the elderly or those having previously been vaccinated with influenza vaccine is a matter for discussion.

Various quality aspects related to live attenuated influenza vaccines require thorough evaluation:

- Safety of the production substrate
- Absence of adventitious agents
- Sterility of the final product
- Genetic stability of live attenuated reassortant viruses prepared from different strains.
- Possible interference with circulating wild type influenza strains and safety aspects in producing vaccines for an emerging pandemic
- Biological stability of the live attenuated reassortants from different strains.

The scientific discussion should also take into account some practicalities such as:

- The time constraints of production of seasonal live attenuated influenza vaccines. It is unclear at present whether production and stringent controls of live attenuated influenza vaccines can be performed within the time frame currently operating for inactivated influenza vaccines.
- Use of live attenuated influenza vaccines in interpandemic and pandemic periods

3. RECOMMENDATION

Other safety and clinical aspects merit discussion by the appropriate experts:

- Possible direct neurotoxic effects induced by the live attenuated influenza virus strains themselves.

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- Possible indirect neurotoxic effects induced by bacterial superinfections following the breaching of the nasal mucosa due to the application of the vaccine virus and the excipients.
- Safety of live attenuated influenza vaccines in immunocompromised individuals, cystic fibrosis patients, asthmatics, individuals with egg allergies, etc.
- Possible environmental effects of shed live reassortant virus
- Measurement of efficacy of live attenuated influenza vaccines (serology, other surrogate markers or long term protection rates).
- Possible interference of live reassortant influenza strains within the trivalent formulation.

It is proposed that a Points to consider be prepared for CPMP giving an EU scientific guidance on these issues to supplement the *CPMP Note for guidance on the harmonisation of influenza vaccines*.

4. TIMETABLE

The Points to consider on live attenuated influenza vaccines should be available for submission to the CPMP in November 1999, for release for external consultation for 3 months. During the annual meeting of the Ad hoc Influenza Working Party in spring 2000, the comments received will be consolidated and finalised for transmission to the CPMP for adoption.