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Final paediatric investigation plan: Expected key elements and requirements for a new DTaP-containing combination vaccine for primary and booster vaccination in infants and toddlers

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1. Background

The EU Regulation states that any marketing authorisation (MA) application for a new medicinal product must include either the results of studies conducted in compliance with an agreed paediatric investigation plan (PIP), or an Agency decision on a waiver or on a deferred PIP. This also applies to authorised medicinal products which are protected by a Supplementary Protection Certificate (or a patent that qualifies for it), for example when a new indication is requested, and to applications for paediatric use marketing authorisation.

This document defines the study outline that applicants should follow when preparing the PIP for a new diphtheria-tetanus-acellular pertussis (DTaP) containing combination vaccine (e.g. pentavalent, hexavalent, heptavalent), for a priming schedule and booster dose before 2 years of age. This document applies to new combinations with known DTaP antigens and components and to those vaccines in which additional antigen(s) were added while retaining the known antigens (e.g. by adding an additional pertussis component). The study design is summarised in Table 1.

The aim of this document is to avoid unnecessary clinical trials in children. Duplication of essentially similar trials by an individual applicant/MAH with slightly different immunisation schedules should be avoided, in line with the objective of the paediatric regulation to avoid unnecessary clinical trials. The schedule proposed for clinical trials in children, i.e. two priming doses at 2 and 4 months of age (first dose at 8 to 10 weeks, second dose 8 to 10 weeks later) and a booster dose at 12 months of age (52 weeks +/- 4 weeks), has been defined by the PDCO and CHMP as the one producing data that for immunogenicity can cover the various vaccination schedules in the individual European Member States, through extrapolation of results to immunologically less challenging schedules. Although studies with different national primary schedules are not necessary, it is recognised that additional studies with concomitant administration of some vaccines may be necessary (e.g. Men C, Men B, and rotavirus). In addition, studies in special populations may be required post-authorisation, but these are considered outside the scope of this document.

In addition, according to the CHMP Guideline on clinical evaluation of new vaccines (CHMP/VWP/164653/2005), as a minimum, the total data from pre-authorisation studies should be sufficient to reliably determine the nature and frequency of local and systemic adverse events occurring at a frequency > 1/1000. This pre-authorisation safety database can be achieved with additional studies focusing on safety only, reducing the overall burden of clinical trials on children, as these safety studies do not require blood sampling. These pre-authorisation safety studies are expected to be included in the PIP and should include a 3-dose primary schedule, if the vaccine is intended to be used in this schedule.

The proposed study outline is not a full protocol and is not intended to substitute the full protocol. Elements that are not cited in Table 1 remain at the discretion of the applicant (e.g. the exclusion criteria).

The principles covered in this document are to be read in the context of present knowledge and may have to be revised. The European Medicines Agency and the PDCO may decide to revise these principles to take into account the evolution of knowledge in the field. This document is without prejudice to the PIP assessment in relation to a specific medicinal product.

2. Paediatric Investigation Plan

The proposed immunisation schedule has been endorsed by a panel of public health vaccinology experts convened by the ECDC and EMA, based on expert opinion.

If the test vaccine fails to demonstrate non inferiority to comparator with this schedule, additional studies with other schedules might be considered upon discussion with regulatory authorities, as less restrictive schedules might still show immunogenicity, and the clinical relevance of the difference should be discussed. Infants following this 2-dose priming immunisation schedule that develop a suboptimal immunological response shall be offered an additional vaccine dose, as appropriate.

National immunisation strategies may vary in different countries regarding the number of doses and the age at immunisation of the mothers. In principle, the applicant should consider conducting the study in more than 1 country to account for infants' pre-immunisation antibody titres variability.

If infants to mothers who were immunised during pregnancy with a dTaP vaccine are to be included in the trials, the applicant should consider stratification according to maternal immunisation status.

The choice of comparator for the clinical trials should be an EU authorised DTaP containing combination vaccine. Regarding the acellular pertussis antigen, the comparator should be the most similar to the investigational vaccine with respect to content and composition of the acellular pertussis component.

The choice of the pneumococcal vaccine is left to the discretion of the applicant.

Table 1: Overview of standard study to be proposed by applicants:

Study identifier	**PIP DTaP-containing combination vaccine**
Study design features and main objectives	Randomised, double-blind, controlled study to assess immunogenicity, safety and tolerability of test DTaP-containing combination vaccine compared to control vaccine, and co-administered with pneumococcal vaccine
Study population and subset definition	Healthy children of 8 to 10 weeks of age
Number of study participants by paediatric subset	At least X* 8 to 10-week old healthy infants evaluable for the primary endpoint (*the X will derive from the non-inferiority margin for the immunogenicity analysis)
Study duration for participants	X-months safety follow-up after last vaccination (to be justified by the applicant)
Dosage, treatment regimen, route of administration	Arm 1: New DTaP-containing combination vaccine, first dose at 8 to 10 weeks of age, second dose 8 to 10 weeks following the administration of first dose, booster dose at 52 weeks of age (+/- 4 weeks), co-administered with any pneumococcal vaccine
Control	Arm 2: Authorised DTaP-containing combination vaccine, first dose at 8 to 10 weeks of age, second dose 8 to 10 weeks following the administration of first dose, booster dose at 52 weeks of age (+/- 4 weeks), co-administered with any pneumococcal vaccine

Study identifier	**PIP DTaP-containing combination vaccine**
Primary endpoint with time points of assessment	Immunogenicity (Blood sampling pre-dose 1, 4-weeks post-second dose, pre-booster and 4-weeks after booster dose): 1. Proportion of subjects achieving 1 month post-booster dose seroprotective antibody values to each of the following antigens (see Table 2): - Diphtheria - Tetanus - others as per the test vaccine 2. For Pertussis: GMTs 1 month post-booster dose 3. Proportion of subjects achieving 1 month post-booster dose seroprotective titres to pneumococcal serotypes
Main secondary endpoints with time points of assessment	1. Proportion of subjects achieving 1 month post-second dose seroprotective antibody values to each of the following antigens (see Table 2): - Diphtheria - Tetanus - others as per the test vaccine 2. Safety assessment according to the CHMP Note for Guidance on the clinical evaluation of vaccines (CHMP/VWP/164653/2005) 3. Cumulative reverse distribution curves of immune response
Statistical plan including study conduct and analysis	- Non-inferiority testing according to the CHMP Guideline on clinical evaluation of new vaccines (CHMP/VWP/164653/2005) - Primary outcome to be assessed according-to-protocol for immunogenicity and total vaccinated cohort for safety
Other	Not applicable
Plan for specific follow-up (not part of the completion of this study)	Not applicable
External Data Safety Monitoring Board	Required
Date of initiation	By <Month> <Year> The initiation of this study is <not> deferred
Date of completion (last patient, last visit)	By <Month> <Year> The completion of this study is <not> deferred

Table 2: Data should be expressed, in order to assess results, according to the following cut-off antibody values (these values are indicative and may depend on the method used):

Antigen	**Antibody value, established correlate of protection**
Diphtheria	≥ 0.01 IU/ml (short-term) ≥ 0.1 IU/ml (long-term)
Tetanus	≥ 0.01 IU/ml (short-term) ≥ 0.1 IU/ml (long-term)
Polio 1, 2, 3	≥ 8 (1/dil)
PRP (Hib)	≥ 0.15 µg/ml (short-term) ≥ 1 µg /ml (long-term)
Hepatitis B	≥ 10 IU/ml (short-term) ≥ 100 IU/ml (long-term)
Pertussis	no established correlate of protection