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EMA/48041/2015
Human Medicines Development and Evaluation

Comments on Paediatric investigation plan: Expected key elements and requirements for a new DTaP containing combination vaccine seeking marketing authorisation (EMA/PDCO/71162/2014)

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1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
IFAPP (international Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Med.)	We only offer one comment: having in mind the age of this population, consider the impact of the blood samples which are suggested to draw.	On a population level the burden to the paediatric population is reduced, as duplicate trials with slightly different immunisation schedules are avoided. On the level of an individual child, four blood samples are suggested to be drawn. Measures to minimise pain and distress during venepuncture are expected to be in place, and the blood volume drawn should be minimised.
IBSS BIOMED S.A.	• is the proposed clinical trial schedule so universal that it considers different (for example Polish) National Immunization Programs (regarding tetanus, diphtertia, pertussis, IPV, HIB,Hep B doses)? • vaccine with what number of pertussis antigens and with what amount of each pertussis antigen are treated as comparator vaccine / any registered aP vaccine can be the comparator vaccine • what is the seroprotective level for pertussis component / will the seroprotective antibody values to each pertussis antigen be known (for comparator vaccine)	• The schedule proposed in the DTaP vaccine PIP has been defined by the PDCO and CHMP as the one producing data that can cover the various vaccination schedules in the individual European Member States, through extrapolation of results to immunologically less challenging schedules. • Regarding the acellular pertussis antigen, the comparator should in general be the authorised DTaP-containing combination vaccine most similar to the new vaccine with respect to content and composition of the acellular pertussis component. This has been clarified in the document. • No correlate for protection for pertussis has been established. Non-inferiority against the comparator vaccine will be evaluated.
Joint Committee on Vaccination and Immunisation	The Joint Committee on Vaccination and Immunisation (JCVI) is an independent body which advises UK health departments on immunisation. The JCVI welcomes the opportunity to comment on this consultation document and this response is submitted on behalf of all members of the Committee.	• Special populations: outside the scope of this document, as data in special populations can be collected after initial authorisation as part of the Risk Management Plan, if considered necessary. • If infants to mothers who were immunised during pregnancy with a dTaP vaccine are to be included in the trials, the applicant should

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	The study population described in the paediatric investigation plan is healthy children. Trials should also be proposed which consider special groups (such as premature infants), provide data for settings in which maternal DTaP is being used, and consider three dose priming schedules.	consider stratification according to maternal immunisation status. • In terms of immunogenicity, three dose priming schedules are immunologically less challenging schedules and hence are considered covered through extrapolation from the schedule proposed in the DTaP vaccine PIP. In terms of safety, pre-authorisation safety studies, conducted to meet the requirements of the CHMP Guideline on clinical evaluation of new vaccines (CHMP/VWP/164653/2005) regarding the size of the pre-authorisation safety database, should include a 3-dose primary schedule, if the vaccine is intended to be used in this schedule. This has been clarified in the document.
Vaccines Europe	The document is considered useful as it clarifies expectations from the Agency. Vaccines Europe welcomes in particular the fact that the document is short with adequate level of detail.	Noted.
	Is it the intention of the Agency to propose similar guidance for other paediatric vaccines?	If the need arises the Agency may propose PIP guidance for other paediatric vaccines.
	The scope of the document should be clarified. Vaccines Europe's understanding is that "new DTaP containing combination vaccine" means includes new combinations with known DTaP antigens and components and does not include new DTaP antigens and components. We would welcome a confirmation of this interpretation.	The requested clarification has been added. This document applies to new combinations with known DTaP antigens and components. It would also apply to vaccines in which additional antigens were added while retaining the known antigens (eg by adding an additional pertussis component).
	The understanding of Vaccines Europe is that for any new DTaP containing combination vaccine, only one clinical study with a 2+1 schedule (2,4,12 months with co-administration of pneumococcal vaccine) is required for the PIP, and that it will cover all possible European	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), although these could be outside the PIP if planned post-MAA.

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	schedules including the 3+1 schedules with other possible vaccines co-administration.	The document's proposal to at least evaluate co-administration of pneumococcal vaccine comes from a panel of public health vaccinology experts convened by the ECDC and EMA. It was identified as being the vaccine the most commonly administered concomitantly to DTP priming across Europe. The additional safety studies required to have a sufficient safety database pre-authorisation would be expected to be included in the PIP.

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Title	Vaccines Europe	Comment: May need to be more specific regarding the population and indication in scope Proposed change (if any): clarify in title that this is for primary and booster vaccination of children of less than 2years of age	Section 1 already states that this document applies to those DTaP-containing combination vaccines for a priming schedule and booster dose before 2 years of age. However, the document's title has been updated to be more specific.
Title		Comment: Vaccines Europe's understanding is that "new DTaP containing combination vaccine" means new combinations with known DTaP antigens and components and does not include new DTaP antigens and components. It would be useful that the Agency confirm/clarify this. Proposed change (if any): The text of the Background section should clarify what scope of "new DTaP containing combination" is.	Comment already addressed above.
1.Background 3rd paragraph Lines 11-13		Comment: Is the statement "Duplication of essentially similar trials with slightly different immunisation schedules is considered unethical and therefore not acceptable" applicable globally to paediatric studies? I.e. for instance that a clinical study conducted by Company A including vaccines from Company A and Company B (e.g. co-administration) should not be duplicated by Company B? If so, would then the 10-year data protection not apply in such a case and published data could used for the purpose of a label update by Company B before the 10-years have elapsed? We would appreciate clarification from EMA/PDCO on this.	The statement applies to duplication of essentially similar trials with slightly different immunisation schedules by an individual applicant/MAH (i.e. considering only studies conducted by Company A or only studies conducted by company B). It should also be highlighted that this document is without prejudice to the rule of data exclusivity and market protection. The wording has been clarified.

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1.Background 3rd paragraph Lines 13-16		Comment: Vaccines Europe is of the opinion that the 2-4-12 month schedule cannot be considered as covering the various vaccinations schedules with regard to safety evaluation. In particular if the intention is to use the new vaccine in a 3-dose primary schedule followed by a booster, the 3-dose schedule should be the object of a specific safety evaluation. Proposed change (if any): Clarify in the PIP that intention to use the new vaccine in a 3-dose primary schedule would require safety evaluation in that schedule.	The wording has been updated to clarify that pre-authorisation safety studies, conducted to meet the requirements of the CHMP Guideline on clinical evaluation of new vaccines (CHMP/VWP/164653/2005) regarding the size of the pre-authorisation safety database, should include a 3-dose primary schedule, if the vaccine is intended to be used in this schedule.
Same section		Proposed change (if any): Clarify that conducting the proposed single trial in a 2-4-12months schedule is the absolute minimum in order to obtain a primary and booster indication.	As stated in the document, additional safety studies would be required to meet the requirements of the CHMP Guideline on clinical evaluation of new vaccines (CHMP/VWP/164653/2005) regarding the size of the pre-authorisation safety database, and additional co-administration studies may be required if a claim for concomitant administration will be made in the SmPC.
Background		Comment: Sample size of the proposed study design is driven by the immunogenicity endpoint, which is non-inferiority vs a licensed comparator. This size is below the 3000 subjects exposed requested for safety. To fill the gap, it is proposed to conduct safety only studies “to reduce the overall burden of clinical trials on children”, but there is no guidance on design for such safety studies.	Some additional clarifications have been added to the section on pre-authorisation safety studies, however the design of these studies is at the applicant’s discretion.
2.Peadiatric Investigation Plan		Proposed change (if any): Clarify the rationale for the choice of 2-4-12 month schedule	As already stated in the document, the proposed immunisation schedule has been

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1st paragraph, 1st sentence		as single schedule to be assessed in Europe.	endorsed by a panel of public health vaccinology experts convened by the ECDC and EMA, based on expert opinion that this schedule produces data that can cover the various vaccination schedules in the individual European Member States, through extrapolation of results to immunologically less challenging schedules.
2.Peadiatric Investigation Plan 1st paragraph, second sentence		Comment: It is not correct that no study has been conducted in the 2-4-12 month schedule. Industry has conducted such a study with Infanrix hexa and an investigational heptavalent vaccine, study results were published in 2014. Proposed change (if any): Delete that sentence.	The sentence has been deleted as study results have now been published (Thollot et al, *Pediatr Infect Dis J* 2014;33:1246–1254).
Same section		Comment: In the 2+1 schedule in Europe the 3rd dose is mandatory. This should be clarified and also that the evaluation of the full series should focus on the post-dose 3 immune response. Proposed change (if any): Clarification	Immunogenicity 4 weeks after the booster dose is already included as a primary endpoint, which clearly indicates that the evaluation should focus on the post-dose 3 immune response. Measurements post-dose 2 are now proposed as secondary endpoints.
Same section		Comment: Even though the protocol allows for the administration of an additional dose of vaccine in the case of a “sub-optimal” immunological response after 2 priming doses, there is no definition for seroconversion or a protective titre for pertussis, unlike the other antigens. Vaccines Europe would therefore like some clarification on how to define “sub-optimal”.	No correlate for protection for pertussis has been established. The relevant assessment is non-inferiority against the comparator vaccine.
Same section Page 3		Comment: The randomisation of groups according to the Tdap vaccination status of the mother will likely prove	If the country where the study is to be performed has a specific recommendation for

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		impractical (either too many or too few Tdap vaccinated mothers in a country). Also such a sub-randomisation would require powering the non-inferiority analysis as compared to the control in each subgroup which would lead to a doubling of the sample size of the immunological part of the study and increase the burden of the study on children in terms of blood sampling. Proposed change (if any): This does not seem realistic and should not be mandatory, and limited to situations where this is possible.	maternal immunisation during pregnancy, the applicant should consider stratification according to maternal immunisation status during pregnancy.
Same section Page 3		Comment: The nature of the DTaP comparator needs to be clarified. Proposed change (if any): Vaccines Europe suggests the recommendation to be in line with the WHO guideline for new Pa vaccines, i.e. to select the closest vaccine in composition and nature to the candidate DTaP).	Comment already addressed above.
Same section Page 3		Comment: Need to be clarified if one single pneumococcal vaccine would lead to generic wording in the SmPC. Proposed change (if any): provide guidance on the choice to pneumococcal vaccine to obtain generic wording in SmPC.	The final wording in the SmPC is subject to assessment of the provided data by the CHMP.
Same section Page 3		Comment: The age proposed at inclusion in the trial is very narrow. Proposed change (if any): Provide a rationale for this window, potentially increase the window to increase feasibility.	The narrow time window is needed to ensure the data collected could be extrapolated to other vaccination schedules.
Same section Page 3		Comment: A safety follow-up of 6-month is proposed in the single study. This is a new requirement.	The duration of the follow-up period after the last dose should be justified by the applicant.

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		Proposed change (if any): Clarify if this is mandatory in the single PIP study only.	The document has been modified accordingly.
Same section Page 3		Comment: The time window around the time of the second vaccine dose is very narrow. This has low feasibility in a clinical trial. Proposed change (if any): Allow increase of the window to increase feasibility.	The time window cannot be extended significantly, as in a 2, 4, 12 months schedule the second dose should be given as close to 2 months after the first dose as possible (i.e. 8-10 weeks).
Same section Page 3		Comment: Vaccines Europe would like to recommend that no pre-dose 1 sample is collected. This can be seen as acceptable especially since no proposed immunogenicity endpoint requires measuring pre-existing antibody levels. This would increase the acceptation of the study procedures by parents.	The pre-dose 1 sample is needed in order to allow for analysis of responses in relation to maternal antibody levels. In addition, for the pertussis component, the percentage of responders with a significant increase above pre-immunisation levels should be analysed, hence a pre-dose 1 sample is necessary.
Same section Page 3		Comment: Clarify the rationale for mandatory co-administration with a pneumococcal vaccine.	Co-administration with a pneumococcal vaccine is included in the key binding elements because the pneumococcal vaccine 2-dose priming schedule overlaps with the proposed 2, 4, 12 months schedule, and vaccination with pneumococcal vaccines is given in the majority of EU countries and should not be delayed in the study participants. Additional co-administration studies may be required if a claim for concomitant administration will be made in the SmPC.
Same section		Comment:	Agreed. The document has been revised

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Page 3		In a 2+1 schedule in Europe, the third dose is mandatory and the complete series includes the 3 vaccine doses. In consequence, the primary endpoints should be after completion of the 3-dose series, measurements at other time points (i.e. post-dose 2) should be secondary endpoints.	accordingly.
		Comment: Please clarify that the PIP is meant to cover only the single study ("standard study"), meaning that only this study would be binding, and that other studies in the clinical development and included in the MAA would be considered out of the PIP.	The additional safety studies required to meet the requirements of the CHMP Guideline on clinical evaluation of new vaccines (CHMP/VWP/164653/2005) regarding the size of the pre-authorisation safety database should also be included in the PIP.
Table 1 – dosage, treatment regimen, route of administration & control		Comment: The time window of enrolment is very tight in practice and can delay to recruitment of subjects and consequently the available of the clinical study data.	Comment already addressed above.
Table 1 – Primary endpoint with time points assessment		Comment: 4-weeks post-second dose should be considered as secondary endpoint.	Comment already addressed above.