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Standard Paediatric Investigation Plan for non-adjuvanted or adjuvanted pandemic influenza vaccines during a pandemic

Introduction

Novel strains of influenza virus, which are highly contagious and harmful to humans, can emerge suddenly. Their potential to cause a pandemic is monitored by the World Health Organization, and the phases of the pandemic are declared following well established rules, in a stepwise approach:

Phase 4 is characterised by verified human-to-human transmission of an animal or human-animal influenza reassortant virus able to cause "community-level outbreaks." The ability to cause sustained disease outbreaks in a community marks a significant upwards shift in the risk for a pandemic. Any country that suspects or has verified such an event should urgently consult with WHO so that the situation can be jointly assessed and a decision made by the affected country if implementation of a rapid pandemic containment operation is warranted. Phase 4 indicates a significant increase in risk of a pandemic but does not necessarily mean that a pandemic is a forgone conclusion.

Phase 5 is characterised by human-to-human spread of the virus into at least two countries in one WHO region. While most countries will not be affected at this stage, the declaration of Phase 5 is a strong signal that a pandemic is imminent and that the time to finalise the organisation, communication, and implementation of the planned mitigation measures is short.

Phase 6, the pandemic phase, is characterised by community level outbreaks in at least one other country in a different WHO region in addition to the criteria defined in Phase 5. Designation of this phase will indicate that a global pandemic is under way.
According to the degree of pathogenicity and the transmission speed in an outbreak, Regulatory Authorities will adapt their level of requirements before giving access to vaccines to different target groups of different ages within the general population.

Scope of the present document and the standard PIP

The EU Regulation foresees that any marketing authorisation (MA) application for a new medicinal product should 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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7040
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

authorised medicinal products which are protected by a Supplementary Protection Certificate (or a patent that qualifies for it), when a new indication is requested. While the PIP should not delay the granting of the MA for any age group, it still needs to be agreed with the PDCO before validation of the MAA.

In order to facilitate such a procedure, this document defines a standard set of data that applicants should include in their application for a PIP for a pandemic influenza vaccine, when submitted during an emergency situation (WHO phase 5 or 6). Manufacturers and Marketing Authorisation Holders are encouraged to anticipate and submit a request for a PIP and a Waiver, or a request of modification of an existing agreed PIP, as early as possible.

The standard PIP is not a guideline, nor a complete protocol; it contains only the so-called "key binding elements", which are the measures and timelines on which compliance check will be performed prior to validation of the MAA or the variation application. Consequently, elements that are not cited in the study tables (e.g., the exclusion criteria), may remain at the discretion of the applicant.

Please note that the principles covered in this template for a Paediatric Investigation Plan are to be read in the context of an emergency (as defined by the WHO). The European Medicines Agency and the PDCO may decide to revise these principles to take into account the evolution of knowledge on this topic.

In addition, this standard PIP document does not define registration criteria: adult CHMP criteria are used for the presentation of the paediatric data, but it remains to the competent authority to agree, based on an overall assessment of the file (adult data included), whether the vaccine can reasonably be judged as efficacious or not in different age groups.

A) Non-adjuvanted vaccines, or vaccines containing a known adjuvant

As soon as the first lots suitable for clinical studies (after upscaling) of the monovalent vaccine (not adjuvanted or containing a known adjuvant) are available, manufacturers should consider some limited dose-finding trials both in adult and children. If this is not possible or not feasible, the same full adult dosing should be provided and administered to children as a first step. A known adjuvant is defined as an adjuvant that has already been studied in children and adolescents as a component of a vaccine against an HN influenza virus.

Efficacy and safety data should be collected on a rolling basis.

Condition: Influenza

Proposed PIP indication: prevention of infection by influenza virus in the context of pre pandemics and pandemics (WHO phases 5 and 6)

A waiver for newborns and infants from birth to less than 2 months should be requested. A waiver for children 2 to 6 months of age may be requested (and should be requested for non-adjuvanted vaccines).

Paediatric Investigation Plans:

1. Overview of standard measures (studies) to be proposed by applicants

Study identifier	Standard PIP non adjuvanted / known adjuvant
Type of study	Prospective open-label single-arm study
Study objective	(Dose-finding,) immunogenicity and tolerability study

Study population and subset definition (incl. stratification)	Children and adolescents from 6 months to less than 18 years. *(This may be part of a combined adult and paediatric study/investigation.)*
Number of study participants by paediatric subset	At least 240 total participants in four subsets of 6 months to less than 12 months (at least 50), 12 months to less than 3 years (at least 50), 3 to less than 9 years old (at least 50), and 9 to less than 18 years old children and adolescents (at least 50) must[1] be investigated.
Main inclusion criteria	Healthy children and adolescents from 6 months to less than 18 years old
Dosage, treatment regimen, route of administration	Vaccination schedule with 2 injections approximately 21 days apart (an interval of 20 to 35 days is acceptable), and with at least a 14-day interval from other vaccines. *(Preliminary data could indicate that for a second step a one dose-priming schedule may suffice for part or most of the population. A 1-dose + placebo approach could be explored in this second stage)* Booster: Among the participants of all subsets (in at least 30 for each subset as above, which must include all patients being tested for NT in each group), a booster dose must be studied. *(The booster will be administered 6 or 12 months after the first vaccination [priming], depending on the evolution of the pandemics [attack rate remains low or slow in phase 6]. The objective is to identify the potential need for boosting in all or part of the paediatric population and to measure antibody persistence.)* Sampling approach Before each of the 2 vaccine doses and after the 2nd dose, a blood sample is to be collected, i.e. at day 0, immediately before the second dose, and 20-40 days after the second dose (3 samples in total) for immunogenicity. Pre- and postbooster samples must also be drawn in the boosted participants. for measurement of HI or SRH as primary endpoint, and NT in all included patients that were previously tested for NT.
Control	No control arm
Primary endpoint with time point of assessment	Immune responses after second injection, to be assessed using the so-called CHMP criteria for influenza vaccines (haemagglutination-inhibition [HI] assay or SRH [SRH preferred] in all participants) Immunogenicity sample collection must be done pre and post vaccination.
Other outcomes with time points of assessment	Neutralisation test [NT] after first and second injection (the three samples must be drawn from the same subjects) in: at least 30% of participants for each subset of children 3 years and older; at least 50% for those 6 months to less than 3 years. HI or SRH (SRH preferred) after first injection in at least 90% of participants. Pre- and postbooster immunogenicity by HI or SRH; pre- and postbooster NT in all included patients that were previously tested for NT.

[1] The terms "must" and "is/are to be" are used throughout, instead of "should", as this reflects the language of the PDCO opinions; these contain the key binding elements, against which compliance will be checked.

Plan for specific follow-up	<u>Safety</u> Safety endpoints should be collected using the same protocol for data collection as for the prospective cohort study described in the CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza vaccines – Rev. 1 *(EMEA/359381/2009*). *(Based on the interim safety and immunogenicity data collected during the investigations of an adjuvanted vaccine, both full dose and at least one lower dose might have to be investigated simultaneously in different study arms. If the safety profile of the full dose raises major concerns, the full dose may be omitted.)* See also specific measures below. <u>Effectiveness</u> The end-point for effectiveness must be determined based on the options proposed, namely a best combination of ECDC recommendations (protocols available in June 2009), and national plans, including availability.
External Data Safety Monitoring Board	No. Safety to be reported as per Risk Management Plan
Date of initiation	At the same time as studies in adults[2]
Date of completion (last patient, last visit)	Primary endpoint (immunogenicity by HI or SRH assay): not later than 20 weeks after initiation of the study. (*Interim immunogenicity results should be submitted and assessed on a rolling basis by CHMP, possibly indicate the need to revise the regimen, or allow competent authorities to officially release the vaccine immediately.)* Secondary endpoints: by 6 months after booster dose, or by end of safety cohorts as per Risk Management Plan, whichever comes last.

B) Vaccines containing a new adjuvant

A new adjuvant is defined as any adjuvant, part of a vaccine against an HN influenza virus, for which data in children of less than 18 years are not available, at the time of the declaration of phase 5 or 6 by WHO.

As soon as the first lots suitable for clinical studies (after upscaling) of the monovalent vaccine containing a new adjuvant are available, manufacturers should start non-clinical studies, and consider some limited dose-finding trials both in adult and children. If this is not possible or not feasible, the same full adult dosing should be provided and administered to children as a first step.

Studies in children should not be initiated until the completion of the whole standard package of non-clinical studies for the new adjuvant.

Efficacy and safety data should be collected on a rolling basis.

[2] "At the same time" should be understood as follows: studies in all paediatric subsets from 6 months of age and older should start within one month from starting studies in adults. Staggered approach is possible within this constraint.

Condition: Influenza

Proposed PIP indication: prevention of infection by influenza virus in the context of pre pandemics and pandemics (WHO phases 5 and 6)

A waiver for newborns and infants from birth to less than 2 months should be requested. A waiver in children 2 to 6 months of age may be requested.

1. Overview of standard measures (studies) to be proposed by (at time of start of investigations)

Clinical study:

Study identifier	Standard PIP / new adjuvant
Type of study	Prospective open-label single-arm study
Study objective	(Dose-finding) immunogenicity and tolerability study
Study population and subset definition (incl. stratification)	Children and adolescents from 6 months to less than 18 years. *(This may be part of a combined adult and paediatric study/investigation.)*
Number of study participants by paediatric subset	At least 240 total participants in five subsets of 6 months to less than 12 months (at least 50), 12 months to less than 3 years (at least 50), 3 to less than 9 years old (at least 50), and 9 to less than 18 years old children and adolescents (at least 50) must[3] be investigated.
Main inclusion criteria	Healthy children and adolescents from 6 months to less than 18 years old
Dosage, treatment regimen, route of administration	Vaccination schedule with 2 injections approximately 21 days apart (an interval of 20 to 35 days is acceptable), and with at least a 14-day interval from other vaccines. *(Preliminary data could indicate that for a second step a one dose-priming schedule suffices for part or most of the population. A 1-dose + placebo and booster can be explored in this second stage.)* <u>Booster:</u> Among the participants of all subsets (in at least 30 for each subset as above, which must include all patients being tested for NT in each group), a booster dose must be studied. *(The booster will be administered 6 or 12 months after the first vaccination [priming], depending on the evolution of the pandemics [attack rate remains low or slow in phase 6]. The objective is to identify the potential need for boosting in all or part of the paediatric population and to measure antibody persistence.)* <u>Sampling approach</u> Before each of the 2 vaccine doses and after the 2nd dose, a blood sample is to be collected, i.e. at day 0, immediately before the second dose, and 20-40 days after the second dose (3 samples in total) for immunogenicity.
Control	No control arm

[3] The terms "must" and "is/are to be" are used throughout, instead of "should", as this reflects the language of the PDCO opinions; these contain the key binding elements, against which compliance will be checked.

Study identifier	Standard PIP / new adjuvant
Primary endpoint with time point of assessment	Immune responses after second injection, to be assessed using the so-called CHMP criteria for influenza vaccines (haemagglutination-inhibition [HI] or SRH assay [SRH preferred] in all participants). Immunogenicity sample collection must be done pre and post vaccination.
Other outcomes with time points of assessment	Neutralisation test [NT] after first and second injection (the three samples must be drawn from the same subjects) in: at least 30% of participants for each subset of children 3 years and older; at least 50% for those 6 months to less than 3 years. HI or SRH [SRH preferred] after first injection in at least 90% of participants. Pre- and postbooster immunogenicity by HI or SRH; pre- and postbooster NT in all included patients that were previously tested for NT. <u>Effectiveness</u> The end-point for effectiveness must be determined based on the options proposed, namely a best combination of ECDC recommendations (protocols available in June 2009), and national plans, including availability.
Plan for specific follow-up	<u>Safety</u> Safety endpoints should be collected using the same protocol for data collection as for the prospective cohort study described in the CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza vaccines – Rev. 1 *(EMEA/359381/2009*). *(Based on the interim safety and immunogenicity data collected during the investigations of an adjuvanted vaccine, both full dose and at least one lower dose might have to be investigated simultaneously in different study arms. If the safety profile of the full dose raises major concerns, the full dose may be omitted.)* See also specific measures below. <u>Effectiveness</u> The end-point for effectiveness must be determined based on the options proposed, namely a best combination of ECDC recommendations (protocols available in June 2009), and national plans, including availability.
External Data Safety Monitoring Board	No. Safety to be reported as per Risk Management Plan
Date of initiation	After completion of the standard non-clinical package, and at the same time as studies in adults[4];
Date of completion (last patient, last visit)	Primary endpoint (immunogenicity by HI or SRH assay): not later than 20 weeks after initiation of the study.

[4] "At the same time" should be understood as follows: studies in all paediatric subsets from 6 months of age and older should start within one month from starting studies in adults. Staggered approach is possible within this constraint.

Study identifier	Standard PIP / new adjuvant
	(Interim immunogenicity results should be submitted and assessed on a rolling basis by CHMP, possibly indicate the need to revise the regimen, or allow competent authorities to officially release the vaccine immediately.) Other outcomes: by 6 months after booster dose, or by end of safety cohorts as per Risk Management Plan, whichever comes last.

C) All vaccines

Co-administration with other vaccines

Co-administration of the influenza vaccine (in a pandemic) with other vaccinations is not advised.

Stepwise approach for the vaccine development

If the immune response in children appears satisfactory but the safety profile is not, the development strategy must be revised and different doses must be investigated immediately (e.g. half dose). Immediate interaction with the Paediatric Coordinator at the Agency, the PDCO Rapporteur and the PDCO Peer Reviewer is requested under these circumstances.

2. Specific measures for long term follow-up of potential safety issues and efficacy in relation to paediatric use, to be proposed at the time of submission of the related application

Safety

Measures to monitor safety of the vaccines must be implemented as per the CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza vaccines – Rev. 1 (EMEA/359381/2009). Once the vaccine is in use, at least 4000 children in 3 cohorts of infants younger than 2 years (at least 500), children from 2 years to less than 9 years (at least 500) and 9 to less than 18 years (at least 3000), must be included in a safety cohort and followed for at least 6 months after the last dose. Adverse drug reactions of special interest (e.g. febrile convulsion, polyneuropathies including Guillain-Barrè syndrome) must be explicitly identified and reported.

Case control studies could be necessary and screening method studies might be helpful to detect modifications of vaccine effectiveness over time (e.g. the strains drifts).

All available pre-authorisation data on immunogenicity and safety must be included in the Safety Specification of the RMP.

Immunisation of pregnant women and paediatric use of vaccines

Special attention should be given to pregnant women. Babies born during a pandemic period are at risk unless the mother is efficiently protected. Maternal vaccination should be considered, with the aim of not only documenting maternal antibody response, but also vaccine impact on acquired neonatal antibodies, and clinical development of the newborn.

3. Reminder

- Studies and trials have to be registered with the EudraCT database. All investigational medicinal products used in the studies or trials must be registered in the EudraVigilance Medicinal Product Dictionary by the sponsor.

- Studies or trials which are inconclusive or not interpretable will be considered non-compliant.
- The Clinical trials should be performed in accordance with Good Clinical Practices and for those conducted outside the community they should be carried out in accordance with the ethical standards of Directive 2001/20/EC.
- The Applicant must ensure that measures to minimise pain and distress are implemented during the whole paediatric development.

Final notes and practical guidance

Format of the PIP application

PIP applications for influenza vaccines during a pandemic should follow the standard format of PIP applications. Templates and guidance can be found in the Guidance for Applicants page in the Paediatrics section of the Agency's website. In particular, consultation of the European Commission guideline on format and content of applications for paediatric investigation plans and of the EMA procedural advice on PIP applications is suggested before applying for a PIP. However, it is considered that a brief discussion is sufficient for parts B and C.

The structure of the application should follow the outline published in the last page of the Electronic template for PIP applications, and also shown in the Template for the PDCO Summary Report.

Please note that the paediatric clinical trials mentioned in this document only cover part D.IV of the application.

For all questions pertaining to this standard PIP, applicants may contact the Paediatric Section at Paediatrics@ema.europa.eu .

Deadlines and accelerated procedure for agreement of the PIP

The normal submission deadlines apply (published in the Guidance for Applicants page). Please note the new PDCO meeting dates for 2010.

An accelerated procedure for agreement on proposed PIPs for influenza vaccines during a pandemic is aimed at a possible positive opinion on the date of the first PDCO meeting at the time of the official start date of the procedure (D0), for the PIPs that follow the "standard PIP" and do not raise additional issues. If there is a need for interaction with the applicant, a possible opinion could be adopted at the second PDCO after the start date (D30).

This standard PIP is a general document, intended to facilitate the work of all parties; clearly, specific cases may not fit in this template, and justified modifications are always possible. However, delays in the accelerated procedure may occur if important modifications are proposed to the standard PIP.

The submission of clinical trial authorisation requests for paediatric studies, or the performance of the studies, is an independent procedure, which does not need to wait for the successful outcome of the PIP application (or even the submission of the PIP application).

Applicants are strongly invited to maintain frequent contact with the Paediatric coordinator at the Agency, the Rapporteur and the Peer Reviewer for their PIP during the paediatric studies, particularly in case there is a need to change the approach, based on the rolling assessment of data.

Compliance check for PIPs relating to pandemic influenza vaccines will also follow an accelerated procedure, and will take into due account the special situation and the need for a limited degree of flexibility.

Guidance for applicants with already agreed PIPs for different strains of pandemic influenza (H5N1)

If an applicant has already obtained a PIP for a pandemic influenza vaccine with another strain (H5N1), the application for the H1N1 PIP should be a separate one, submitted and agreed as above. The applicant may, if required, also apply for a modification of the agreed (existing) PIP for the H5N1 strain, for example to request a deferral for completing the relevant studies.