EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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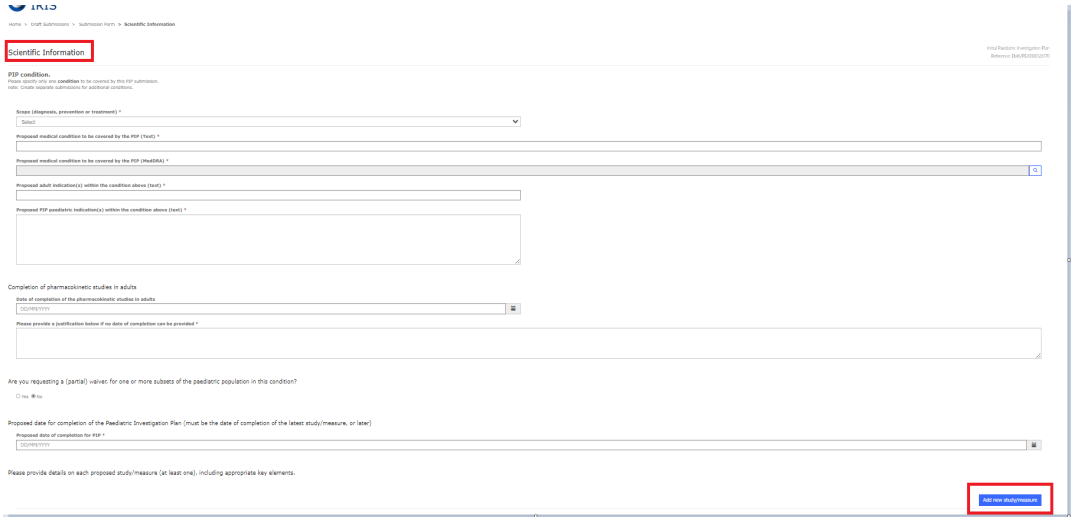
Human Medicines Division

Paediatric investigation plan (PIP) - Key elements guidance

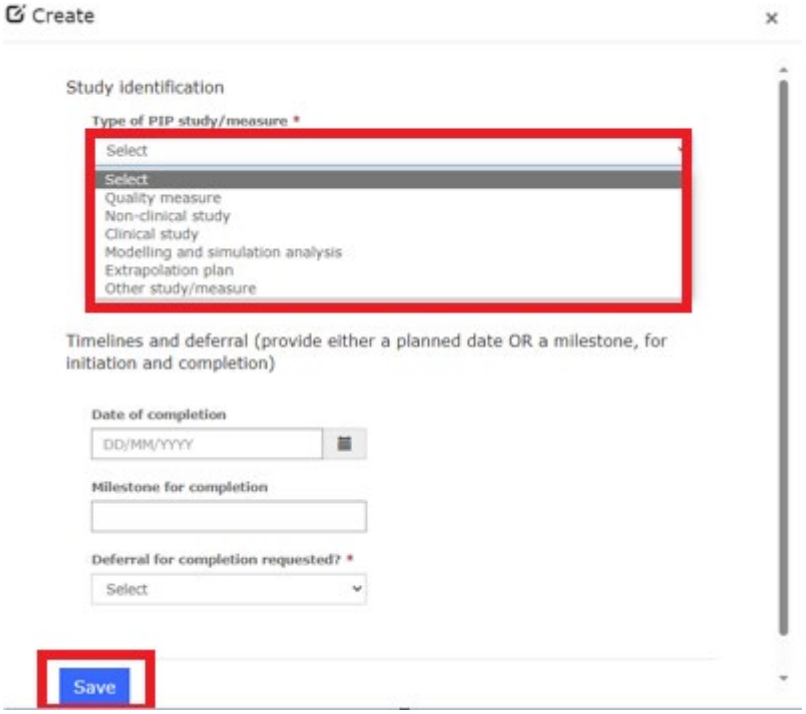
General guidance

Please do not submit this document but the information in IRIS using this document as a guidance.

While completing the Submission form in IRIS, use **Add new study/measure** button to include each study under Scientific Information tab.



Chose the type of Study/measure from the drop-down menu to populate the necessary fields. Always "Save" once all mandatory fields are completed.



1. Details of the proposed measures

1.1. Measures to be performed according to the specified timelines

1.1.1. Quality-related studies

Key elements field	*Guidance on how to complete in IRIS*
Study identifier	Include study identifier or put "Not available" in the free text field.
Study description and objectives	*In this field, describe objective of quality study using wording analogous to the examples provided below; e.g., "Development of <pharmaceutical form, e.g. granules> <an age-appropriate formulation"* *Refer to EDQM for standard terms* • *Specify liquid or solid for oral form if known* • *Specify route of administration (if known) (e.g. oral use, intravenous use, gastroenteral use)* • *Include only age-appropriate formulation planned to be developed* *Examples of wording:* • Development of new route of administration: ><for use in <paediatric population subset> • Development of a <preservative-free eye / ethanol-free> pharmaceutical form> <not containing <certain excipients> • Development of <lower strength appropriate to the paediatric population> <vial containing less than 10-fold of the lowest dose for adults> <scored tablet> of <existing dose form • Development of a medical administration device <with suitable graduation to be added to the liquid formulation>><development of an appropriate dispensing device for granules • Generation of data on acceptability and palatability during the clinical trial(s) with the target population
Date of completion	*Select a "**Date of completion**" from the calendar* ***Or*** *Include a milestone in "**Milestone for completion**" field.*

	There must be a date, or optionally a milestone, if measure is not deferred and it is not the last study. *The completion date should correspond, in principle, to the completion of the PIP. However, the formulation is usually expected to be available at the time of the relevant clinical study.* *Example of wording for milestone:* <Before submission of the MAA for adults for <condition>> *Select* **Yes/No** *from the drop-down menu to complete the question "***Deferral for completion requested?***"*

1.1.2. Non-clinical studies

Key elements field	***Guidance on how to complete in IRIS***
Study identifier	*Include study identifier or put "Not available" in the free text field.*
Study description, objectives and outcome measures	*In principle only the objective, species, and duration should be mentioned in this field.* *There is no need for the age of the animals at study start – it is sufficient to say "juvenile".* *Add outcome if specific: e.g., histopathology of brain.* *Add control group if specific: e.g., excipients.*
Test system/species (age of the animal)	• *Species and/or model* *Click on the magnifying glass symbol and chose the species from the Lookup records.* • *Age of the animals at study start* *Currently there is no free text area for this field in the system, please add age of the animal under "Study description, objectives and outcome measures".* *It is not necessary to include the number of animals.*
Duration of dosing	*Include duration of dosing and, if applicable, recovery period in this field.*
Route of administration	*Click on the magnifying glass symbol and chose the species from the Lookup records.*
Date of initiation	Select a **"Date of initiation"** from the calendar.

	Or Include a milestone in **"Milestone for initiation"** field. *Examples of wording for milestone:* To be initiated only after the completion of the development of the age-appropriate formulation Must be initiated before submission of the regulatory application for condition x *Select **Yes/No** from the drop-down menu to complete the question **"Deferral for completion requested**?"*
Date of completion (final study report signed)	Select a **"Date of completion"** from the calendar. Or Include a milestone in **"Milestone for completion"** field. There must be a date, or optionally a milestone, if measure is not deferred and it is not the last study. The completion date should correspond, in principle, to the completion of the PIP. However, the formulation is usually expected to be available at the time of the relevant clinical study. Example of wording for milestone: Before submission of the MAA for adults for <condition> When completion is required for a paediatric clinical trial, specify this as initiation requirement in the concerned trial in the "Milestone for completion" field. Select **Yes/No** from the drop-down menu to complete the question **"Deferral for completion requested?"**

1.1.3. Clinical studies

In cases where elements cannot be defined in full, a milestone should be added specifying how the element will be defined in the future (e.g. to be agreed with the PDCO within x months after completion of non-clinical study X, or a specific study in adults, or results from a study in a different paediatric population or a different condition, etc (include study identifiers if known).

Key elements field	***Guidance on how to complete in IRIS***
Study identifier	*Include study identifier or put "Not available" in the free text field.*
Study design features, main objectives and study population	*A short summary of the study design features and study population should be added in this field. Age (from birth/x weeks-months-years of age to less than y weeks-months-years of age), sex and condition to be included, and any other study population details (e.g. specific eligibility criteria such as 'diagnosis of glaucoma and intraocular pressure above 21mmHg') as considered necessary.* • *Do **not** mention:* – *study phase (e.g., I, II, or IIIb)* – *patient numbers* – *abbreviations (expand)* – *concept of 'efficacy' trial - if it is e.g. an open, uncontrolled trial, use 'activity'* • *Do mention (as applicable, based on the information available at the time the PIP is submitted):* – *the **design and the objective** briefly, add-on, in combination* – ***periods** such as "with x-month open-label extension to evaluate safety"* – ***population** to be included: brief qualification e.g. naive, experienced* – ***age groups** or other subsets (e.g. "from 8 years to less than 18 years of age", "post-menarcheal girls")* – *if comparator-controlled, use the INN of the comparator. (Exceptionally it can be an invented name if otherwise too long, e.g. with vaccines.)* • *Follow the examples of wording below as much as possible (order of elements, etc.)*

	<Open-label>, <double-blind>, <randomised>, <assessor-blind>, <single/multiple dose>, <active/placebo <external/concurrent/historical> controlled> trial to evaluate <pharmacokinetics>, <safety>, <activity>, <efficacy>, <activity>, <acceptability/palatability>,<immunogenicity> of <active substance(s)> <as add-on to best standard of care/X> <compared to Y> in children from <age> to less than <age> <years> <months> of age with <broad definition of the population or other subsets> *Additionally, select from the objectives below, and add others if relevant. There is no need to repeat in detail objectives/outcomes as they will be listed separately below.* in terms of <superiority of X over placebo/control>, <reduction of Y> <non-inferiority of X as compared to Y with respect to Z> <estimation of treatment effects> and <to provide <PK/PD data to support the extrapolation of efficacy from other populations **including pre-specification of success criteria>** *Cross-reference clinical studies that have extrapolation as an objective to section 1.1.6, as necessary* <to contribute to modelling of the PK/PD/exposure/dose-response relationship> in children from age to age < (and adults)> with <broad population definition>, <with extension study to evaluate safety>
Number of study participants by paediatric subset (e.g. age, sex, severity or stage)	*Include randomisation and number per subset as appropriate using the format 'at least' in this field.* *Depending on the type of study, e.g. for PK, the sample size can be precisely defined. In other cases where many elements are not known (e.g. the effect size in adults) and it is difficult to define, it may be appropriate to define the sample size in the most vulnerable groups (e.g. very young children) as a percentage of the overall sample size.* At least x patients/subjects evaluable for the primary analysis *(or enrolled, randomised, followed up until x etc. as appropriate)* *A condition can be added here if a sample size cannot be defined, according to the examples of wording below:* <Number of subjects to be recruited/randomised/evaluable for the primary analysis> <to be agreed by the PDCO before initiation of the study> <to be estimated to achieve at least

	xx% power for an effect size of x in the primary analysis to demonstrate superiority/non-inferiority> <using a two-sided hypothesis test at 5% error level/with at least 95% probability using Bayesian decision-making> *and add further assumptions, e.g. power, significance level, expected treatment effect, variance response if known, based on data from ongoing adult programme, augmenting/incorporating prior information from external data*
Duration of study (for participants)	*Complete this field using bullet points for each study period.* • Treatment duration: must be planned for at least x days/weeks/years in protocol *e.g. one year (including 12-week double-blind and 9-month open-extension)* *In cases where the duration of study participation cannot be defined at the time of agreement of the PIP, a condition can be added, e.g. in line with adult efficacy and safety studies, or milestone agreed for PDCO discussion/agreement. It may be appropriate to define a minimum duration in certain cases.* • Follow-up duration (part of completion of this study): must be planned for at least x days/weeks/years in protocol *In this section a bullet point can be included for long-term follow-up studies if appropriate, specifying that this is not part of the PIP.* • Long-term follow-up study/duration><<not> part of the PIP
Dosage, treatment regimen and route of administration	*Mention exact doses to be studied only if known in this field. Otherwise, if dose not known, describe on what basis the dose will be selected (e.g. based on results from the PK study x and/or modelling and simulation study y)* *Specify if multiple doses tested.* *If add-on design, describe add-on therapy* <using pharmaceutical form developed in study x> <once-daily/twice-weekly/…>, <route of administration>, <dose>/<dose to be based on results of study x>
Control	*Include placebo or active comparator (INN/other name e.g. for vaccines, dosage, route of administration) in this field.*

	If external control, exact description including source of data (including study identifier, if applicable) *In cases where a control cannot be defined at the time of agreement of the PIP:* • *a condition can be included, e.g. 'the control must be agreed with the PDCO once data from study X are available'* • *or the control could be a class of products* • *or it must match the control used in adult studies*
External Data Safety Monitoring Board	*Select* **Yes/No** *from the drop-down menu.*
Key evaluations and outcomes	*Complete this field using bullet points.* *List with time point(s) of assessment as applicable.* *This section should include* ***only the critical evaluations and outcomes important for establishing the paediatric indication****. These are usually the primary endpoint but not necessarily limited to this.* *In cases where a primary endpoint cannot be defined it may be acceptable to include a primary objective here, e.g. to collect efficacy information and further details on the primary endpoint to be added following a certain milestone (e.g. from a study in adults, or an earlier phase study in children). For small open-label studies it may be appropriate to not define endpoints as primary or secondary, as such studies are not powered for the primary endpoint.* *When secondary endpoints are required to be included in the opinion* ***only the most relevant*** *should be added here. This is not intended to be a copy of all endpoints included in the protocol but a summary of those considered most relevant to support the overall objective of the study. Occasionally exploratory endpoints are considered very important (e.g. important endpoints to advance the field on a specific issue).* *Examples of wording for evaluation of PK:* <Pharmacokinetic parameters including, e.g., Cmax, AUC, t1/2, Csteadystate, Ctrough> <using <number> samples per participant> <using sparse sampling>

Statistical plan	*Complete this field using bullet points.* *This section should be kept at a high level without too many details (and without repeating details that are stated elsewhere), e.g. evaluation of superiority, descriptive statistics, Bayesian decision-making, etc. and further details to be included only in cases where there is a justified need to do so.* *Specify if interim analysis is planned. Specify if data will be used for modelling/simulation; if used to support extrapolation (ie cross-referenced to section 1.1.6 [extrapolation plan] reflect on pre-specification of success criteria.*
Other	*E.g. include in this field information if internal experts are considered necessary to participate to a data safety monitoring board, for example to safe-guard patients in a first in child study.*
Date of initiation	Select a **"Date of initiation"** from the calendar Or Include a milestone in **"Milestone for initiation"** field. *Either a date of initiation or milestone must be proposed, but the PDCO will decide whether this date should be specified in the adopted opinion; in most cases it will not be specified.* *Examples of wording for milestone:* Must be initiated before the adult MAA submission. To be initiated only after the completion of the development of the age-appropriate formulation (study 1…) To be initiated only after the completion of non-clinical study number 2… To be initiated within x months after completion of adult study XX To be initiated only after consultation with relevant academic consortia confirming a clinically relevant effect size estimate observed in study X warranting pivotal development in an identified target population *Select **Yes/No** from the drop-down menu to complete the question "**Deferral for completion requested?**"*
Date of completion	This date refers to last patient, last visit. Select a **"Date of completion"** from the calendar.

	Or *Include a milestone in "**Milestone for completion**" field.* *There must be a date, or optionally a milestone, if measure is not deferred, and it is not the last study.* *Examples of wording for milestone:* Before submission of the MAA for adults for <condition> x months after completion of study y *When completion is required for another paediatric clinical trial, specify this as initiation requirement in the concerned trial.* *Select **Yes/No** from the drop-down menu to complete the question "**Deferral for completion requested?**"*

1.1.4. Modelling and simulation analyses

Physiologically based model (PB-PK)

*Choose this **Physiologically based model (PB-PK)** from Model type drop-down list**

Key elements field	***Guidance on how to complete in IRIS***
Study identifier	*Include study identifier or put "Not available" in the free text field.*
Study description and objectives[1]	*Please note that the use of PB-PK to predict drug interaction in children is out of scope; this should be discussed in the scientific document.* *Choose **one or more** of the following:* 1. Use of PB-PK to predict initial paediatric doses to be used in further clinical studies. 2. Use of PB-PK to analyse (sparse) PK data collected in paediatric studies to inform dosing recommendation in paediatric subjects. 3. Use of PB-PK to simulate PK in paediatric subjects, to be used as a basis for extrapolation and choice of paediatric posology from age <X> to age <X> 4. Use of PB-PK to extrapolate PK outside the studied age range to inform dosing recommendation for paediatric subjects.

[1] Due to technical reasons some fields have the exact same title, however this key element is named as **Model** description and objectives in the opinion.

	5. Other
Model type	*Choose from the drop-down menu: ** • ***Physiologically-based model (PB-PK)***
Data to be used to build the model	*Specify PK data in adults as well as PK data in older children to be used, e.g. study identifier or number of studies or type of study. It is important to mention source/reference for the input parameters/data. Use examples of wording below.* Adult Paediatric data *And* Age subsets providing data
Methodology	Description of PB-PK platform: *Describe the PB-PK model and platform where ontogeny and age (weight) related changes are incorporated (if relevant for the age group, e.g. for metabolising enzymes and drug transporters, or renal clearance).* *Specify used PB-PK platform name (examples of commercial platforms include SimCYP, Gastroplus, PK Sim.* *Specify if the PB-PK platform (system model) is qualified for the objective (if needed).*
Population and physiological parameters (PBPK model)	Paediatric patients from <X> <years/months/days> to <X> <years/months/days> of age <with the following characteristic: X> *Specify which mechanistic assumptions, pertinent physiological and population parameters are included in the model.*
Model evaluation / qualification	*Qualification is mainly relevant for objectives 3 and 4 in the field of "Model description and objectives".* *Here the section should be split into 2 sections:* 1. Platform qualification of the system model *As a general rule, qualification is required where the regulatory impact of the model is high, therefore this is dependent on the objective as stated above. This is particularly important where the model is used for* ***extrapolation****.*

	However, to predict initial dose(s) for a paediatric trial, no PBPK platform qualification is needed. *Posology recommendations in paediatric patients that are supported by only sparse clinical exposure/PK data and heavily rely on PBPK modelling are considered to be high regulatory impact applications and thus require platform qualification in the following cases (see 1. and 2.)* *1. When sparse exposure data are available in that age range, the platform qualification could consist of a minimum of two compounds with similar ADME properties with PK data in the particular age range.* *2. When PB-PK modelling is used without PK data from a selected age range, the platform qualification needs to meet additional requirements including a larger number of similar compounds and to also consider ontogeny, if relevant (see Guideline on the reporting of physiologically-based pharmacokinetic (PBPK) modelling and simulation).* *Examples of drugs useful for qualification packages are amikacin for renal clearance or digoxin for clearance by P-glycoprotein (Pgp).* No PBPK qualification needed since PB-PK platform will be used to predict initial dose(s) for a paediatric trial. *Or* PB-PK platform qualification of <product name> in <intended use> using data from <compound(s) 2. Substance model evaluation *The adult PB-PK model should be evaluated comparing the observed vs predicted PK data. Sensitivity analyses for uncertain parameters should be performed.* Evaluation of the drug PBPK model to be performed comparing data from study <X> versus predicted data. *The paediatric PB-PK model should be evaluated against PK data in children, when available, comparing observed vs predicted PK data. Sensitivity analyses for uncertain parameters used to inform the paediatric model should be performed.*

	Figures and tables should be provided as appropriate in the scientific document. *The following can be added if considered necessary:* Outcome of the evaluation to be presented using: • Plots of the comparison of the simulated and the observed plasma concentration-time data using linear and semi-log plots and as tabulations • Visual predictive plots • Other
Date of completion	*Should be aligned to the objective, e.g. before study initiation if initial paediatric dose is required.* *Select a "**Date of completion**" from the calendar.* *Or* *Include a milestone in "**Milestone for completion**" field.* *Example of wording for milestone:* Before submission of the MAA for adults for <condition> *Select **Yes/No** from the drop-down menu to complete the question "**Deferral for completion requested?**"*

Population (Pop-PK) model and PK/PD analysis

*Choose **Population (Pop-PK) model or PK/PD analysis** from Model type drop-down list**

Key elements field	***Guidance on how to complete in IRIS***
Study identifier	*Include study identifier or put "Not available" in the free text field.*
Study description and objectives[2]	1. Use of PopPK(/PD) to predict initial paediatric doses to be used in further clinical studies. 2. Use of PopPK(/PD) to confirm or modify the paediatric posology compared to the regimen used in clinical trials. 3. Use of PopPK(/PD) to simulate PK in children to be used as a basis for extrapolation and paediatric posology form age XYZ to age XYZ. 4. Other

[2] Due to technical reasons some fields have the exact same title, however this key element is named as **Model** description and objectives in the opinion.

Model type	*Choose from the drop-down menu either: ** • *Population (Pop-PK) model* *Or* • *PK/PD analysis*
Data to be used to build the model	*Specify PK and PD data sources in adults as well as other paediatric age group(s) in this field. PK and PD data in older children to be used, e.g. study identifier or number of studies or type of study, number of subjects.* *Examples of wording:* Data on clearance pathways, plasma protein binding, and distribution from X Models for organ ontogeny should be considered for relevant age groups: from study X. Knowledge of disease (progression) and PD in children from study X *if available*
Methodology	*The population PK model must be developed using non-linear mixed effects modelling. The general approach to the population PK modelling will involve development of a base structural model.* *Preferably models should be developed in order of increasing complexity, beginning with very simple models (e.g. 1-compartment with 1st-order elimination) and proceeding until further improvement in fitting the model is not supported by the data.* *A pre-specified modelling plan should be provided. Any assumptions, e.g. concerning physiological processes in the model should be discussed, and covariates to be tested pre-specified. More detail can be found in the CHMP Guideline on reporting the results of population pharmacokinetic analyses.* *Example of wordings:* Description (e.g. Pop-PK model based on adult data to be updated with emerging data from paediatric patients to determine x to characterize the PK profile of y/to describe z Step 1: text Step 2: text, etc.
Covariates	*Following development of the base structural model, the impact of demographic covariates should*

	be investigated. In particular, covariates relevant to the paediatric population such as weight and age should be investigated. Additional covariates such as body surface area (BSA) may also be considered if deemed necessary. Explain as appropriate if the covariates are just included or only tested. *Examples of wording:* Body size parameter (e.g. weight / height / BMI)
Model evaluation /qualification	*Model evaluation should be based on goodness of fit plots, final parameter estimates and a prediction corrected visual predictive check (VPC). VPCs stratified according to age and weight groups, and individual plots of predicted versus observed for individuals of interest, might be considered. More detail can be found in the CHMP Guideline on reporting the results of population pharmacokinetic analyses.* *Examples of wording:* By: Goodness of fit plots Visual predictive checks Assessment of plausibility of parameter estimates Assessment of parameter uncertainty estimation
Date of completion	*Should be aligned to the objective, e.g. before study initiation if initial paediatric dose is required.* *Select a "**Date of completion**" from the calendar.* *Or* *Include a milestone in "**Milestone for completion**" field.* *Example of wording for milestone:* Before submission of the MAA for adults for <condition> *Select **Yes/No** from the drop-down menu to complete the question "**Deferral for completion requested?**"*

Other

Choose "Other" from Model type drop-down list for presenting different models if needed.

1.1.5. Extrapolation plan

Cross-refer to the study(ies) that are part of the agreed extrapolation plan, i.e. all studies (clinical, M&S and/or others) with the objective to support the extrapolation of efficacy as per the summary.

<Study(ies) XYZ, <are> <is> part of the extrapolation plan of efficacy data from <adult> <adolescents> <paediatric patients> to the paediatric population <from birth to less than 18 years of age> <the paediatric population from birth / xx months / xx years to less than yy years of age> / <preterm newborn infants> / <term newborn infants from birth to less than 28 days of age> <infants and toddlers from 28 days to less than 24 months of age> <children from 2 years to less than 12 years of age> <adolescents from 12 years to less than 18 years of age> <other subset(s)> with condition XYZ.>.

1.1.6. Other studies

Use this section in case additional study(ies) beyond the clinical and modelling and simulation study(ies) are considered necessary to further substantiate the extrapolation plan, e.g. literature review on disease similarity, or a certain biomarker equally applicable across populations.

Key elements field	***Guidance on how to complete in IRIS***
Study identifier	*Include study identifier or put "Not available" in the free text field.*
Study description and objectives	*Add additional details as relevant.* *Examples of wording for study description:* Analysis of e.g. existing <in house>, and/or <external clinical> and <literature> data on <mechanism of action of>, <active substance(s)>, <class of medicines> on <condition definition to demonstrate <objective> *Examples of wording for study objectives:* <To provide data in support of efficacy assumptions in the paediatric population as per extrapolation concept, <evidence synthesis of different data sources> e.g. via meta-analysis, <including some specificities, e.g.>, from <source population> <To present data supporting the assumption that the outcome of treatment is likely to be similar in paediatric subsets by age and by any other relevant characteristics compared to adults by providing an analysis of <define> <Target population: paediatric <patients> <subjects> from age to age>
Methodology	*Examples of wording:* <Short description (max 40 words) of the methods of the analysis/study>

Study population and stratification	*Examples of wording:* Disease/population description included in the analysis as source of data Studies: reference to adult/paediatric studies included in the analysis Registries: <product or disease registry used for source of data>
Date of completion	*Select a "**Date of completion**" from the calendar* *Or* *Include a milestone in "**Milestone for completion**" field.* *Example of wording for milestone:* Before submission of the MAA for adults for <condition> *Select **Yes/No** from the drop-down menu to complete the question "**Deferral for completion requested?**"*