Scientific document

Related to an IRIS application for a:

Paediatric Investigation Plan (PIP)

with a (partial) waiver

with a deferral for one or more studies

Product-specific waiver

<Active substance(s)>

<Submission number> - Include submission number before uploading.

Ensure that the information above is the same as in the IRIS submission.

Guidance text is in green italics. You may like to make a copy of this template with the drafting notes, then delete them all at once by:

Clicking on Ctrl-Alt-Shift-S to view the “styles” window. Select “Drafting notes (Agency)” and click on the icon on the right, chose “Select all XXX instances”, press the “Delete” key on the keyboard.

Do not amend or delete the titles and the numbering style (add “Not applicable” where necessary).

Do not delete the comment boxes.

Recommended font: Verdana 9.

Paragraph tab: alignment: left, outline level: body text, indentation: 0, spacing before: 0pt and after: 7pt; line spacing: at least, at: 14pt.

Inserting tables: Please use plain table and where possible in portrait layout.

Inserting pictures and figures: Keep the document flowing, do not use section breaks (unless your table can not fit in portrait layout).

Do not use links, fields and citations; keep the document free of footnotes and endnotes.

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1. Application Summary

This application is submitted to meet the paediatric requirements under Regulation (EC) No 1901/2006 as amended.

This overview is to inform about the main aspects of the proposal for a PIP and/or waiver. Please do not exceed 750 words and ensure consistency of the information provided in other documents. Please add N/A where information is not available or not applicable.

**Active substance(s):** <Text>

**Product name(s) in EEA:** <Text> if authorised in the EEA

**Product name(s) outside EEA:** <Text> if authorised outside of EEA

**Authorised indication(s):** <Text> as mentioned in EPAR (or Product Information)

**Type of authorisation:** <Text> e.g. centralised or national

**Planned indication(s) in adults:** <Text> as mentioned in the IRIS submission

**Condition:** <Text> as mentioned in the IRIS submission; it should be relevant to the mechanism of action. Refer to policy *EMA/272931/2011*. State whether it is “treatment”, “prevention” or “diagnosis”. **Please note that a self-standing PIP is required for each condition.**

**Proposed indication(s) in children:** <Text> as mentioned in the PIP application form.

**Potential benefit for children:** <Text> Summary of potential significant therapeutic benefit for this medicinal product in relation to therapeutic needs in children.

**Pharmaceutical form:** <Text> Identify if there is a need for development (based on proposed age groups and indication). If potentially yes, describe plans including timing of availability of age-appropriate formulation for paediatric studies.

**Route of administration:** <Text> Use EDQM standard terminology

**Waiver(s):** <Text> Brief justification for product-specific waiver or partial waiver request in relation to proposed paediatric subsets.

**Deferrals:** <Text> Summarise milestones of proposed paediatric studies, if relevant, in relation to adult development.

**Non-clinical plans:** <Text> Brief overview of how proposed non-clinical study programme and/or existing data support studies and use in children. Brief summary of proposed non-clinical studies or justification for absence of proposed studies.

**Extrapolation:** <Text> *Brief overview of the efficacy extrapolation concept from the reference to the target paediatric population and source of efficacy data*. Modelling of PK and/or PD if used for decision-making should be mentioned. Source data (study, population) and target age groups should be clear.

**Clinical development:** <Text> Brief summary of proposed studies (type, age, numbers), including short justification for proposed study programme (underlying strategy), including how feasibility of proposed studies is ensured*, and whether networks and communities have been contacted*.

1. Overview of the disease(s), condition and pharmacological rationale
   1. Pharmacology and mechanism of action

*Only a high-level summary is expected in this part, related to mode of action and proof of concept in support of your proposed paediatric development.*

*Already available (clinical) information at the time of submission of the PIP, including description of planned adult development and existing data should be submitted in section 4.*

*For example, if applicable and necessary, information on ontogeny should be reported in this section: are any of the ADME pathways involved still under maturation in the target population which may justify differences in efficacy and/or safety? (e.g. are they subject to differences between adults and children? Justification should be presented.)*

*Are data on exposure-response relationship available in adults and children or are there plans to generate it?*

*Description of the relationship (e.g. is the exposure/response or PK/PD relationship investigated or defined, and have any covariates been identified; e.g. age, body weight, body surface area(BSA))?*

*Are there any maturation and development parameters known, leading to difference in exposure/response in the relevant age subsets, e.g. age-related differences in immunoglobulins, receptor expression, etc?*

*Is the therapeutic window wide/narrow?*

*Have pharmacodynamic (PD) parameters/biomarkers been identified with respect to the drug’s mode of action in the relevant population?*

<Text>

* 1. Summary of differences/similarities in the condition between populations (e.g. adult vs paediatric)

The proposed condition(s) should be discussed in the context of current medical practice related to the mechanism of action of medicine, paediatric needs and potential use. The proposal should consider the MedDRA classification system and relevant orphan medicine designation(s), starting from the indication(s) being developed and/or authorised for use in the adult population if applicable.

Please include clear information on the paediatric age range subset(s) concerned by the disease/condition.

A description of the incidence or prevalence of the condition in different paediatric age subset must be provided including databases/sources.

If the disease does not occur in subsets of the paediatric population, evidence to support this statement must be submitted and discussed later in the paragraphs on the grounds for waiver in section 3.

This paragraph could include high-level considerations setting out the basis of the extrapolation concept. Reference is made to the published guidance: Committee for Medicinal Products for Human Use(CHMP) Structured guidance on the use of extrapolation EMA/CHMP/13622/2022: https://www.ema.europa.eu/en/documents/scientific-guideline/structured-guidance-use-extrapolation\_en.pdf.

<Text>

* 1. Current methods of diagnosis, prevention or treatment in paediatric populations

Provide a high-level discussion on existing strategies for the diagnosis, prevention or treatment of the targeted disorder (depending on the proposed condition for this application) that are available in the European Union (EU), including unauthorised treatment methods if they represent the standard of care (e.g. if mentioned in internationally-recognised treatment guidelines).

Please contextualise the discussion, as applicable, including the tables, with available treatment guideline(s) and recommendations.

The list of available treatments, including those authorised by the national authorities or via the centralised procedure should be included in the table below.

The invented name and the approved use of medical devices marketed in the EU should be provided if applicable.

This section should include information to facilitate and inform the discussions in section 2.4 below. Do not duplicate information under sections 2.3 and 2.4, but only cross reference.

**Use this table for non-authorised or off-label products in the proposed condition**

Not authorised or off-label medicinal products in the proposed condition

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Active substance or INN** | **Indication and age groups** | **Product used off-label** (e.g. for indication, age, dosage, formulation) | **Product not authorised** | **Source of recommendation (e.g.: treatment guideline)** |
|  |  |  |  |  |
|  |  |  |  |  |

**Use this table for authorised medicinal products in the proposed condition**

Authorised medicinal products in the proposed condition

|  |  |  |
| --- | --- | --- |
| **Invented name and active substance or INN** | **Indication and age groups** | **Type of authorisation (e.g. centralised, national, mutual recognition)** |
|  |  |  |
|  |  |  |

<Text>

* 1. Description of the fulfilment of therapeutic needs and/or significant therapeutic benefit

**Related to therapeutic needs**

Acknowledging all currently available products as referenced in the tables above, are they authorised for the intended target indication? In which paediatric age ranges? If not, is their use evidence based e.g. recommended in relevant treatment guidelines, etc?

Where would you currently see limitations in the use of the available products? In which age groups, etc?

*Is there any need for a specific age-appropriate pharmaceutical form or route of administration?*

<Text>

**Related to significant therapeutic benefit**

Based on the identification of a target population with existing unmet medical needs above, how do you envisage your product contributing to potential significant therapeutic benefit for **uncovered** preventative, therapeutic, diagnostic needs in the proposed target indication; in which age ranges?

The following points should be considered when outlining the significant therapeutic benefit of the product where applicable. This should be based on current knowledge, taking into account the mechanism of action, including potential toxicities/potential harm and pharmacodynamic drug interactions, etc, leading to:

* reasonable expectation for safety and efficacy to treat a paediatric condition where no authorised paediatric medicinal product is on the market;
* expected improved efficacy in a paediatric population compared to the current standard of care for the treatment, diagnosis or prevention of the condition concerned;
* expected improvement in safety in relation to either adverse events or potential medication errors;
* improved dosing scheme or method of administration leading to improved safety, efficacy or compliance;
* availability of a new clinically relevant age-appropriate formulation;
* availability of clinically relevant and new therapeutic knowledge for the use of the medicinal product in the paediatric population leading to improved efficacy or safety of the medicinal product in the paediatric population: needs, subsets;
* different mechanism of action with potential advantage for the paediatric population(s) in terms of improved efficacy or safety;
* existing treatments are not satisfactory and alternative methods with an improved expected benefit/risk balance are needed; and
* expected clinically relevant advantage or a major contribution to patient care based on either of the above points;
* expected improvement in the quality of life of the child.

<Text>

* 1. Proposed indication(s) in relation to the proposed condition and selected paediatric subsets

Based on the above, conclude on the most appropriate target indication and identified paediatric age subset(s) for which the product, under the proposed condition is able to be of potential significant therapeutic benefit and/or addressing an unmet therapeutic medical need. Cross reference to other sections of this template accordingly.

Within the PIP condition the product could potentially be developed in one or more indications, based on the selected paediatric subgroups. Please discuss the scientific rationale of the choice proposed. This is the proposed indication in the paediatric population for the purpose of a PIP, and at the time of submission of the PIP, within a specific condition, for example, “treatment of acute asthma episodes”, whereas the condition is simply “treatment of asthma”.

Refer to specific guideline(s)if available and discuss their recommendation (if appropriate to paediatric development).

The Regulation does not require that the PIP is limited to the proposed wording of the adult indication, but it is assumed that there should be some relationship between development in adults and in the paediatric population.

In addition to age, the selected paediatric subsets may be based on other variables, such as gestational age, pubertal stages and gender.

<Text>

* 1. Summary of regulatory advice

This should be in line with, and in addition to the information provided in the IRIS submission table.

Any regulatory advice feedback documents received should be annexed, but a very high-level summary of key outcomes described such as type of advice received (e.g. quality, non-clinical, clinical from CHMP, SAWP, FDA, etc).

Summarise the main points of the advice with relevance to the proposed paediatric development. In case of divergence, ie if advise not followed, summarise the main relevant points, including justification for the different proposal.

<Text>

* 1. Feedback received from networks, experts and patient groups

If applicable, describe in which way paediatric networks/experts have been approached; summarise and submit the feedback received from networks/experts.

Explain involvement of patients and their organisations/involvement of young people and summarise/submit the feedback received from patients and/or young people.

Discussions regarding feasibility of performing clinical trials in the target indication can also be reflected here (lack of feasibility might be grounds for a waiver – cross reference to other sections as necessary).

<Text>

1. Application for waiver(s)

This section is applicable for either product-specific waiver applications for all paediatric subsets (full waiver), or for waiver applications in a sub-population, when a PIP is being proposed (partial waiver).

If this application is for a full waiver, sections 4 and 5 of this template are not applicable.

If this application does not include any type of waiver request, put “Not applicable” for the entire section, and remove the subheadings.

<Not applicable>

* 1. Overview

Summarise the grounds for the requested waiver.

In case a paediatric sub-population is planned to be excluded, the applicant is invited to reference the respective section 2, including a discussion on whether other medicinal products are available or another standard of care has been established to cover the treatment option for the respective paediatric population.

The justification for waiving the obligation to study the paediatric population (either as a whole or in part) needs to be discussed based on principles and scientific evidence reflecting the pharmacological properties and mechanism of action of the product, as well as the target condition and its epidemiology and the identified need, taking into account available licensed treatments. Reference may be made to discussion in section 2.

The following considerations should be reflected in the general discussion:

* Why might the medicinal product not be useful in paediatrics or in a paediatric subpopulation in the proposed target condition?
* What evidence is there to support the argument that there may be no identifiable paediatric (sub-) population in whom a positive benefit-risk can be meaningfully demonstrated?
* Identify which additional scientific information is needed to promote further clinical research with this product in paediatrics. Discuss and explain if there are limitations to access part of the paediatric population (e.g. infants below a body weight of 6 kg for stem-cell harvesting).
* Factors specific to the population targeted by a waiver that are related to maturation and organ development (e.g. sexual development, maturation of the immune or coagulation system) that would support a waiver.
* The justification for waiving paediatric studies/development should reference scientific and clinical research-based evidence as available. This may change over the course of time as more evidence becomes available during the development of a medicinal product.

In the sections below, the applicant should discuss the grounds for the requested waiver(s). The justification per paediatric sub-population may differ according to the grounds given in the Paediatric Regulation. If applicable, each paediatric sub-population for which a waiver is requested needs to be justified with an appropriate ground from Article 11 of Regulation (EC) No 1906/2006.

To identify the most appropriate waiver ground, each ground should be examined consecutively and hierarchically. If applicable, therapeutic need should be considered.

<Text>

* 1. Ground 1: the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset(s)

*Condition not existing (i.e. no disease exists in children covered by the agreed condition. Includes diseases where only very few paediatric cases have been reported, such as conditions occurring predominantly in adults (e.g. breast cancer or lung cancer).*

<Text>

<Not applicable>

* 1. Ground 2: the specific medicinal product does not represent a significant therapeutic benefit

*Condition exists in children but there is no therapeutic need (no therapies needed, or other therapies are adequate and the product is not expected to be of additional benefit).*

*Evidence should be provided of alternative or authorised therapies applicable for the paediatric population.*

*With cross reference to section 2, when discussing the rarity and epidemiological paucity in the potential target population, the applicant should also provide information on the ability/feasibility to conduct meaningful clinical trials. It should be considered that unnecessary trials in the paediatric population should be avoided (e.g. trials which are not likely to provide any evidence to support a potential marketing authorisation application).*

<Text>

<Not applicable>

* 1. Ground 3: the specific medicinal product is likely to be ineffective or unsafe

*Condition exists in children and unmet need present, yet development is not warranted since based on pharmacological properties the product is not expected to be effective and/or not safe (relative to the unmet need in the condition).*

*In case evidence suggests that the medicinal product may be associated with a safety concern in the treatment of the paediatric target population, the applicant should include whether additional research may be applicable to further analyse the potential important safety issue. This research could include further animal studies but may also include additional research in the use in the adult population. Therefore, a discussion should be included on whether a deferral due to lack of evidence proving the safety concern may be more relevant than a waiver. In addition, it should be discussed how the safety concern could be monitored or mitigated.*

*This research should also include whether there is a likelihood of the medicinal product being ineffective in the target paediatric population and what the rationale is for lack of efficacy (e.g. pathophysiology, lack of receptors, etc).*

<Text>

<Not applicable>

* 1. Conclusion

*After a discussion of the various potential grounds, the applicant is asked to make a proposal for the most appropriate grounds for the waiver, respecting the hierarchy: first consider ground 1, then ground 2 and finally ground 3. Only one ground for each paediatric subgroup group should be proposed.*

<Text>

1. Proposed paediatric investigation plan

*This section is not applicable for product-specific waiver applications for all paediatric subsets (“full waiver” request), please put “Not applicable” here and delete the subheadings.*

<Not applicable>

* 1. Quality aspects
     1. Existing pharmaceutical forms

*Please provide a brief overview of the existing formulations (as described in in the IRIS portal webforms) regarding their relevance to the paediatric population or subsets. Discussion of the suitability of the existing formulations for the subsets of the paediatric population.*

<Text>

* + 1. Proposed pharmaceutical forms for paediatric use

The rationale for the proposed quality study/ies with key elements in the IRIS portal webform, along with the advantages and disadvantages of a particular dosage form and a particular route of administration. This should be justified in context of intended age group(s) focusing on the youngest age group(s).

Aspects to be considered include, at least, the condition(s) to be treated, the treatment duration, the properties of the active substance, the necessity of particular excipients (and their safety), any measuring and administration devices, stability issues, dosage requirements, risk of dosing errors, and user aspects such as the ease of administration and patient acceptability (Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012 Rev. 2: https://www.ema.europa.eu/en/pharmaceutical-development-medicines-paediatric-use-scientific-guideline)

In particular (some sections would need to be updated before clinical studies are started in paediatric patients if not available, please highlight any gap in knowledge):

* Discuss the need (or not) for development of paediatric formulation(s): are the existing formulation(s) adequate for the paediatric population, considering the different subsets covered and estimated dose range, and need for dose flexibility (weight-tiered, mg/kg or mg/m2)?
* Similarly, also discuss the intent to use interim formulations, and risks in case this involves modification of existing (adult) formulations (see points of discussion below for alternative administration strategies).
* Justify the proposed pharmaceutical development strategy and discuss all various options. If it is considered that a specific paediatric-appropriate formulation is unfeasible, provide development data (e.g. physico-chemical, ADME(absorption, distribution, metabolism, excretion), pharmaceutical, biopharmaceutical, pre-clinical, early clinical) to demonstrate/support.
* Consider the need for a specific formulation for neonates. Consider specific aspects related to neonate medicine administration (for instance the use of dextrose solution as solvent of dilution instead of sodium chloride solution to prevent hypernatraemia that may be caused by “flushing” with physiological sodium chloride solution (Guideline on the investigation of medicinal products in the term and pre-term neonate EMEA/536810/2008)).
* If applicable, discuss alternative administration strategies (e.g. for those children unable to swallow an oral solid preparation) and justify their need and feasibility and dose accuracy (e.g. dispersing, crushing or subdivision of tablets, opening of capsules, mixing or co-administration with food).
* Discuss whether acceptability (including palatability) needs to be assessed in paediatric clinical studies with the target paediatric population and carers.
* If applicable, for administration with food:
  + provide a risk assessment of potential effects on bioavailability of the medicine, based on pharmaceutical and biopharmaceutical properties,
  + provide or propose compatibility studies with food/drink.
* If relevant, discuss the need of administration through feeding tubes. Where administration through feeding tubes is used, either as a main route or as a very likely option, the feasibility of administration through the feeding tube needs to be addressed.
* Discuss the necessity of each excipient and quantity used in the paediatric formulation, in particular for new excipient and excipients with potential (dose-related) local or systemic pharmacological action. Based on estimated doses, justify safety of each excipient in relation to maximum daily exposure (mg/kg), target age group, route of administration and duration of treatment. When there is no or insufficient evidence in a particular age group, this should be discussed in relation to extrapolation from other age groups and risk.
* If available, discuss additional safety data that is/will be available from pre-clinical studies and safety measures, and clinical data to be gathered from paediatric studies.
* If already available, justify the choice of primary packaging(s) selected, justify the packaging size in view of the posology and discuss possible risk of overdosing.
* Discuss if any dosing/administration device is needed and its suitability for the proposed age groups. Consider that accuracy of measuring devices for paediatric medicines with a steep dose/pharmacodynamic response curve or narrow therapeutic window may require special considerations. For other devices, the ease of administration by the child or its caregiver, difficulties in administration to unwilling children, and the robustness of the device in daily practice should be considered.
* Confirm that the guidelines were followed or justify deviation:
  + Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012 Rev. 2: <https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-pharmaceutical-development-medicines-paediatric-use_en.pdf>

and

* + Reflection paper: formulations of choice for the paediatric population EMEA/CHMP/PEG/194810/2005: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-formulations-choice-paediatric-population\_en.pdf

<Text>

* + 1. Justification of qualitative and quantitative composition

*Discuss briefly the necessity of each critical excipient, use, and quantity of excipient used in the paediatric formulation(s) planned to be used in the paediatric population, in particular for new excipient and preservative. For critical EXCIPIENTS justify safety of each excipient in relation to maximum daily exposure and target age group, route of administration and duration of treatment (see EMA website on Paediatric formulations: https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/paediatric-medicines-research-and-development/paediatric-investigation-plans/paediatric-formulations).*

*If this information is not yet available, please discuss how and when it is planned to be agreed with the PDCO.*

*Ensure that quality aspects provided in IRIS platform is justified here.*

<Text>

* 1. Non-clinical aspects
     1. Existing non-clinical data

Mode or mechanism of action

*This should be brief: data summarised below is needed to support development and justify the studies/key elements included in the IRIS portal webforms. It should not be a duplication of the Investigator’s Brochure IB.*

*Provide an overview of the pharmacological rationale and relevant proof of concept data (in vitro, in vivo) to support the use of the compound in the intended paediatric population. Cross-refer to section 2.1 as needed.*

*To also be addressed:*

* *Species differences in PD-activity.*
* *Paediatric-specific pathophysiology, if relevant.*
* *Potential for off-target effects.*
* *Is it a first-in-class compound? Similarity to/difference compared to other compounds in class?*

*Is there an indication that effects on growth and/or maturation may be a concern? Please summarise:*

* *Age-related differences in PD-activity, e.g. information on the ontogeny of expression and function of the targeted receptor(s)/enzyme(s)/pathway(s), if differences are expected and such data is available*
* *Potential for on- or off-target activity in organs undergoing significant development in (part of) the target population.*

<Text>

Safety pharmacology

*Please summarise:*

* *Organ systems evaluated, also if safety pharmacology endpoints were included in the repeat-dose toxicity studies,*
* *Adverse findings, if any, with exposure margins over clinical anticipated exposure.*

<Text>

Pharmacokinetics (PK)

*Please summarise:*

* *CYP involvement, non-clinical species relevance in terms of metabolism,*
* *Distribution incl. potential to distribute to the brain,*
* *Substrate for drug transporters?*
* *Major elimination route,*
* *Significant species and/or sex differences in PK parameters, if any.*

<Text>

Repeat-dose toxicity studies

*Please describe species, duration, route, regimen, age of the animals at study start, target organs for toxicity, reversibility of effect.*

*Discussion of the clinical relevance of the observed adverse findings including exposure margins over clinical anticipated exposure and if available, findings confirmed in clinical studies thus far should be included here.*

*Discuss potential underlying mechanism for unexpected findings.*

<Text>

<Not available>

Reproduction

*Describe outcome of embryo-foetal development (EFD), fertility and early embryonic development (FEED) and (enhanced)* *pre- and postnatal ((e)PPND) study(ies) incl. endpoints assessed in the offspring and pup exposure, if available.*

*Describe outcome of juvenile animal toxicity studies (JAS), if such study(ies) are already conducted. This should include the species, route, regimen, age range of the animals, endpoints. Discuss whether the study identified novel and/or enhanced toxicities, their reversibility, clinical relevance and exposure multiples over clinical anticipated exposure. Discuss whether significant age-related differences in systemic exposure were observed compared to adult animals treated with a similar dose.*

*Describe planned monitoring for adverse findings, where relevant.*

<Text>

<Not available>

Genotoxicity

*Describe outcome in standard battery, if relevant.*

<Text>

<Not available>

Carcinogenicity

*Please list any study conducted and main findings, if available.*

<Text>

<Not available>

Other

*E.g. mechanistic studies as follow-up to certain findings in studies described above, tissue-cross reactivity studies, published data on viability, development, fertility of relevant knock-out animals.*

<Text>

<Not applicable>

* + 1. Proposed non-clinical development
* Description of the proposed non-clinical strategy to support paediatric use in addition to classical non-clinical development.

<Text>

* + 1. Justification of overall strategy and juvenile safety studies
* Weight-of-evidence discussion of the need for additional non-clinical safety investigations incl. JAS (refer to ICH S11 guideline). For anti-cancer products, applicants are also referred to the EMA/FDA Common Commentary concerning paediatric oncology development plans.
* If studies in juvenile animals are proposed in the IRIS portal webform, justification of the selected species and study design taking into account the youngest intended patient age and developmental periods of organ system(s) of toxicological concern (refer to ICH S11 guideline).
* Discussion of the need for additional non-clinical proof of concept data. Do animal models exist? Are they appropriate to study the effect of the product and to extrapolate the results?
* Discussion of the prerequisites to human administration and in particular paediatric administration.
* *Justification of the studies proposed in the IRIS portal webform should be included here, focusing on species, route, regimen, age of the animals at study start, dosing period, endpoints, reversibility, toxicokinetics (TK). Generally, each juvenile animal study should include the core endpoints defined in ICH S11. Each additional endpoint should be justified to address an identified safety concern.*
  1. Clinical aspects
     1. Existing clinical data and planned studies in adults

*Discussion of the overall strategy for clinical development.* *This should be brief: data summarised below is needed to support development and should not be a duplication of the IB. Please point out planned studies in adults that could produce data relevant for paediatric development.*

*Please focus on what data have demonstrated so far, and which confirmatory data are expected.*

<Text>

Pharmacokinetic properties

*Summary of ADME (absorption, distribution, metabolism, excretion) and toxicity data. Are there consequences of the ADME and toxicity data for the pharmacological/dosing strategy in children?*

*Describe the main available pharmacokinetic parameters:*

1. *Linearity of the kinetics, Tmax, Cmax, absolute bio-availability, volume of distribution, plasma clearance, half-lives (T½,terminal T½); hepatic extraction ratio for medicinal products primarily eliminated through the liver (comparison of plasma clearance to normal liver blood flow).*
2. *If extrapolation of efficacy data is planned, list the available PK and PD data, or in which studies further data will be generated.*
3. <Text>

Pharmacodynamic properties

*Describe available data on PD parameters clinical and biomarkers.* *Are there data on pharmacodynamics (effect of interest and other effects) in animals and/or in adults? How does maturation influence the PK-PD relationship? Is there data on the age at which 90-100% of adult maximum PD response as a function of plasma concentration is reached?*

<Text>

Interaction with other medicinal products

*Although the PIP is not intended to include all the elements necessary for drug development, some requirements may have to be included.*

<Text>

Summary of efficacy data

*Provide a summary supporting efficacy and outcome measure used. Emphasis on total duration of exposure per patients and total number of patients treated.*

<Text>

<Not applicable>

Exposure-response analysis

*Mention any performed or planned analysis and parameters used.*

<Text>

<Not applicable>

Summary of safety data

*Provide a summary identifying any signals, particularly serious AEs and reactions that could have a worse outcome in children or could be of concern (e.g. effects on growth, sexual maturity, neurobehavioral development).* *For the most common adverse events (AE) reported, discuss impact on the paediatric population, particularly if this can have a greater severity or outcome.*

<Text>

<Not applicable>

* + 1. Proposed clinical development

Summary of overall strategy and extrapolation plan

*Provide a strategic overview of your paediatric development plan, linking:*

* *adult development (if related),*
* *existing evidence,*
* *unmet needs, and*
* *potential significant therapeutic benefit (cross-referencing sections 2 and 3, no specific or detailed information are expected here).*

*This section could be used to reflect on identified challenges as regards the overall paediatric development strategy, related to any part you consider important to highlight.*

*This should include a conclusion on identified uncertainties as part of* ***extrapolation concept discussions*** *if applicable (as already reflected upon in sections 2.1 and 2.2 above), and* ***how these will be addressed as part of the extrapolation plan.***

*Reference is made to EMA/CHMP/13622/2022 (https://www.ema.europa.eu/en/documents/scientific-guideline/structured-guidance-use-extrapolation\_en.pdf) and to the information available in https://www.ema.europa.eu/en/extrapolation-efficacy-safety-paediatric-medicine-development-scientific-guideline.*

*The extrapolation plan is essentially all M&S and clinical studies proposed as part of the PIP – cross-reference to other studies mentioned in section 4 which are part of the plan).*

*Details of extrapolation plan should be discussed in this section.*

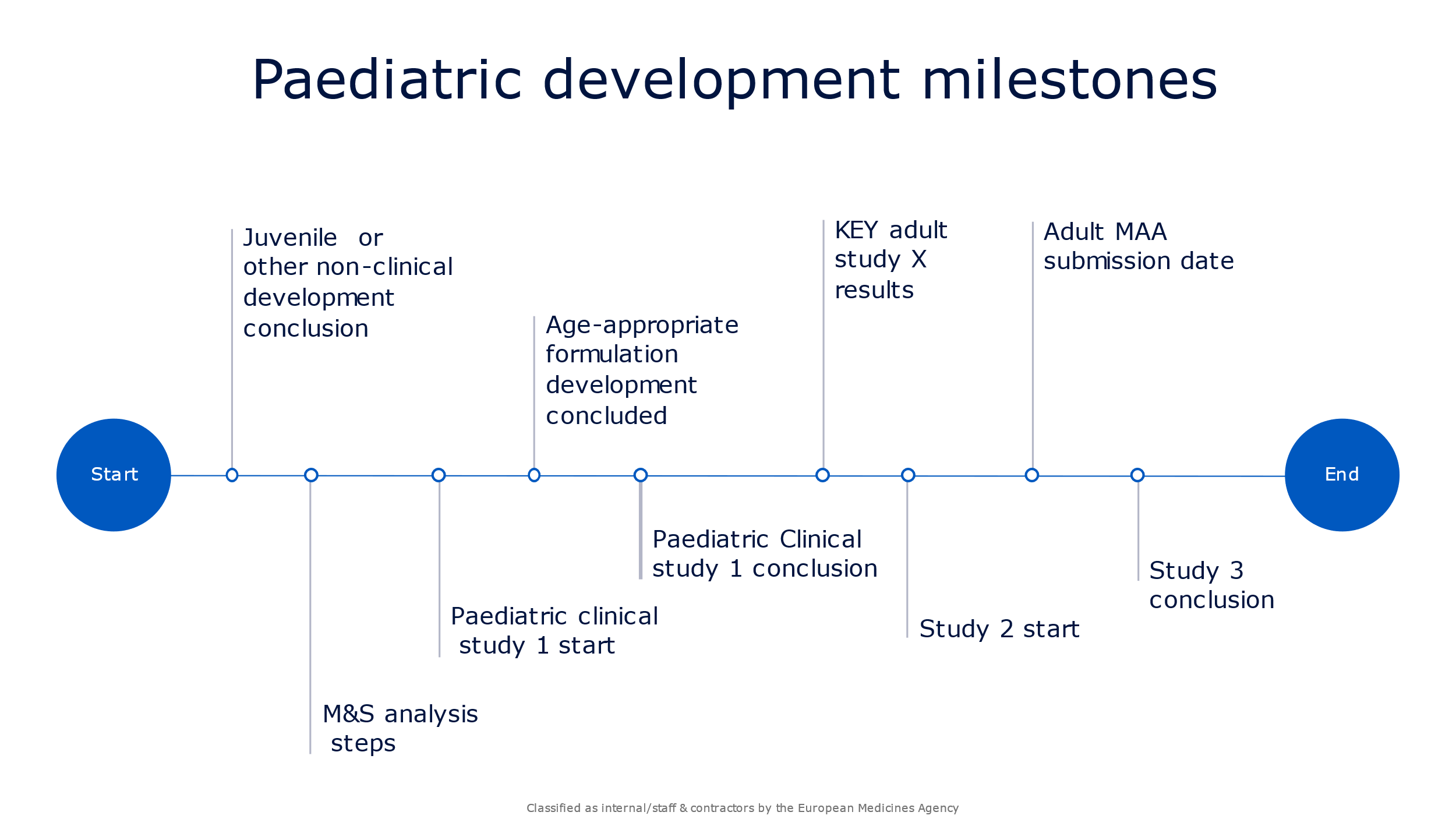
<Text>

Graphic overview of milestones and timelines

A graphic representation of timelines, in relation to adult planned development, non-clinical data availability and pharmaceutical form development milestones, is requested. Please see the example below. If a graphic format is not possible, please provide the information in a table.

Should be consistent with section 5, which will report the initiation and conclusion dates of the studies part of the PIP.

Timelines of the overall development plan, including the availability of formulations, completion of non-clinical studies, and other milestones that are conditional to the paediatric clinical development strategy. Please indicate any relevant adult study that would be used as a milestone for paediatric development.



* + 1. Strategy for paediatric dose selection and PK/PD evaluation

1. Summarise the high-level principles guiding the strategy for paediatric dose selection, e.g. matching PK exposure with adults, targeting similar PD responses, need for exposure response characterisation in children, based on pre-clinical evidence, etc.
2. The strategy for paediatric dose selection should be based on the expected differences in exposure response and disease progression between adults and children, considering pharmacology, real word data/evidence (RWD/E) and literature data. Please refer to Committee for Medicinal Products for Human Use ICH guideline E11A on paediatric extrapolation EMA/CHMP/ICH/205218/2022 (https://www.ema.europa.eu/en/ich-guideline-e11a-pediatric-extrapolation-scientific-guideline) Step 2b, Dose Selection.
3. <Text>

Modelling and simulation analyses supporting paediatric development

1. Describe the modelling and simulation (M&S) analyses proposed and role in the development.
2. Consult Modelling and simulation on the EMA website for any relevant update: https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/clinical-pharmacology-and-pharmacokinetics/modelling-and-simulation-questions-and-answers.
3. If **modelling and simulation analyses are planned** as a substantial (or exclusive) part of the PIP, justification should be here for the proposed objective, data to be used and methodology. The relevant key elements should be entered in IRIS portal webforms.
4. Provide all relevant model information which is available in adults and prediction at the time of PIP submission. The KEF should include clear objectives and high-level information regarding the M&S analysis and plan, detailed information and justification (e.g. objective of the model-based analysis, description of the current available model(s), description of the planned model analysis).
5. Clarify what the scope and role of M&S is in the development: describe, characterise, replace development.
6. Clarify proposed PK sampling and sampling volumes and how it will be done in the proposed study. It should be clear which studies will contribute to paediatric dose selection.
7. <Text>

**Modelling and simulation analyses as part of the extrapolation plan**

1. If extrapolation of efficacy is pursued trough M&S, the methodology and how the analysis will be performed should be discussed here.
2. <Text>
3. <Not applicable>
   * 1. Proposed clinical studies
4. **FOR EACH STUDY** included in the PIP application in IRIS with its key elements, please use the structure indicated below to detail justifications for the choice of - AT THE VERY LEAST - the key aspects indicated (cross-refer where applicable). All clinical studies, irrespective of the objectives (e.g. PK, PD, safety, efficacy), need to be included here. However, there is no need to repeat here the key elements table already provided in the submission.

*Please justify, cross referencing to “Overall strategy”, the number of studies to be conducted, the paediatric subgroups to be enrolled in each of them and scientific rationale underpinning the chosen design (RCT vs single arm, etc.) in consideration of their interdependencies.*

1. *Issues of relevance across the proposed studies, such as study design including use of alternative study design and analysis, use of placebo or active control, age-appropriateness of endpoints, use of surrogate markers, potential need for short-term and long-term safety studies, and differential risks by age group.*
2. *Timelines should be described at a high-level, explaining which studies will be conducted first, in which population and why.*

*This should be reflected in context of how any uncertainties identified as part of the extrapolation concept (as applicable) are able to be adequately addressed as part of the extrapolation plan which includes the proposed paediatric clinical study(ies). Also, cross-reference to other sections as appropriate.*

Study <study identifier or number>

**Study design**

1. *Brief justification of type of study, study design and methodology;*
2. *Justification of the dose of the proposed product and its regimen, and the type of control (e.g. placebo or active control, with dose to be used; justification of the proposed duration of treatment, and duration of post-treatment observation if included in the study).*
3. <Text>

**Population to be included**

1. *This should be consistent with the identified target population in section 2.5. Justification of the relevant age groups or subsets included in the study (and of staggered inclusion where applicable). Justification of main inclusion/exclusion criteria.*
2. <Text>

**Choice of control(s)**

*Discussion on the comparator: placebo as control, or active comparator (authorised, not authorised/standard of care) in phase 3 trials*, *external control arms, historic controls, etc.*

*This should be consistent with reflections provided in section 2.*

<Text>

<Not applicable>

**Sample size**

*Description of the sample size/power calculation (as appropriate, with expected effect size in children) used to determine the proposed number of subjects (male/female). This discussion should include, where possible, a sensitivity analysis (a tabulation with varying assumptions and statistical parameters, and the resulting sample sizes). If other statistical approaches are used, describe them below.*

<Text>

**Outcome measures and statistical analysis**

Justification of the choice of outcome parameters/endpoints (primary, secondary) their time and justification and, if needed, a more detailed description of statistical methods than that contained in the key elements. Please refer to previous studies as applicable.

<Text>

* 1. Other studies

Provide here additional information on other studies proposed, literature analysis, Real World Evidence sources, etc. that do not fall under the previous sections but are relevant to addressing identified uncertainties as part of the extrapolation plan.

<Text>

Considerations for planned long-term follow-up

<Text>

<Not applicable>

Based on the proposed development and the known safety profile, discuss relevant risks that could be important for the paediatric population for which post-authorisation studies are expected. Refer to Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations Chapter IV: Paediatric population: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-product-or-population-specific-considerations-iv-paediatric-population\_en.pdf

This can be reflected in Section 5 of the PDCO Opinion. Despite this information not being part of the PIP commitments, it will support clarifying how any gap in safety profile will be fulfilled.

1. Timelines and deferral(s)

*This section is not applicable for product-specific waiver applications for all paediatric subsets (full waiver).*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study identifier (paediatric study)** | **Population (age group)** | **Area**  **(quality, non-clinical, clinical)** | **Date of initiation[[1]](#footnote-2) and deferral requested (Y/N)** | **Date of completion[[2]](#footnote-3) and deferral requested (Y/N)** | **Planned regulatory submission** |
| N/A |  |  |  |  |  |

Outline how the plan for paediatric development will integrate into the overall development of the proposed medicinal product and/or the proposed condition/indication(s)in terms of timelines.

Include justification for the proposed timelines of the PIP with respect to planned or ongoing regulatory steps (e.g. marketing authorisation application for indication xyz in adults) and discuss the justification for a deferral (initiation-conclusion) based on the grounds provided by the Paediatric Regulation. Ensure consistency with the GRAPH provided in section 4.2.

Based on the justification and **timelines** described above, state the justification for the **deferral request** in accordance with the grounds of the Paediatric Regulation.

*Where it is not planned for a study or other measure in the PIP to be initiated or completed before the submission of the corresponding marketing authorisation application in adults, a deferral may be requested. Requests for deferral should be justified on scientific and technical grounds, or on grounds related to public health.*

*In accordance with the Paediatric Regulation a deferral will be granted when:*

* *it is appropriate to conduct studies in adults prior to initiating studies in the paediatric population; or*
* *studies in the paediatric population will take longer to conduct than studies in adults.*

**Reminder:** in general, a clinical study report (CSR) is required for the PDCO to perform a compliance check. This should be considered in the final timelines of submission.

<Text>

1. References

List all literature references, articles, bibliography, etc. related to the scientific discussion.

1. First patient included in trial. [↑](#footnote-ref-2)
2. Last patient, last visit. [↑](#footnote-ref-3)