



# Outsourcing Paediatric Investigation Plans

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# Overview



- Planning your PIP submission
- Which in-house departments should be involved?
- Interaction with CRO/ writer
- Interaction with the PDCO
- Key points for successful PIP outsourcing

# Planning your PIP submission



According to Article 16 of Regulation EC 1901/2006 “the paediatric investigation plan or the application for waiver shall be submitted with a request for agreement, except in duly justified cases, **not later than upon completion of the human pharmacokinetic studies in adults**”

Taken literally this means the PIP has to be submitted to the PDCO when the phase I studies have been completed, unless a postponement is justified

# Planning your PIP submission



However, according to the published FAQ on regulatory aspects of Regulation (EC) No 1901/2006 (Paediatric Regulation), in response to question No 3:

**“When can we submit a request for a paediatric investigation plan (PIP) or a waiver?”**

The answer states... **“it is up to applicants to determine for themselves when would be the best time to submit a request for a paediatric investigation plan, or for a waiver, for their medicinal product”**

# Planning your PIP submission



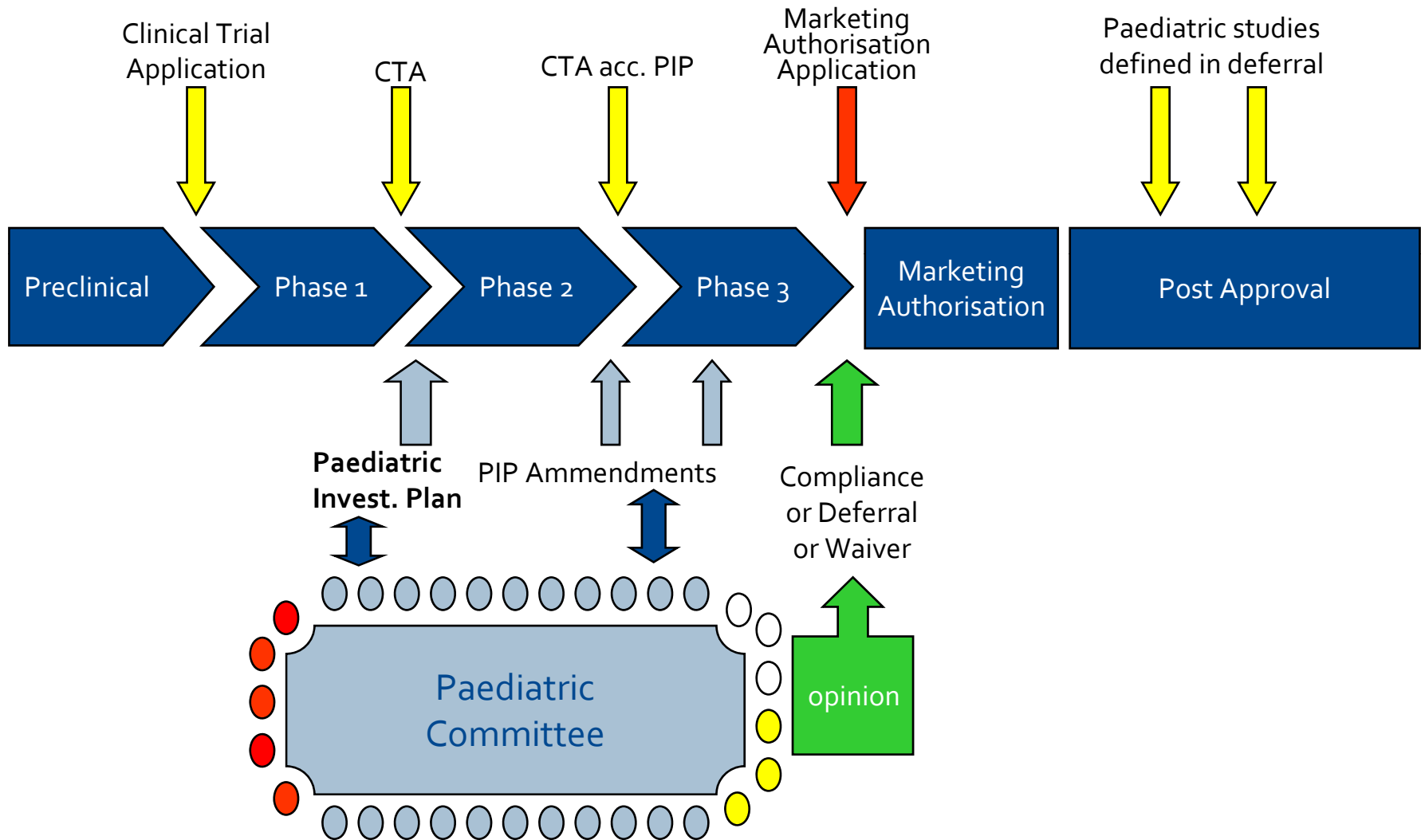
## Question:

What is the correct time point in product development to start preparing a PIP?

## Answer:

The preparation of a PIP needs to be planned into the development of a product from a very early stage and should be developed in parallel to the conduct of the clinical studies in adults

# Timing of PIP development



# Which in-house departments should be involved?



It is **VERY** important that the entire **R&D** and **Marketing** team in your company are made aware of the pivotal role of the PIP in the timing of submission of a marketing authorisation application for the product and the indications for use

The consequences of non-compliance with a PIP at the time of MAA submission must be made very clear to the **clinical development teams** in-house and must also be communicated to **any CRO involved** in the paediatric studies!

# Which in-house departments should be involved?



Very early during product development, **critical strategic decisions** need to be taken on the paediatric development of a product. It is therefore essential that **company upper management** are aware of the consequences of these decisions for the timing of a potential submission and the effect an approved PIP has on the indications that can be granted for the product

# Which in-house departments should be involved?



## Input required from R&D for the PIP

- Are any indications required for children and, if so, for which age groups?
  - Clinical trials required and timing in relation to adult studies
  - Deferrals for certain age groups?
  - Waivers for certain indications or age groups?
- Are additional pharmaceutical forms required for children?
  - Development timelines for suitable paediatric products

# Which in-house departments should be involved?



## Input required from R&D for the PIP

- Is scientific advice required from the PDCO?
  - Plan SA application as early as possible! ► **Submission timelines!**
- Are preclinical studies required in juvenile animals?
- Clinical trials required in children and timing in relation to adult studies
  - Choice of CRO and involvement in clinical development
  - Contact between clinical trials management in-house and CRO writing PIP ► **Feasibility!**

# Which in-house departments should be involved?



## Input required from R&D for the PIP

- Orphan indications
  - Request for waiver or clinical studies in age groups with low prevalence?
  - Full vs. Partial waiver (combined with PIP): specific for
    - Each indication
    - Each age group (evaluation/ justification)
    - Each formulation
    - Each route of administration
- Planned submission date for PIP
  - PDCO submission dates ► **Submission deadlines and timeline for opinion!**

# Which in-house departments should be involved?



## Input required from Marketing for the PIP

- Which other similar products are available to treat children and is there a need for approval of paediatric indications (significant therapeutic benefit /fulfilment of therapeutic needs)?
- Are paediatric indications to be included in the initial MA or preferably later in the product life-cycle?
  - Clinical trials required and timing in relation to adult studies

# Which in-house departments should be involved?



## Input required from Marketing for the PIP

- Additional market exclusivity for paediatric indications needs to be considered
  - Planning of paediatric trials in relation to patent protection – timing of deferrals for studies
- Orphan indications
  - Does prevalence justify or allow clinical studies?
  - Additional market exclusivity (10 + 2 years) if studies are performed

# Interaction with CRO/ writer



## Why outsource PIP writing?

- Lack of in-house experience in preparing PIPs
- Lack of resource in-house to write the PIP
- Beneficial effect of previous experience of CRO/ writer with PDCO assessments for other PIPs
- Beneficial effect of CRO knowledge of feasibility of planned paediatric studies and access to paediatric KOLs involved in previous studies

# Interaction with CRO/ writer



## Choice of CRO/ PIP writer - criteria

- ☑ Experience in PIP writing and PIP approvals
- ☑ Understanding of the regulatory legislation and the requirements for the PIP content
- ☑ Understanding of the work and views of the PDCO
- ☑ Ability to interact with all members of regulatory, R&D and clinical team
- ☑ Fluent written English and long term availability

**Do not compromise on any of the above in order to save minimal costs!**

# Interaction with CRO/ writer



## When to involve CRO/ PIP writer?

- PIP writer should be involved as early as possible
- An understanding of the entire development plan for the product is required
- A comprehensive literature search is mandatory – and takes time!
- Allow time for multiple review cycles prior to submission, involving regulatory, R&D, marketing and (possibly) upper management for certain strategic decisions

# Interaction with CRO/ writer



## Defining responsibilities

- Conducting literature searches and obtaining articles
- Providing non-clinical and clinical study reports, investigator brochures, study protocols
- Input for proposed clinical studies (feasibility!)
- Submitting the Letter of Intent
- Submitting the PIP
- Interacting with the PDCO – writer availability at critical times in the PIP assessment!

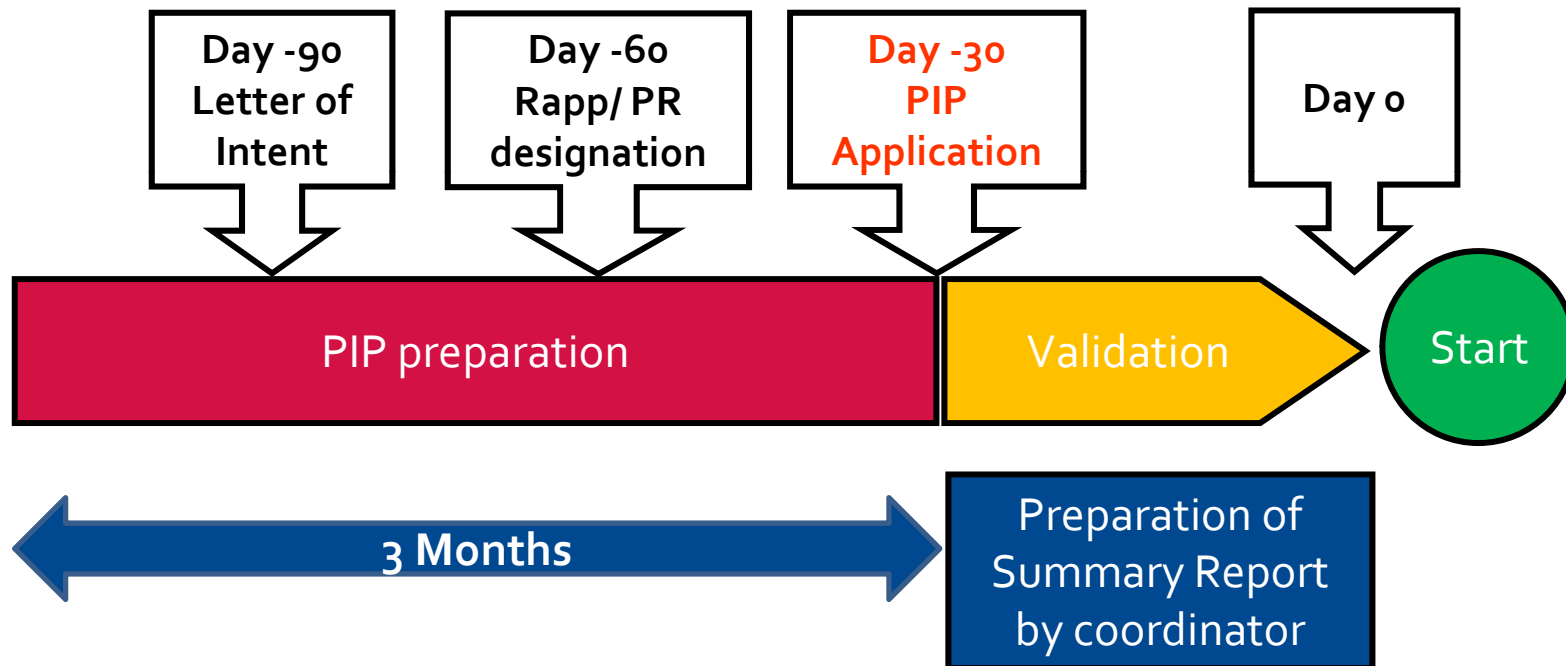
# Interaction with CRO/ writer



## Timelines and deadlines

- Always keep in mind that an approved and compliant PIP is required for validation of the marketing authorisation application
- It takes approximately 11 months to receive a PIP opinion after submission of the application
- The letter of intent has to be submitted 2 months prior to the PIP
- An experienced CRO/ writer will require 8 - 12 weeks to prepare the PIP, including your review process

# PIP Submission Timelines for validation



# Interaction with the PDCO



The **Paediatric Coordinator** of the procedure acts as the interface between companies and PDCO

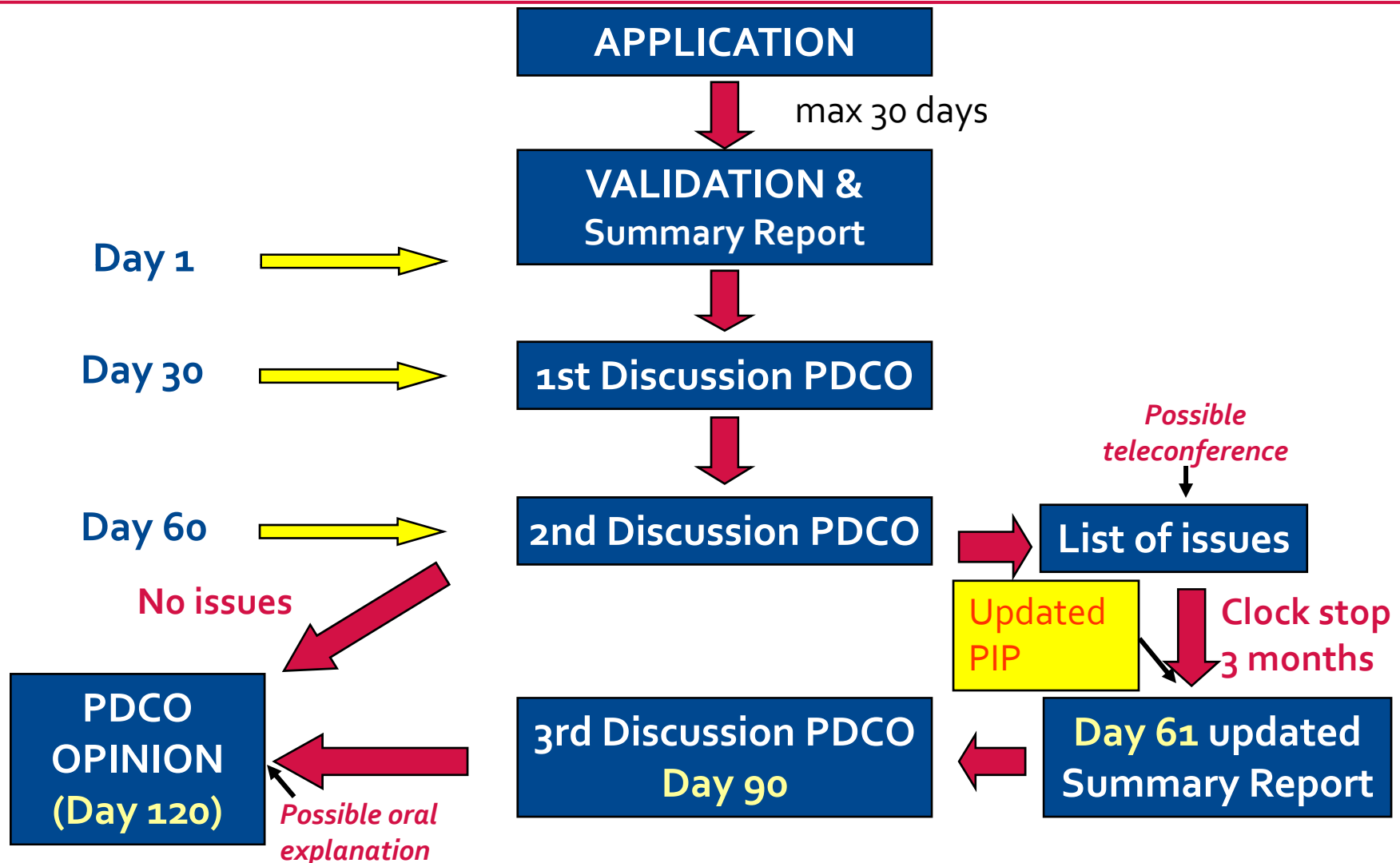
- Performs regulatory checks (validation)
- Writes and comments on the draft version of the **Summary Report**
- Participates in the PDCO meeting
- Writes PDCO documents i.e. requests for modification, opinions
- Assists and initiates the preparation of scientific and regulatory procedural advice

# Interaction with the PDCO



- PDCO Members and Alternates share the workload
- Designated **Rapporteur** and **Peer Reviewer** both review and comment on the Summary Report, (Day 30) then present to PDCO (Day 60)
- Other Members comment on it during and after discussion (verbally or in writing)
- Achieve consensus or vote if necessary
- Experts invited if necessary
- **Teleconference with applicant may be requested**
- Oral Explanation meetings possible

# Interaction with the PDCO



# Interaction with the PDCO



- Establish a close cooperation with EMA coordinator
- Consider that major changes can occur between Day 30 and Day 60 Summary Report
- Major issues are difficult to clarify during the procedure e.g.
  - new indications/age groups etc are required
  - requested switch from full waiver to PIP (if a waiver is refused this means the PIP procedure has to be started again from the beginning)
- Important issues should be clarified prior D61 and you will need your PIP writer to be available to modify the PIP
- *(difficult to solve major issues between D61 and 120, even with a face to face meeting)*

# Interaction with the PDCO



## Before Day 61:

- Teleconference with EMA coordinator, Rapporteur, Peer Reviewer and external experts
  - discuss draft response (submitted previously together with questions) and **include the PIP writer in discussions**
  - If high risk exists for PIP/Waiver refusal: Exclude “critical” conditions (re-submit separately)

## Day 90 - 120: Meeting/Teleconference

- Final PDCO position and issues communicated to the applicant
  - Last chance for clarification in oral explanation
  - No submission of additional or modified documents possible

# PIP Modifications



Always possible if there are difficulties with the PIP implementation i.e. the original plan is either unworkable or is no longer appropriate

- Preferably prospective – but this can be difficult if changes are required during a study
- Multiple modifications possible
- 60-day procedure - same EMA coordinator / Rapporteur / Peer Reviewer
- New waivers/deferrals can also be requested
- New opinion/decision supersedes original

*Changes have to be justified and should not be perceived to gradually erode the original PIP requirements*

# Key points for successful PIP outsourcing



- ➡ Plan your PIP strategy early
- ➡ Involve all the necessary company stakeholders
- ➡ Request scientific advice if appropriate
- ➡ Consider the timelines and submission deadlines
- ➡ Select an experienced CRO/ writer with knowledge of the paediatric regulation and the implication of the PIP on product development
- ➡ Establish a close relationship with the coordinator and ensure that the PIP writer is integrated into the PIP discussions with the PDCO



**Any Questions?**

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**Thank you for your attention!**

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