EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

PIP assessment procedure

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Objectives of the EU Paediatric Regulation

- Improve the health of children
  - Increase high quality, ethical **research** into medicines for children
  - Increase **availability** of authorised medicines for children
  - Increase **information** on medicines
- Achieve the above
  - Without unnecessary studies in children
  - Without delaying authorisation for adults

What is a PIP? (1/2)

• Basis for development and authorisation of a medicinal product for all paediatric population subsets.

• Includes details of the timing and the measures proposed, to demonstrate:

- Quality
- Safety
- Efficacy

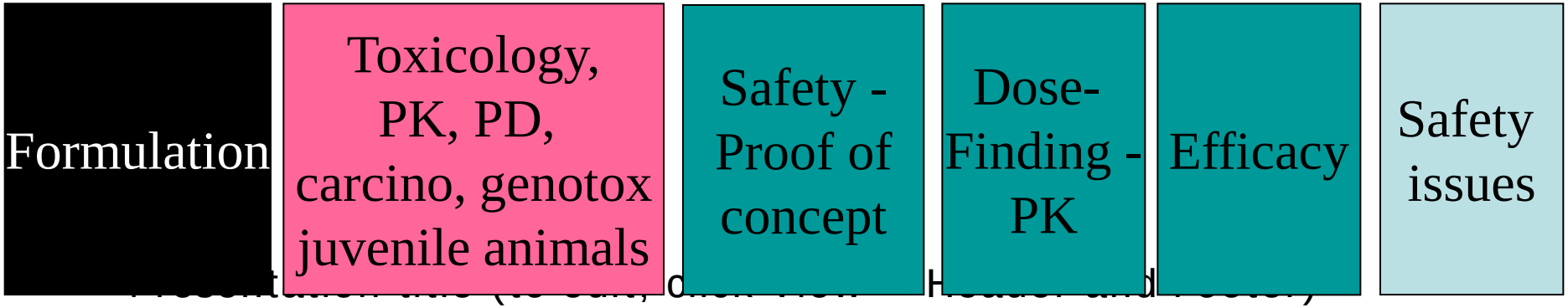
Marketing Authorisation Criteria

• To be agreed upon and/or amended by the PDCO

• Binding on company → compliance check
(but modifications possible, at the company's request)

What is a PIP? (2/2)

- Data on efficacy, safety and age-appropriate formulation are needed
- Timelines for start and completion of each study
- *In practice: discussion on each condition/indication and formulation, for each paediatric subset (not only age-groups).*



When is a PIP/Waiver necessary?

• Pharmaceutical companies need to produce data from paediatric studies, done in accordance with an agreed PIP, at the time of:

- Applying for a new marketing authorisation
- In case of an already authorised product, for new indications / routes of administration / formulations (but not for new strengths)

+/- Deferral for completing the studies/measures

• Alternatively, they need a total waiver (for all indications/conditions, in all paediatric subsets). If total waiver: no PIP

When is a PIP/Waiver not needed?

• Authorised products that do not have a valid Supplementary Protection Certificate (SPC) or a valid patent that qualifies for it. (i.e. off-patent products already authorised in the EU)

• New medicinal products that belong to some specific groups:

- Herbal medicinal products, Homeopathic products

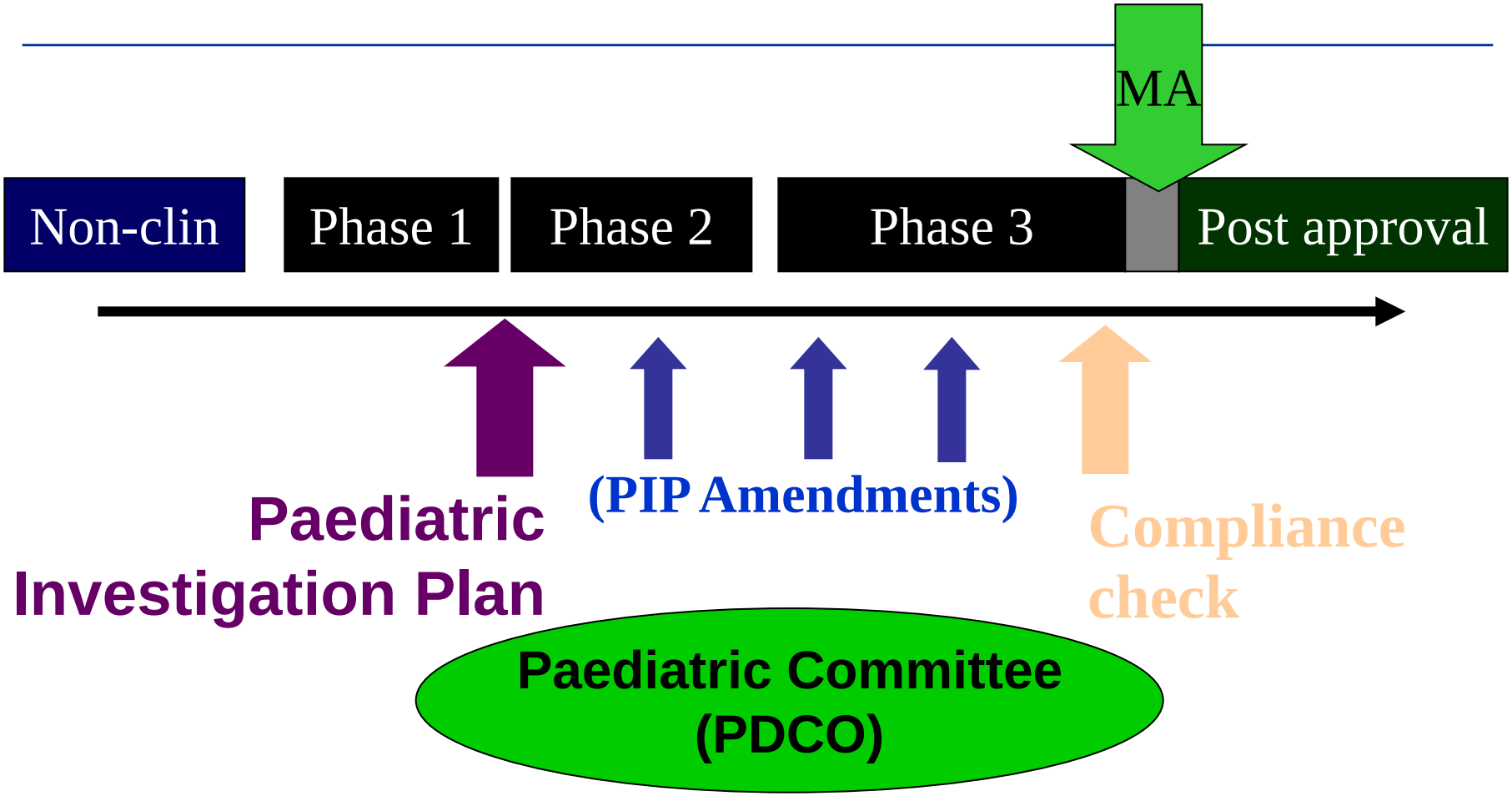
- Generic products, Hybrid products, Biosimilar products

• Class-waivers:

- For a class of products in a condition

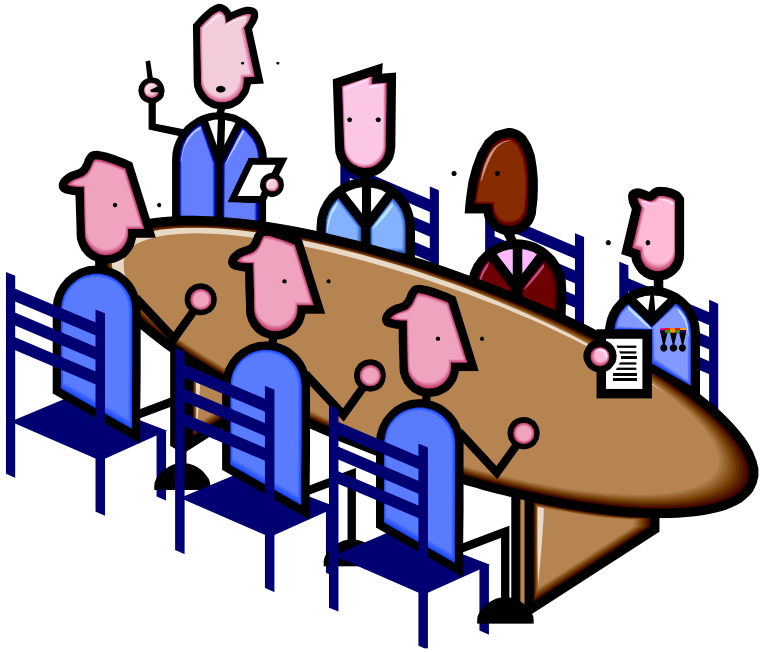
- For all products in a condition

When should the PIP be requested?



How is the PIP assessed?

EMA



PDCO

How is the PIP assessed? (1/2)

1) Validation

- Information correctly and completely provided in forms
- Structure of application is correct
- Enough scientific information and references are provided

2) Evaluation

- 60 (+ 60) days procedure with clock stop
- Comments by EMA paediatric coordinator → PDCO Rapporteur → PDCO Peer Reviewer
- 2 (+ 2) discussions in PDCO
- Request for Modifications (usually adopted at D60)

How is the PIP assessed? (2/2)

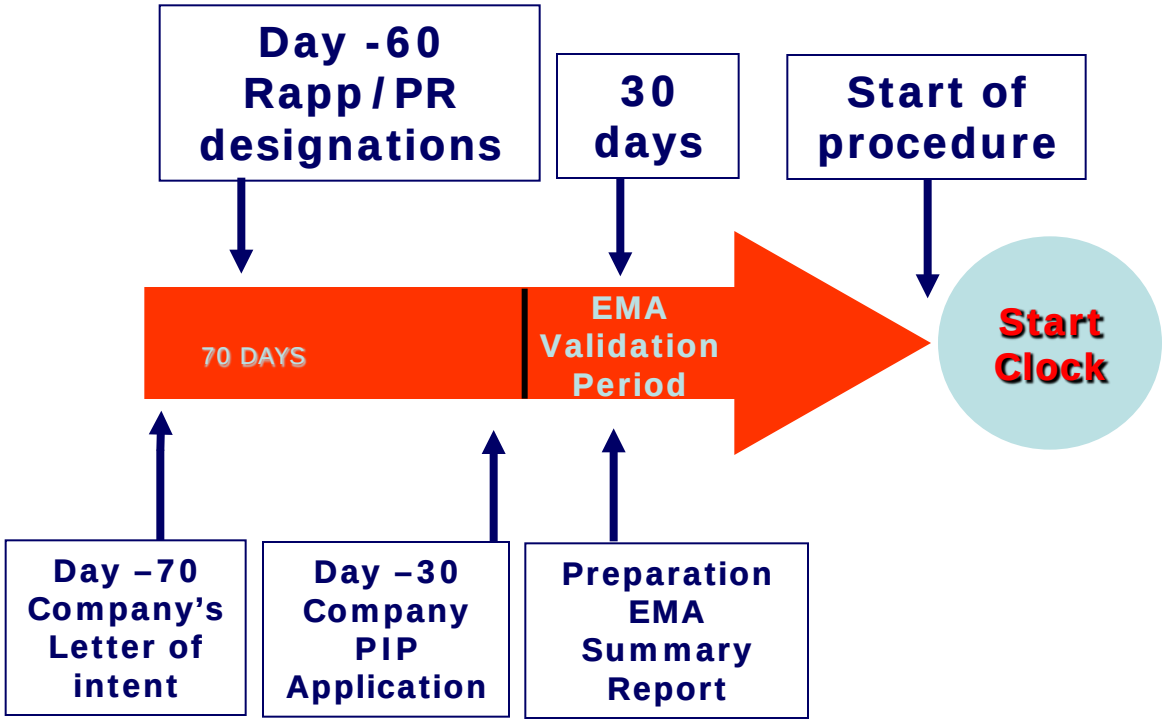
3) Opinion

- Adopted at D60 or D120 by PDCO
- May be subject to re-examination

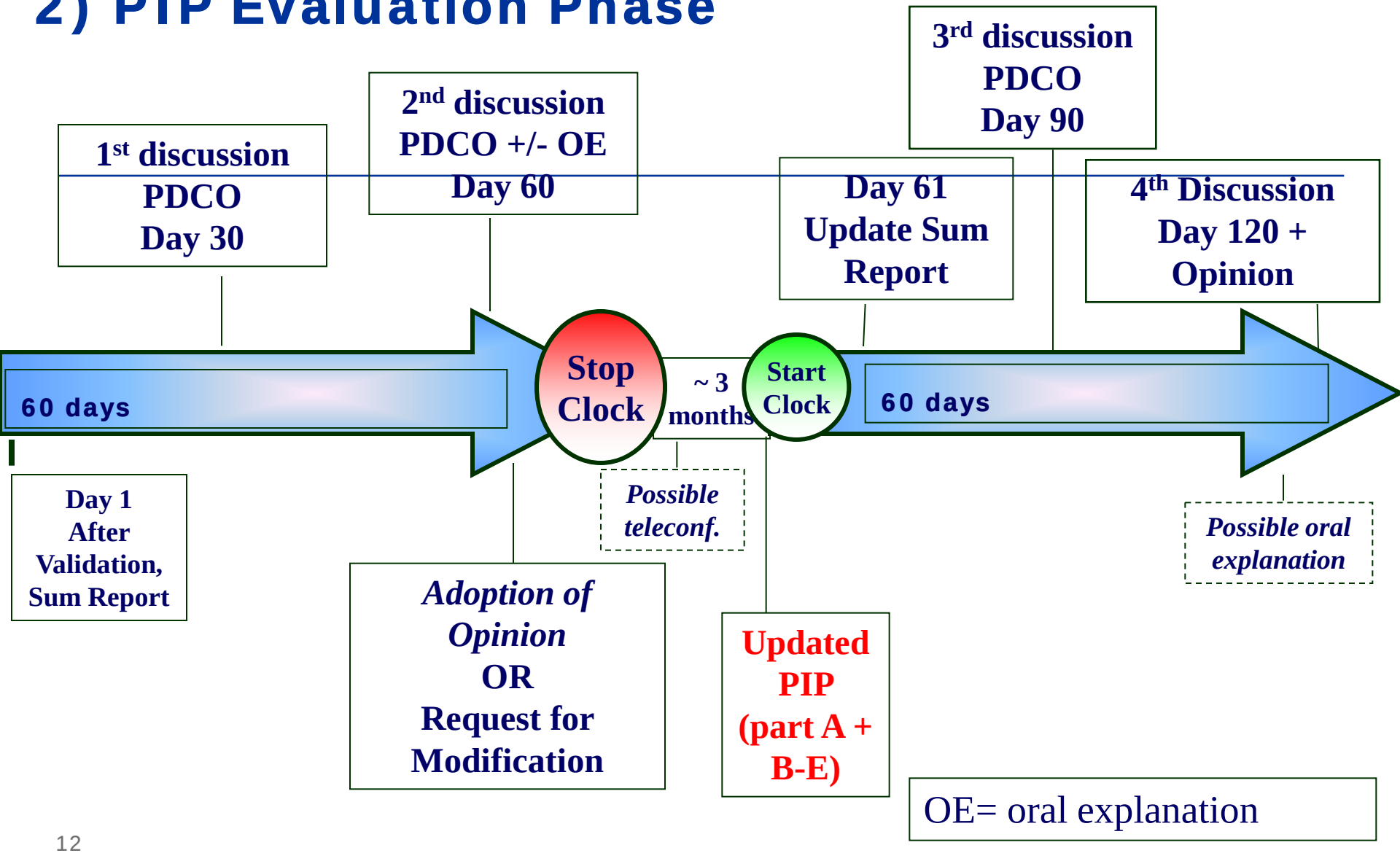
4) Decision

- Adopted by EMA (Executive Director) and not EU Commission
- Published on website

1) PIP Procedure Validation Phase



2) PIP Evaluation Phase



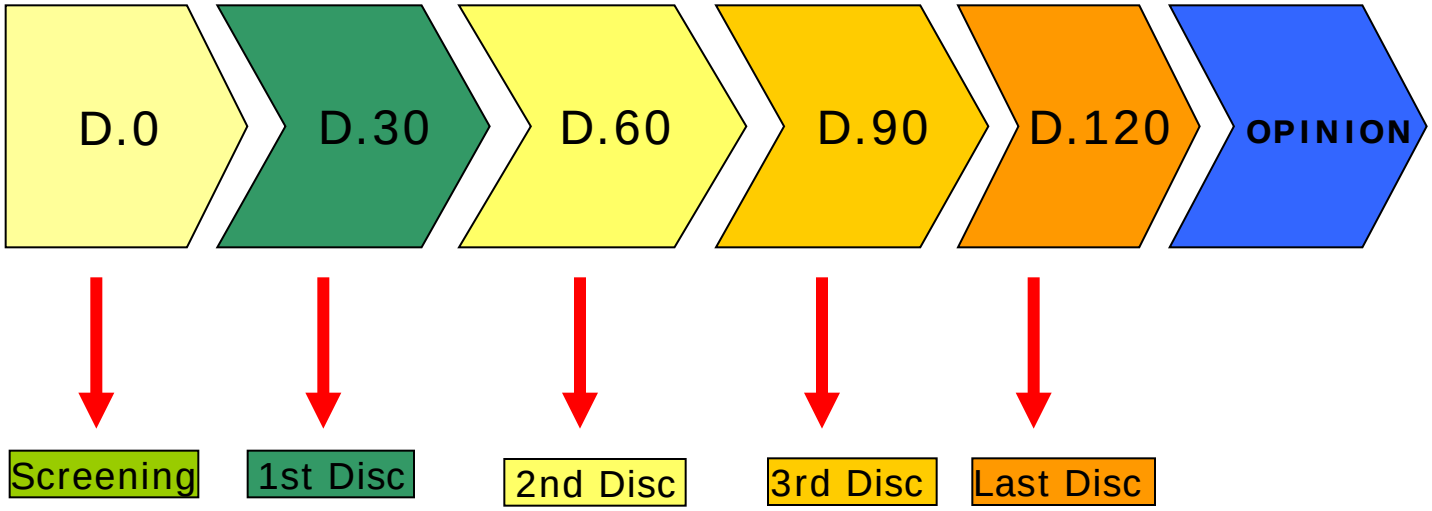
PDCO FWG in the PIP procedure (1/3)

- Role: supports PDCO in the review process of the quality section of PIPs
- Not assessing the data (e.g. stability) but evaluating issues related to paediatric formulation development strategy (e.g. safety of excipients)
- Composition: 15 formulation experts from PDCO, QWP, NCAs, hospitals and academia + 2 US FDA representatives as observers
- Close cooperation with EMA Quality team
- Team work: 1 PIP = 1 Quality PTM + 1 FWG Topic Leader

PDCO FWG in the PIP procedure (2/3)

- Discussion before D30 and/or D60 PDCO meeting: proposals for Request for Modification
- Discussion after clock stop, before D90 PDCO meeting: review of answers provided by applicant, proposals for key binding elements in the Opinion
- FWG's comments are reflected in the summary report and, if endorsed by the PDCO, in the RfM and/or Opinion + comments in the EMA Paediatric database

PDCO FWG in the PIP procedure (3/3)



Summary Report on PIP/Waiver

- To be prepared by the Agency within 30 days following receipt of the request [for agreement to a PIP] (Article 16) and validation of application
- Contains the Applicant's position
- Contains comments from EMA Coordinator, PDCO Rapporteur, PDCO Peer Reviewer, [PDCO members], PDCO FWG conclusions, NcWG conclusions
- Is usually sent to applicants four times (D30, D60, D90, D120) for transparency

Where to find Quality information in SR?

- D.I.c Information on the existing quality, non-clinical and clinical data
- D.II Quality aspects
  - D.II.a Strategy in relation to quality aspects
  - D.II.b Outline of each of the planned and/or ongoing studies and steps in the pharmaceutical development
- FWG conclusions and PDCO discussion minutes

Compliance check and MAA

- The paediatric development must be in compliance with measures and timelines agreed in PIP Decision
- Positive compliance check compulsory for validation:

- New MAA;
- New indication;
- New route of administration;
- New pharmaceutical form

- MAA assessment: PIP information available in Module 1.10

Conclusion

- The PIP is an integral part of the clinical development programme
- Development of suitable paediatric formulations required
- PIP assessment procedure and comments from experts involved reflected in the Summary Report
- Binding elements reflected in the PIP Opinion at the end of the PIP assessment
- PIP Decision published on EMA website and submitted in Module 1.10 at time of MAA

Back-up slides

Overall structure of a PIP application

A: Administrative and Product Information

B: Overall development of the product

- Information on product/mode of action/condition
- Significant therapeutic benefit / therapeutic needs

C: Waiver request

D: Overall strategy for development in children

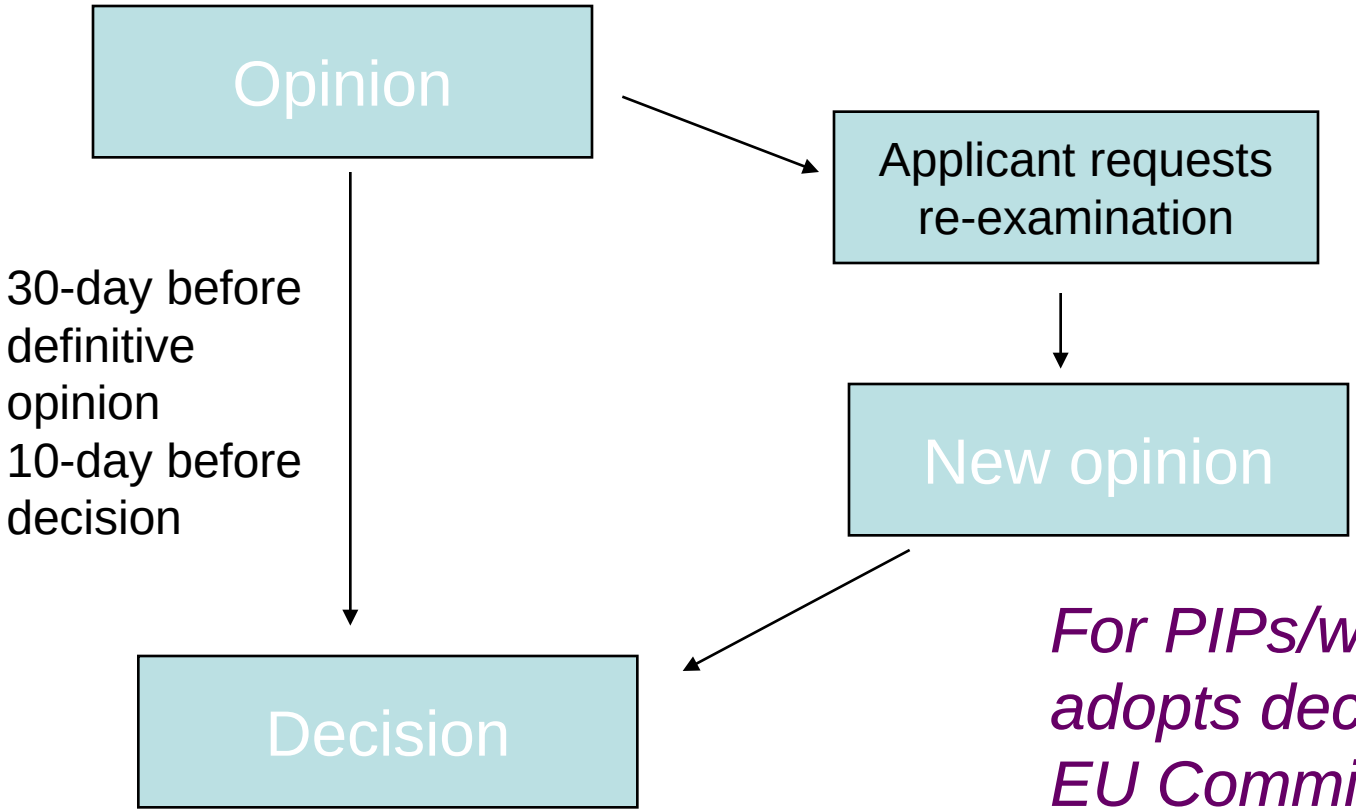
- Existing data (in adults and children)
- Proposed studies (ongoing or planned) and timelines

E: Request for deferral

PDF file

Scientific document
(Word + PDF)

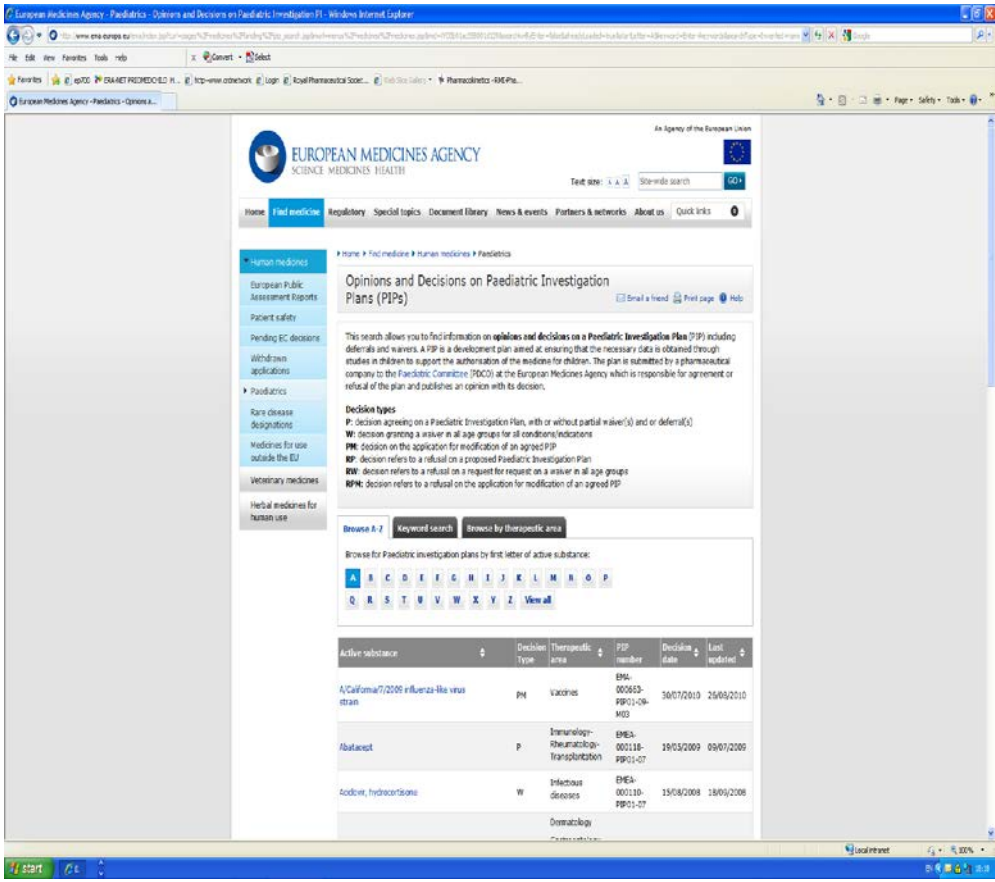
What happens of an agreed PIP?



For PIPs/waivers, EMA adopts decision (not EU Commission)

What happens of an agreed PIP?

- EMA PIP Decisions published as summary on EMA Website (outline of studies not published)
- Mandatory inclusion of paediatric information in Product Information
- European database of all clinical trials (EudraCT): protocol and results-related information for all paediatric studies to be **public**



Published decision/opinion

- For each condition/indication:

Partial or total waiver, paed subset(s) for the PIP, formulation(s) for the PIP

- Table of all studies/measures

(Pharmaceutical, non-clinical, clinical)

- Not published: Details on individual studies/measures

A. CONDITION(S)

Subependymal giant cell astrocytoma
Angiomyolipoma

B. WAIVER

- **Condition**

Angiomyolipoma

The waiver applies to:

All subsets of the paediatric population from birth to less than 18 years of age

for tablet for oral use and dispersible tablet for oral use

on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset(s).

C. PAEDIATRIC INVESTIGATION PLAN

- **Condition to be investigated**

Subependymal giant cell astrocytoma

- **Proposed PIP indication**

Treatment of patients with subependymal giant cell astrocytomas (SEGA) associated with tuberous sclerosis complex (TSC)

- **Subset(s) of the paediatric population concerned by the paediatric development**

From birth to less than 18 years

- **Formulation(s)**

Tablet for oral use
Dispersible tablet for oral use

Published decision/opinion

- **Studies**

Area	Number of studies	Description
Quality	-	Not applicable
Non-clinical	-	Not applicable
Clinical	3	Randomized, double-blind, placebo-controlled, parallel-group, dose-titration, comparative, multi-centre study to evaluate pharmacokinetics, safety, tolerability and activity of everolimus in children from birth to less than 18 years of age Relative bioavailability study between intact 1 mg tablet and 1 mg tablet dispersed in water in adults Bioequivalence study between intact 1 mg tablet and 2 mg dispersible tablet in adults

Measures to address long term follow-up of potential safety issues in relation to paediatric use:	**Yes**
Date of completion of the paediatric investigation plan:	**By October 2011**
Deferral for initiation of some or all studies contained in the paediatric investigation plan:	**No**
Deferral for completion of some or all studies contained in the paediatric investigation plan:	**No**

Published decision/opinion

- **Formulation(s)**

- Nebuliser solution for inhalation
- Solution for infusion for subcutaneous administration
- Solution for infusion for intravenous administration

- **Studies**

Area	Number of studies	Description
Quality	1	Development of an age-appropriate inhalation device for children from 2 years old to less than 6 years old.
Quality	1	Development of an Intravenous formulation.
Clinical (inhaled form)	1	Multi-centre, open-label, single-dose, dose-escalating study of inhaled treprostinil sodium using an Inhalation Device in paediatric patients from 6 years old to less than 18 years old with pulmonary arterial hypertension.
Clinical (inhaled form)	1	Randomized, double blind, Placebo controlled add-on to baseline therapy, multiple-dose, parallel group study of the safety and efficacy of inhaled treprostinil sodium using an Inhalation Device in paediatric patients from 6 years to less than 18 years old with pulmonary arterial hypertension.
Clinical (inhaled form)	1	Open-label safety and tolerability study using an age-appropriate inhalation device, in paediatric patients from 2 years to less than 6 years old with pulmonary arterial hypertension.
Clinical (inhaled form)	1	Randomized, double-blind, Placebo controlled add-on to baseline therapy study using an age-appropriate inhalation device, in paediatric patients from 2 years to less than 6 years old with pulmonary arterial hypertension.
Clinical (Subcutaneous form)	1	Analyses of existing data to clarify the safety and efficacy of the parenteral formulation of treprostinil in children aged from 12 to less than 18 years, as systematic review.
Clinical	1	Randomized, double-blind, Placebo controlled add-on to baseline

Study synopsis 1/2

Study identifier(s)	*Code and/or acronym only, not company title*
Type of study, study design	*Reflect the design briefly, e.g., randomised, add-on, in combination, double-blind, multicentre, single/multiple dose, placebo or active controlled, consecutive phases and age-staggered, ...* *Avoid mentioning other elements here (e.g. inclusion criteria)*
Study objective(s)	*E.g., efficacy, safety, pharmacokinetics, tolerability*
Study population and subset definition (incl. stratification)	*Here only high level information, e.g. age groups for staggered design*
Number of study participants by paediatric subset (e.g., age, sex, stratum)	*Indicate if a proportion of children needs to have some characteristics, or needs to be representative of the EU population in terms of genetic, standard of care, lifestyle, etc. for scientific reasons*
Main inclusion criteria	
Main exclusion criteria	*Specific ones only*
Location (e.g. regions)	*Only if justified scientifically*
Study duration	*By each phase, incl. run-in, active treatment and follow-up*
Dosage, treatment regimen, route of administration	*Dosing should not use abbreviations, but state explicitly e.g., twice daily*
Control(s)	*E.g., placebo, for active: use INN, if too complex then use descriptive (e.g., vaccine). Avoid brand names. Include doses for active*
Primary endpoint(s) with time point(s) of assessment	*In case of PK study or assessments, specify rich / sparse sampling, method of modelling (e.g., population PK),* *In general, number of samples and sampling per patient, blood volume per sample, method of analysis, sample volume is driven by expected variability* *Time point of assessment*

Study synopsis 2/2

Main secondary endpoint(s) with time points(s) of assessment	
Statistical plan	*Include the population analysis (intention to treat for superiority in general, per protocol for non-inferiority)* *Specify interim analysis(es)* *Handling of missing values* *Type of statistical analysis*
Stopping rule(s)	*Only if specific for the trial*
Rescue treatment	*Only if appropriate*
Measures to minimise pain and distress	*When specific*
Plan for specific follow-up	*E.g., open label extension of the study* *Attention: specify whether the PIP covers the outcome of the extension or the outcome is part of the post-authorisation measures*
External Data Safety Monitoring Board	Yes / No *Should be requested in all studies in neonates, in safety/efficacy studies in other age groups* *No need to mention tasks*
Date of initiation	<No later than < month> <year>> <After the benefit/risk is established in adults/subsets> <After completion of <measure>> <Not before <date or measure>
Date of completion (last patient, last visit)	By *<specify which month and year>* *do not include the date of finalisation and/or submission of the study report*
Plan in case of recruitment issues	*If specific*
Notes	

Modification of an agreed PIP

- Always possible if there are "*difficulties with its implementation as to render the plan unworkable or no longer appropriate*"
- Multiple modifications possible
- Application has same structure as original
- 60-day procedure; same EMA coordinator / Rapporteur / Peer Reviewer if possible
- New waivers/deferrals can also be requested
- New opinion/decision supersedes the original

Two must-read

- EU Commission guideline on Format and Content of applications for agreement or modification of PIP/waivers/deferrals
- EMA Procedural advice: Q&A on website

Additional reading

- FAQ on regulatory aspects of Regulation (EC) No 1901/2006 (Paediatric Regulation) amended by Regulation (EC) No 1902/2006.
- Scientific guidelines of specific paediatric relevance