EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Support to paediatric medicines development

SME Info day "Supporting innovative medicines development and early access"

Presented by Rocio Fernandez
Human Medicines Research & Development Support Division

Agenda

1. What is a PIP, what is a waiver?
2. Timelines and interaction with EMA
3. Where to find information and guidance to prepare a PIP
4. What does a PIP look like?
5. Modifications
6. Compliance checks
7. Incentives
8. Take-home messages

Paediatric Regulation in the EU

- Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006
  - Committee for Paediatric Medicines (PDCO)
  - Paediatric Investigation Plan
  - Procedures
  - Incentives

- EC Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies (2014/C 338/01)

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 authorization for adults

Paediatric Investigation Plan (PIP)

- 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
- 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 waiver?

- Exemption to produce results from measures studies in one or more paediatric subsets, for a given condition
- Not a prohibition to perform (paediatric) studies
- However, a reward can only be given if some measures have been completed, in compliance with a PIP
- Types: product-specific waiver/class waiver

When is a PIP/Waiver necessary?

Needed	Not needed

• New marketing authorisation (art 7)
 	
• Already authorised product (art 8)
  ○ New indications
  ○ New routes of administration
  ○ New formulations (but not for new strengths)
	• Off-patent products already authorised in the EU
	
	• New medicinal products in group:
	  ○ Herbal medicinal products
	  ○ Homeopathic products
	  ○ Generic products
	  ○ Hybrid products
	  ○ Biosimilar products
	
	• Class-waivers

Important: Class waivers revocation

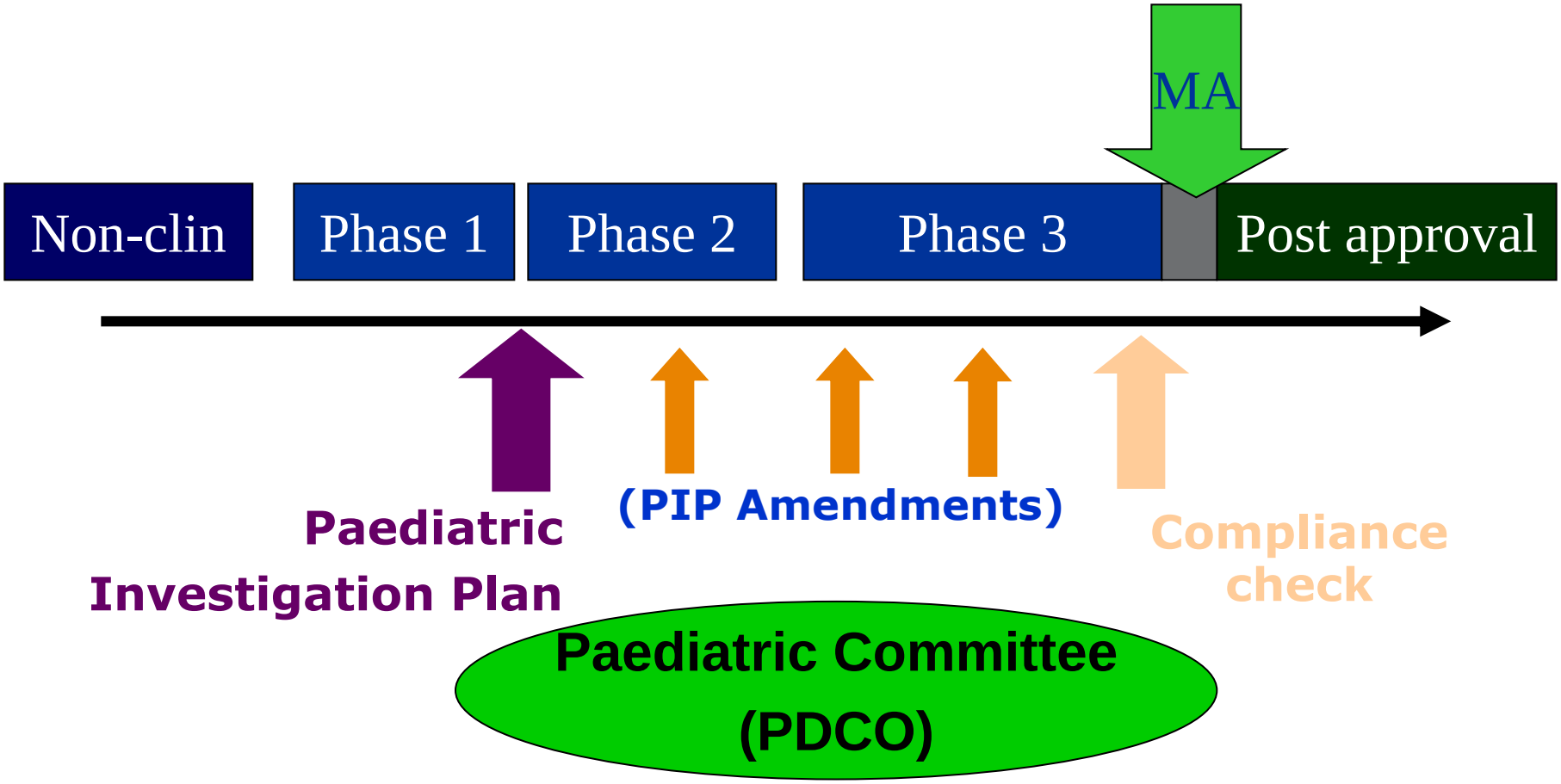
- Class waivers are an exemption from the obligation to submit a PIP request, for classes of medicines intended for specific conditions.
- The PDCO adopted a **review of the class waiver list** in 2015
- It has revoked 8 class waivers, updated 15 class waivers and confirmed 9 class waivers
- This will come into force after a 'transition phase' of 3 years on **27 July 2018.**
- Companies will need either a PIP or a product-specific waiver for medicines for all those conditions not class waived any longer

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000036.jsp&mid=WC0b01ac0580925cca

Paediatric-use marketing authorisation (PUMA)

- New dedicated type of Marketing Authorisation application (MAA) for exclusive paediatric use
- For products already authorised
- Intended for off-patent medicinal products
- It's not necessary to target the whole paediatric population; the age group with the highest unmet need can be targeted
- Incentives:
  - ✓ 10 year marketing protection (compliance with agreed PIP necessary) on data contained in the PUMA (8+2 years)
  - ✓ Fee reduction for MA/post-authorisation activities

Timelines - When should the PIP be requested?

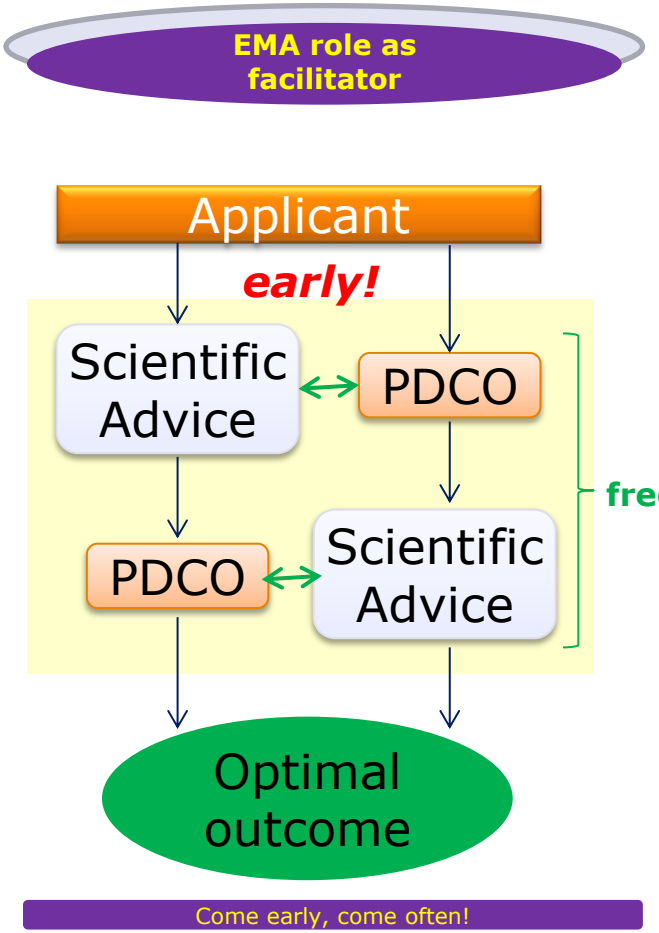


Timelines – Important to note

- The Paediatric Investigation Plan needs to be discussed and agreed early, long before Marketing Authorization is requested and after Phase I in adults and before trials are started in children
- Agreeing a PIP takes on average 8-12 months from start to finish

Interaction with EMA: Scientific Advice

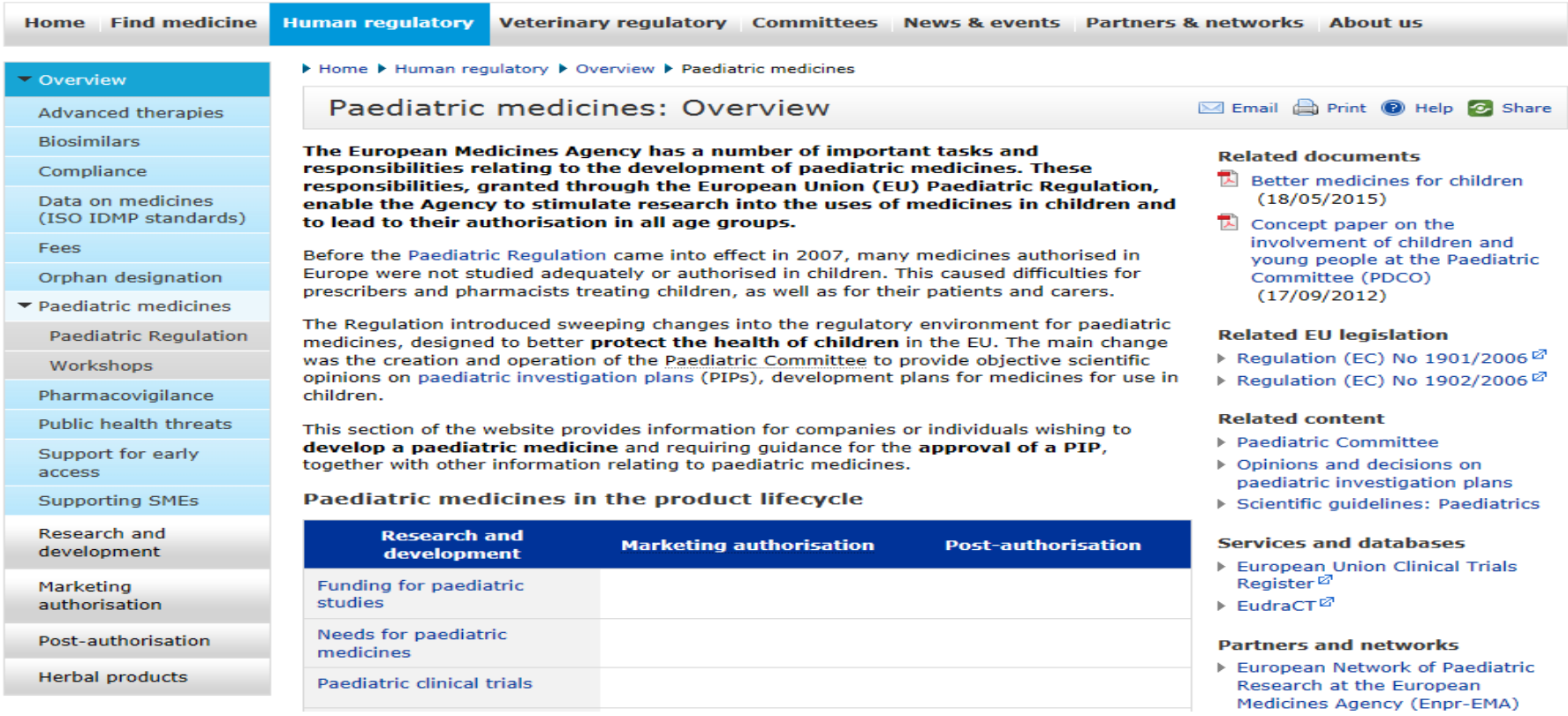
- Free for paediatric questions
- Protocol Assistance = Scientific Advice for orphan-designated products (75% discount, 100% for SME)
- Can be asked before or after the PIP (but beware of timelines)
- The committees in charge (PDCO and SAWP) cooperate for questions on paediatric development studies



Where to find information and guidance to prepare a PIP

- Paediatric Regulation
- EC Guideline on Format and Content of PIP applications
- EMA Procedural Advice (Q&A)
- Other documents/guidelines

Guidance on the website



Home | Find medicine | Human regulatory | Veterinary regulatory | Committees | News & events | Partners & networks | About us

- Overview
- Advanced therapies
- Biosimilars
- Compliance
- Data on medicines (ISO IDMP standards)
- Fees
- Orphan designation
- Paediatric medicines
  - Paediatric Regulation
  - Workshops
- Pharmacovigilance
- Public health threats
- Support for early access
- Supporting SMEs
- Research and development
- Marketing authorisation
- Post-authorisation
- Herbal products

Home ▸ Human regulatory ▸ Overview ▸ Paediatric medicines

Paediatric medicines: Overview

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The European Medicines Agency has a number of important tasks and responsibilities relating to the development of paediatric medicines. These responsibilities, granted through the European Union (EU) Paediatric Regulation, enable the Agency to stimulate research into the uses of medicines in children and to lead to their authorisation in all age groups.

Before the Paediatric Regulation came into effect in 2007, many medicines authorised in Europe were not studied adequately or authorised in children. This caused difficulties for prescribers and pharmacists treating children, as well as for their patients and carers.

The Regulation introduced sweeping changes into the regulatory environment for paediatric medicines, designed to better **protect the health of children** in the EU. The main change was the creation and operation of the Paediatric Committee to provide objective scientific opinions on paediatric investigation plans (PIPs), development plans for medicines for use in children.

This section of the website provides information for companies or individuals wishing to **develop a paediatric medicine** and requiring guidance for the **approval of a PIP**, together with other information relating to paediatric medicines.

Paediatric medicines in the product lifecycle

Research and development	Marketing authorisation	Post-authorisation
Funding for paediatric studies		
Needs for paediatric medicines		
Paediatric clinical trials		

Related documents

- Better medicines for children (18/05/2015)
- Concept paper on the involvement of children and young people at the Paediatric Committee (PDCO) (17/09/2012)

Related EU legislation

- Regulation (EC) No 1901/2006
- Regulation (EC) No 1902/2006

Related content

- Paediatric Committee
- Opinions and decisions on paediatric investigation plans
- Scientific guidelines: Paediatrics

Services and databases

- European Union Clinical Trials Register
- EudraCT

Partners and networks

- European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA)

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000023.jsp&mid=WC0b01ac0580b18c75

PIPs: Questions & Answers

Table of contents

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000015.jsp&mid=WC0b01ac0580925cc7

Contact on matters regarding Paediatric Medicines

- Contact at EMA: either the assigned paediatric co-ordinator or paediatrics@ema.europa.eu
- Presubmission meeting: to ensure a smooth validation when the PIP is almost ready for submission. Aim at regulatory/administrative questions
- Clarification of the PDCO requests for modification: to clarify any details of the PDCO's request for modification, during clock-stop. It may involve scientific discussion.

Part A: Product and Regulatory Information

Part B: Application Summary.
Targeted conditions/indications, general pharmacology of drug, paediatric medical needs by age groups (with prevalence) and potential therapeutic benefit of drug versus alternatives.

Part C: Waiver request per age group.

Part D: Summary of existing data on drug and **details** of the proposed paediatric development for the drug: quality, pre-clinical and clinical.
Timelines of the individual studies.

Part E: Deferral request.

Part F: Annexes

Key elements form: **concise** proposal of quality, pre-clinical and clinical studies.

Application Form
(PDF form)

Scientific part B-E
(Word document, free format)

Key Element Form
(PDF form)

Part E: Deferrals

- A deferral means that results of studies which are deferred do not have to be provided at the next regulatory submission

- A deferral does **NOT** mean that a **PIP application** can be submitted late (e.g. after completion of adult development) **but** that the **agreed measures** in the PIP can be initiated and/or completed **later** in relation to the adult development.

- A deferral may be applicable to some or all measures in PIP opinion. It may apply to only completion or also initiation

- A deferral is granted when adult study results are deemed necessary prior to initiating studies in children or when paediatric studies will take longer to conduct than studies in adults.

Common errors

- Old application form (part A, PDF file)
- Errors / missing information in part A: validation issue
- Insufficient information in any part of the scientific document (part B-E): validation issue
- Request for deferral for condition/indication, but studies not proposed: validation issue (deferral is for doing the studies, not for proposing them)
- Hyperlinks

Procedures evaluated by the PDCO

- PIP application: 120-day procedure, clock-stop at D60 (Request for Modification)

Deferrals for initiation and/or completion of some measures are possible

- PIP modification: 60-day procedure, no clock-stop

  → PDCO Opinion, EMA Decision (partially published on EMA website)

- PIP Compliance check: 60-day procedure, no clock-stop

  → PDCO Opinion (outcome published on EMA website)

- Confirmation of class waiver
- Inclusion of an indication within an agreed condition

Modification of an agreed PIP

When to modify a PIP?

- The PIP is binding for the company
- As the development progresses there may be a need to apply for a modification of the agreed PIP
- When the measures contained in the PIP are no longer appropriate or unworkable
- E.g. change of formulation, recruitment difficulties, extension of timelines

Compliance check

- Compliance check is the verification that some or all studies/measures agreed in a PIP have been conducted in accordance with the PIP decision. CCs are necessary prior to MAA or modification of a MA.
- A CC can be full (on all measures) or partial (on measures not deferred at the time of regulatory submission).
- To be submitted at least 2 months prior to the planned submission of a Regulatory Application
- Applicants may request the PDCO to confirm compliance in advance of their Regulatory Applications; alternatively compliance will be checked as part of the validation procedure of a MAA or other procedures

Incentives for Paediatric medicines

- Reward is given to completed PIPs
  - if development is compliant with agreed PIP (**compliance statement** in MA)
  - if results of studies (positive or negative) included in SmPC + patient's leaflet
  - if product is authorised in all MSs (except for PUMA)
- Non-orphan products: 6-month extension of SPC (patent protection)
- Orphan medicinal products: + 2 additional years of market exclusivity
- PUMA: 8 + 2 years of data + market protection

Product-specific or class waiver does **NOT** trigger the reward

Inconclusive studies in PIP do **NOT** trigger the reward

Achievements of the EU Paediatric Regulation

Positive impact on paediatric drug development *:

- More medicines for children (from 2007 until 2016, 267 new medicines for use in children and 43 new pharmaceutical forms appropriate for children were authorised in the EU), better and more information for prescribers and patients (by the end of 2015, approximately 140 updates of the product information);
- Better paediatric research and development;
- More regulatory support for paediatric matters;
- Paediatrics now being an integral part of medicine development.

*https://ec.europa.eu/health/sites/health/files/files/paediatrics/2016_pc_report_2017/ema_10_year_report_for_consultation.pdf

Examples of new medicines for the paediatric population


Impact of the European paediatric legislation in paediatric rheumatology: past, present and future

Nicolino Ruperto,[1] Richard Vesely,[2] Agnes Saint-Raymond,[2] Alberto Martini,[3] for the Paediatric Rheumatology International Trials Organisation (PRINTO)

Rheumatology: before 2007 very limited therapeutic options → since then 14 completed PIPs 8 new paediatric indications

"In recent years, following the inception of paediatric legislation in the US and EU, the development of new treatments for children with rheumatologic diseases has seen a significant surge." (Ruperto N et al, 2013)

Cardiovascular diseases: Several anti-hypertensives and cholesterol-lowering agents

Infectious diseases: New treatments for hepatitis C, HIV infection, fungal infections, and new antibiotics

Oncology: First treatment for paediatric neuroblastoma and new less toxic regimens

Indications where there were no approved pediatric medicines OR in age groups where there were no treatments approved.

Importance of bringing stakeholders together

Motivations include:

- Rapid developments in **innovation** hence need to ensure that **paediatric needs** are addressed
- Refine endpoints and study design to address the **clinical trials challenges**
- Set **priorities** in future **research** in the field like post-marketing tools

Facilitating of constructive interactions between relevant stakeholders

All documents are available on www.ema.europa.eu

Take-home messages

Think paediatric in advance:

- Bear in mind paediatric needs/requirements in most drug developments
- PIP/waiver request to be prepared during or before phase I studies in adults (or equivalent)
- Consider time needed to prepare final study report when calculating compliance check and marketing authorisation application deadlines

Paediatric regulation applies also to “national” products, not only centralised ones

Make use of opportunities for interaction!

Thank you for your attention

Further information

Please contact: paediatrics@ema.europa.eu

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