# The EU Paediatric Regulation

# Children: a neglected population

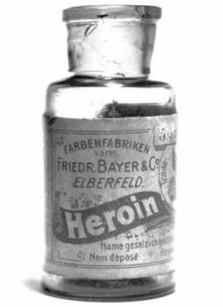
**Problems:**

**- 20% of the EU population, i.e. 100 million, is aged less than 16 years**
**⇒ premature neonate, term neonate, infant, child, adolescent**
**- 50-90% of medicines used in children have not been tested and evaluated**
**- Age appropriate formulations are often missing**

***Risks:***

***- adverse effects (overdosing)***
***- inefficacy (underdosing)***
***- improper formulation***
***- delay in access to innovative medicines***

**Bayer's Heroin.**
**Between 1890 and 1910 heroin was also used to treat children with strong cough.**




**Cocaine drops for toothache**
**Very popular for children in 1885.**


**Evidence of harm from off-label or unlicensed medicines in children**
http://www.ema.europa.eu/pdfs/human/paediatrics/12632704en.pdf

# Objectives of the EU Paediatric Regulation

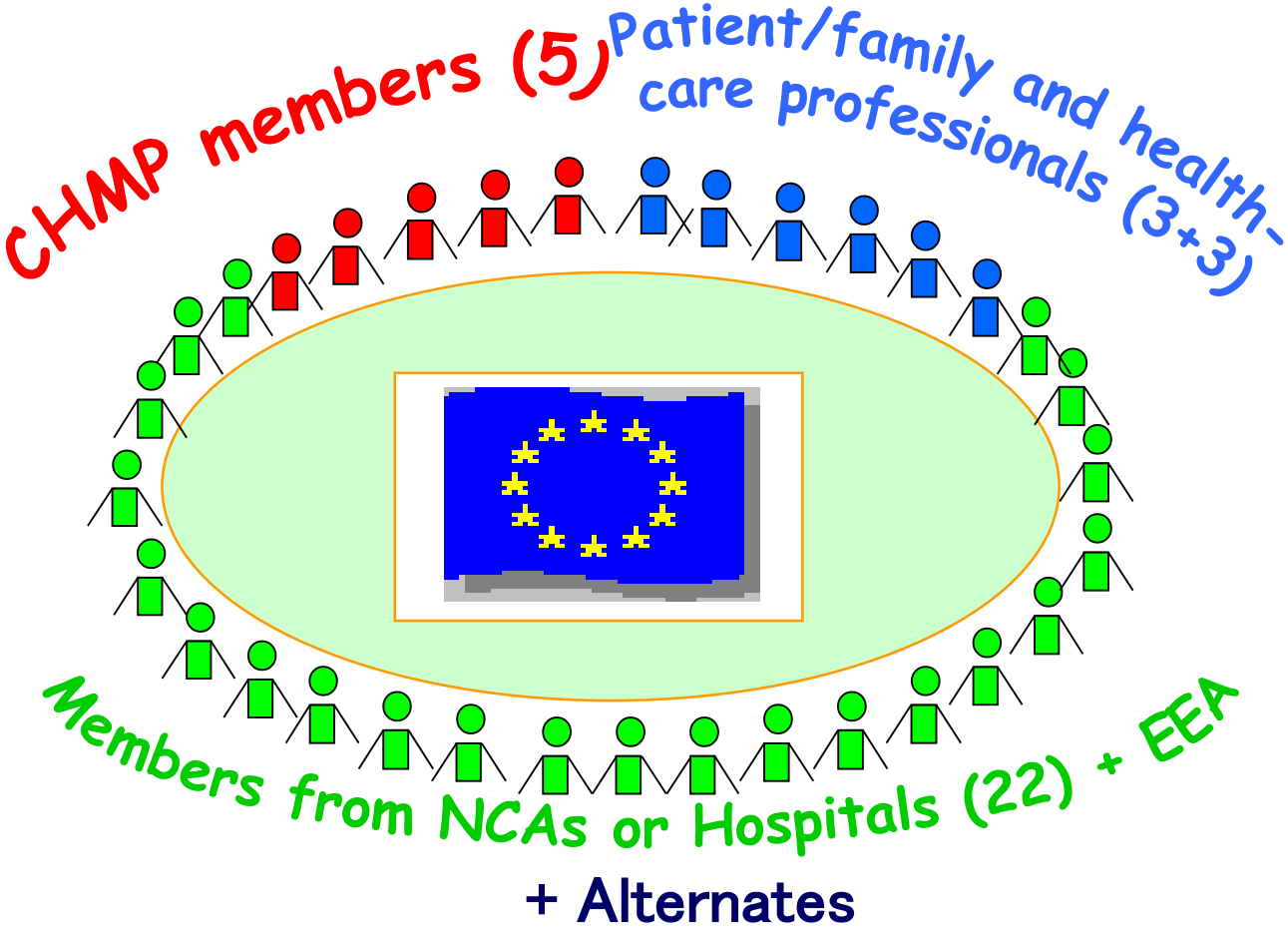
- Improve the health of children:
  - Increase high quality, ethical **research** into medicines for children
  - Increase **availability** of authorised medicines for children
  - Increase **information** on medicines
- Achieve the above:
  - Without unnecessary studies in children
  - Without delaying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

# Pillars of the Paediatric Regulation

- EMA and its Paediatric Committee (PDCO)
- Paediatric Investigation Plan (PIP)

-> *system of OBLIGATIONS and REWARDS*

# EMA Paediatric Committee (PDCO)




**Main role**:

agree development plans of medicinal products in children (PIPs)

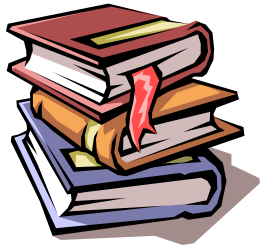
# What is a Paediatric Investigation Plan (PIP)

Research and development programme

details timing & measures for paediatric indication

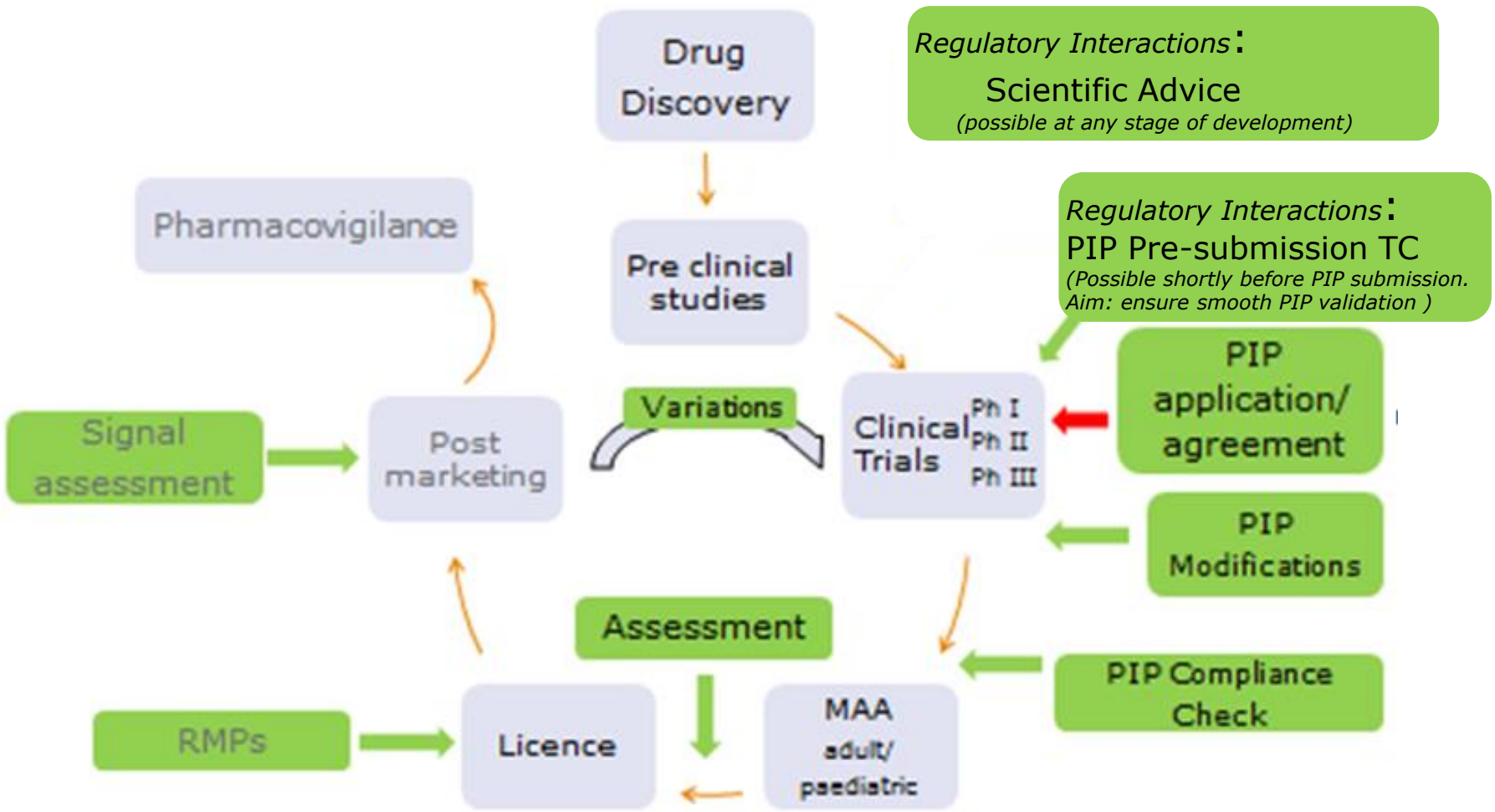
**Quality**
**Pre-clinical**
**Clinical**

→ **Marketing Authorisation**

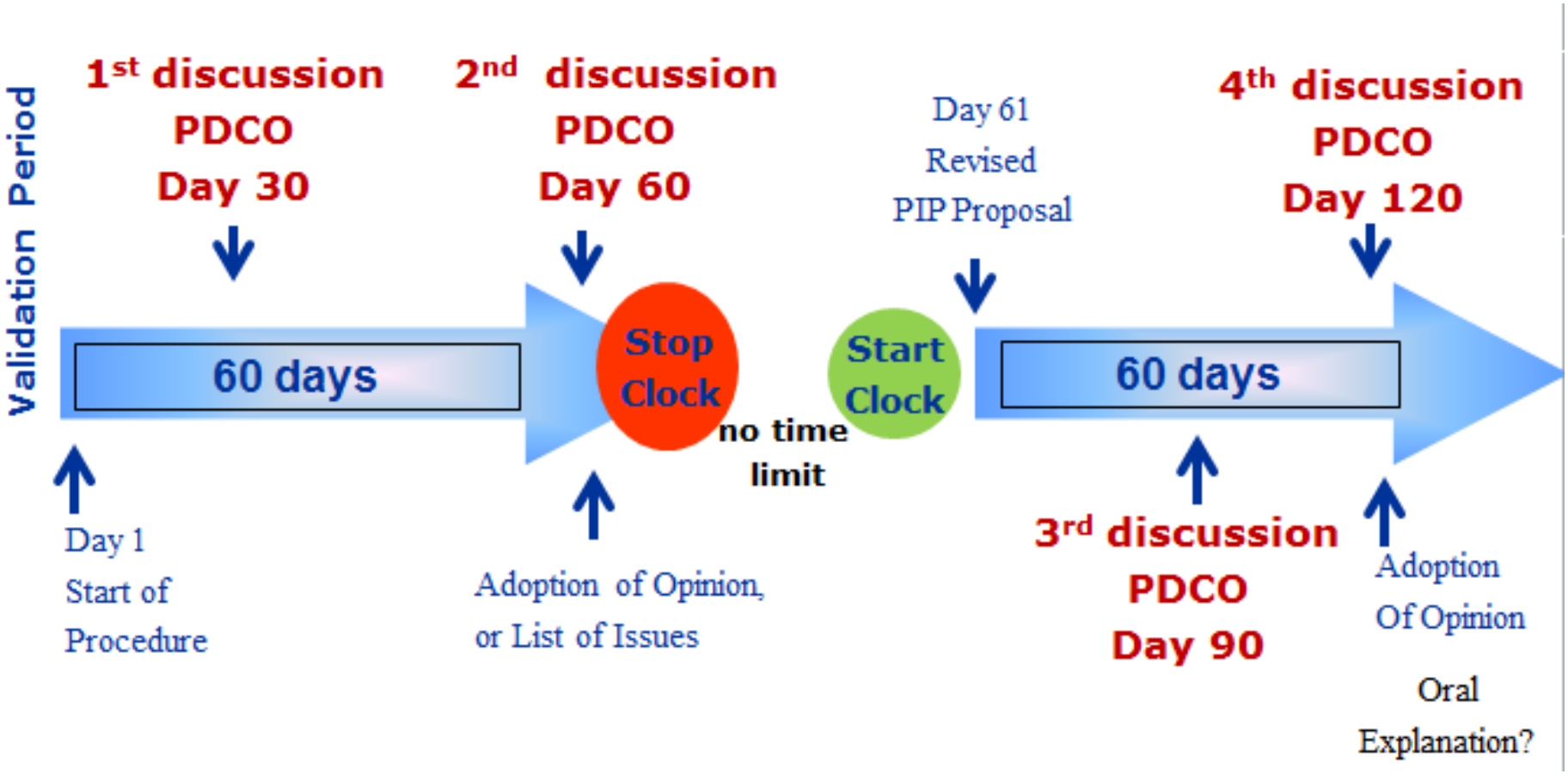


**Binding upon company!**

# Paediatric drug development within the overall drug lifecycle



# Overview PIP Procedure



# **Waiver** in children for **all** or **some** age groups

a) **Medicinal product likely ineffective or unsafe**

b) **Disease does not occur**

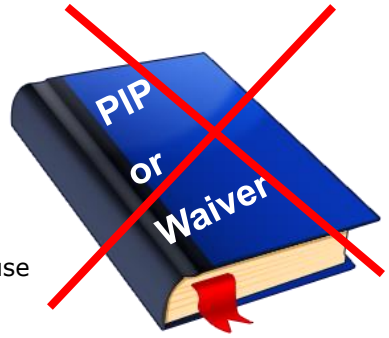
c) **Medicinal product does not represent a significant therapeutic benefit over existing treatments**

# PIP or Waiver **NOT** needed:

**Off-patent products** already **authorised** in the EU (if company is Marketing Authorisation Holder).

**New medicinal products** in group:

- Generic products *(Art 10 (1), Directive 2001/83)*
- Hybrid products *(Art 10 (3), Directive 2001/83)*
- Biosimilar products *(Art 10(4), Directive 2001/83)*
- Well Established Use *(Art 10a, Directive 2001/83)*
- Homeopathic products *(Art 13, Directive 2001/83)*
- Traditional herbal medicinal products *(Art 16a-i,* "traditional-use registration", *Directive 2001/83)*



# PIP
# Opinion/Decision

**WAIVER** *(e.g. T2D: 0-10 years)*

**PIP** *(e.g. T2D: 10-18 years)*

- Quality,
- Pre-clinical ,
- Clinical

-> Timelines
-> Deferral

# PIP Modifications

**What is it?**

Regulatory Procedure to change any of the details (Key Elements) in a PIP Opinion/Decision.

**When is it needed?**

If Paediatric Plan is unworkable or no longer appropriate and if necessary changes affect the Key Elements of PIP Opinion/Decision.

**How long is the procedure?**

It is a 60 day procedure.

**Who performs the PIP Modifications?**

The PDCO will review the Modification Requests and adopt new PIP Opinions.

Opinion adopted: positive even if only one of the modifications requested has been accepted

New opinion replaces previous opinion and contains all key binding elements, not just those modified

Opinion and decision process is the same as for original opinion

## PIP Opinion/Decision

**Key Elements:**

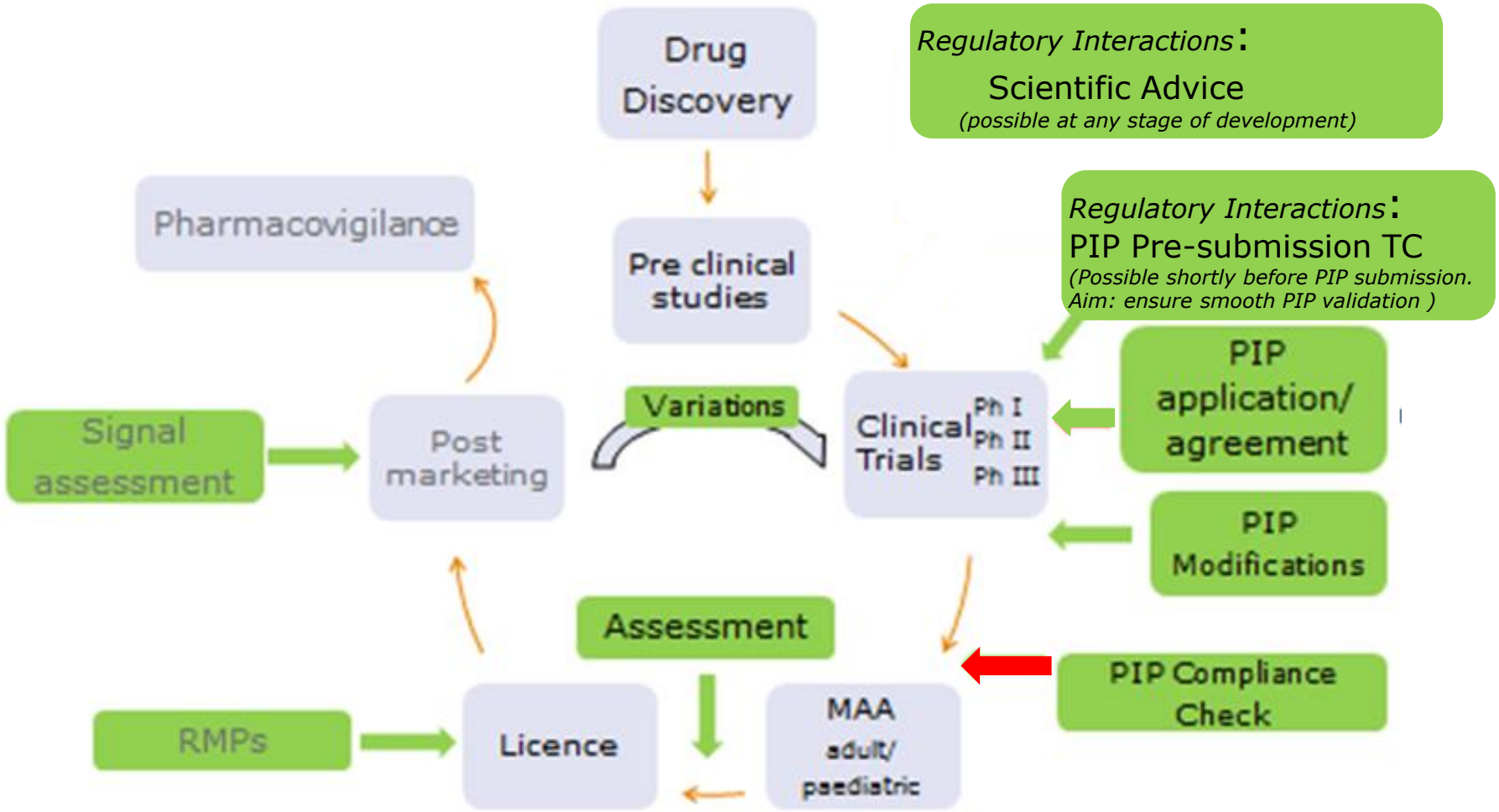
**Waiver**

**Quality**
**Pre-clinical**
**Clinical**

**Timelines**

**Deferral**

# PIP Compliance Check



# Obligations vs Reward

| Type of MP | Obligation | Reward | Comments |
|---|---|---|---|
| **New Medicinal Product** *Article 7* | PIP (or Waiver) | 6 months Extension of SPC (patent)* | **A reward for a PIP can only be given once for any medicinal product (GMA concept).** |
| **Authorized Medicine, On-patent** *Article 8* | PIP (or Waiver) | 6 months Extension of SPC (patent)* | • New indication,<br>• New route of admin.,<br>• New pharm. form |
| **Authorized Medicine, Off-patent** *Article 7* *Article 30* | • **non-MAH**: PIP (or Waiver)<br>• **MAH: No Obligation Voluntary PIP!!** | PUMA: 8+2 years Data/Marketing Protection* | Research funds may be available through European Commission<br>Paediatric Use Marketing Authorization (PUMA) is a possibility |
| **Orphan Medicine** | PIP (or Waiver) | 2 additional years of Market Exclusivity* | In addition to 10 years Market Exclusivity already given to Orphans |

MAH: Marketing Authorization Holder

* *Please see next slide*

# COVID-19 treatments and vaccines

## -> *accelerated procedures possible*

- No pre-specified PIP submission deadlines;
- PIP review min. of 20 days (from 120 days), exact timelines case by case (*considering: complexity of PIP, response time to questions, TL MAA)*
- EMA decision following a review is reduced to 2 days (from 10 days);
- Focused scientific documentation, agreed on case-by-case basis;
- Compliance check can be reduced to 4 days.
- Joint procedural information on PIP and iPSP from EMA and US FDA *(efficient simultaneous submissions: compare requirements + focus information)*

**Key message: regulatory flexibility for COVID-19 treatments and vaccines**

# Enpr-EMA

## European network of paediatric research at EMA

An umbrella network of research networks,

investigators and centres with recognised expertise

in performing paediatric clinical trials in Europe

**Contact:** enprema@ema.europa.eu

**Web:** https://www.ema.europa.eu/en/partners-networks/networks/european-network-paediatric-research-european-medicines-agency-enpr-ema

# Enpr-EMA:
## overview of all networks currently registered within the Enpr-EMA

## Member networks by type & category

| National | Oncology/ Haematologic Malignancies | Diabetes/ Endocrinology/ metabolic disorders/ Gynaecology | Gastroenterology/ Hepatology | Allergology/ Immunology/ Rheumatology | Stem Cell /Organ Transplantation/ Haematology/Haemostaseology | Respiratory diseases /Cystic Fibrosis |
|---|---|---|---|---|---|---|
| DCRI | ITCC | EUCADET | EPLTN | PRINTO | EBMT PDWP | ECFS-CTN |
| NIHR-CRN | Newclastle-CLLG | | PEDDCReN | JSWG of PRES | | SPACE |
| ScotCRN | I-BFM-SG | | | JIA uveitis WG | | |
| FinPedMed | | | | PIBD-Net | | |
| Pedmed-NL | EORTC CLG | | | | | |
| MICYRN | CEPOETA | | | | | |
| CICPed | | | | | | |
| RIPPS | | | | | | |
| OKIDS | | | | | | |
| NorPedMed | | | | | | |
| MCRN-Hungary | | | | | | |
| IPCRN | | | | | | |
| Futurenest CR | | | | | | |
| SwissPedNet | | | | | | |
| RECLIP | | | | | | |
| NCCHD-Japan | | | | | | |
| c4c | | | | | | |
| HunPedNet | | | | | | |
| NETSTAP | | | | | | |
| PCIC-Belgium | | | | | | |
| PEDSTART | | | | | | |
| STAND4Kids | | | | | | |
| Red SAMID, | | | | | | |

**Category 1:** Networks fulfilling all minimum criteria for membership of Enpr-EMA.
**Category 2:** Networks potentially fulfilling all minimum criteria – but needing to clarify some issues before becoming a member of Enpr-EMA.
**Category 3:** Networks currently not yet fulfilling minimum criteria.
**Category 4:** Networks not performing clinical trials; e.g. methodology, infrastructure, etc.

**SPECIAL ACTIVITIES / AGE GROUPS**

| Psychiatry/ Neurology | Infectious diseases/ Vaccinology | Intensive Care/Pain/ Anaesthesiology/ Surgery | European neonatal network | European paediatric pharmacists | special activities (Phv, long term follow up, community paediatricians) | Expertise in clinical trial methodology |
|---|---|---|---|---|---|---|
| EUNETHYDIS | PENTA-ID | ESPNIC | GNN | | FP-MCRN | TEDDY |
| ECAPN | UKPVG | | INFANT | | | eYPAGnet |
| | ReSViNet | | Neo-circulation | | | PedCRIN |
| | | | | | | EAPRASnet |
| | RITIP | | ESDPPP | | | TREAT-NMD |
| | | | | | | |

# Enpr-EMA:
*working for patients with patients*

- **Patient organisation representatives** are **members** of Enpr-EMA Coordinating Group.
- **Enpr-EMA reaches out** to patients and patient organisations (*e.g. public consultation on trial preparedness guidance*).
- Usually there is an **annual open Enpr-EMA workshop** where we would encourage patients and parents to take part and get involved.
- **Patient representatives** and **young persons' advisory groups** have been involved in various Enpr-EMA working groups (*e.g. consent/ assent guidance*).
- **Patients can reach out** to Enpr-EMA to suggest issues to tackle and/or get involved in, enprema@ema.europa.eu

# Global Paediatric Development

# Differences EU (Paediatric Regulation) / USA (BPCA-PREA-FDASIA)

| | US BPCA | US PREA/** | EU |
|---|---|---|---|
| **Scope** | Active moiety (can expand to other indications than adult indication)<br><br>-> OPTIONAL | Pediatric indication mirroring adult indication.<br><br>** All potential paediatric cancer indications for the active substance (MoA based)!<br><br>-> MANDATORY | Scope determined by condition (broad disease entity based on adult indication)<br><br>-> MANDATORY |
| **Instrument** | Written Request | Pediatric Study Plan (PSP) | Paediatric Investigation Plan (PIP) |
| **Waivers** | N/A | Yes (3 grounds)<br><br>** Yes (similar grounds as non-cancer drugs) | Yes (3 grounds) |
| **Timing** | End of phase 2 | End of phase 2<br>-> deferral may be possible | End of phase 1<br>-> deferral may be possible |
| **Reward** | 6 months exclusivity | None -> but paediatric studies can be incl in Written Request (Reward under BPCA) | Main: 6 months SPC extension (patent) |
| **Orphan** | Included | Excluded<br>** Included | Included |

*** US PREA-cancer (as of 19 August 2020) – RACE for Children Act***
***Incorporated as Title V of the FDA Reauthorization Act (FDARA), enacted August 18, 2017***

# FDA-EMA Interactions

- **Monthly EMA/FDA "paediatric cluster" TCs**
  (*incl also HealthCanada, PMDA -Japan, TGA-Australia*)
- **Monthly EMA/FDA "rare disease cluster" TCs**
- **Parallel EMA/FDA scientific advice**

# Summary (1)

- **EMA** is scientific EU Agency, coordinating & contributing to **authorization of medicinal products** (centralized procedure) & oversees their **safety**
- Many ways for **regulatory/scientific interaction** with EMA
- **Committee for Human Medicinal Products** (CHMP) issues opinions on safety & efficacy of new human medicinal products -> leading to their licensing (or not) in all EU counties at the same time
- Medicinal products developed for **rare diseases** can get incentives through obtaining an Orphan Designation

# Summary (2)

- Objective of **EU Paediatric Regulation**: increase information & availability of authorised medicines in children

- **Paediatric Investigation Plans** (PIPs) are binding research and development plans that detail quality, non-clinical and clinical measures necessary for obtaining a paediatric indication, agreed with the Paediatric Committee (PDCO) at end of phase I studies in adults

- PIPs can be **modified**

- **Reward** is possible upon PIP completion

# Summary (3)

- **European network** of **paediatric research** at **EMA** (Enpr-EMA) -> expertise in performing paediatric clinical trials
- **Patient representatives** are **involved** in the work of Enpr-EMA
- **Paediatric development** is **global**: paediatric legislations also in US, EMA & FDA regularly interact on paediatric developments

# Thank you!

# Further Reading

1. ICH E11: Clinical Investigation of Medicinal Products in the Paediatric Population

3. Ethical considerations for clinical trials on medicinal products conducted with the paediatric population http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-10/ethical_considerations_en.pdf

5. EMA guideline on Pharmaceutical Development of Medicines for Paediatric Use

6. Non-clinical testing in juvenile animals

7. EMA Reflection paper on extrapolation of efficacy and safety in paediatric medicine development, Oct 2018 (final) https://www.ema.europa.eu/en/documents/scientific-guideline/adopted-reflection-paper-use-extrapolation-development-medicines-paediatrics-revision-1_en.pdf

8. General scientific guidelines on quality, nonclinical and clinical development:

http://tinyurl.com/EMAguidelines

9. Standard paediatric investigation plans:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000412.jsp&mid=WC0b01ac0580925cc8

10. EMA Paediatric Public Website:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000023.jsp&mid=WC0b01ac05800240cd

# Further Reading

11. Policy on the determination of the condition(s) for a Paediatric Investigation Plan/Waiver (scope of the PIP/waiver) - EMA/272931/2011

    http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/09/WC500133065.pdf

12. Paediatric Expert Workshops organized at EMA:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000416.jsp&mid=WC0b01ac0580925cc6

13. Regulatory Interactions- *Research and development support at EMA*

https://www.ema.europa.eu/en/human-regulatory/research-development

14. Accelerated procedure for COVID-19 treatments and vaccines

https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans#accelerated-procedure-for-covid-19-treatments-and-vaccines-section