EPTRI General Assembly and Scientific Meeting Warsaw, 28-29 July, 2026

Past, Present and Future of Regulatory Science for Paediatric Medicines

Viviana Giannuzzi

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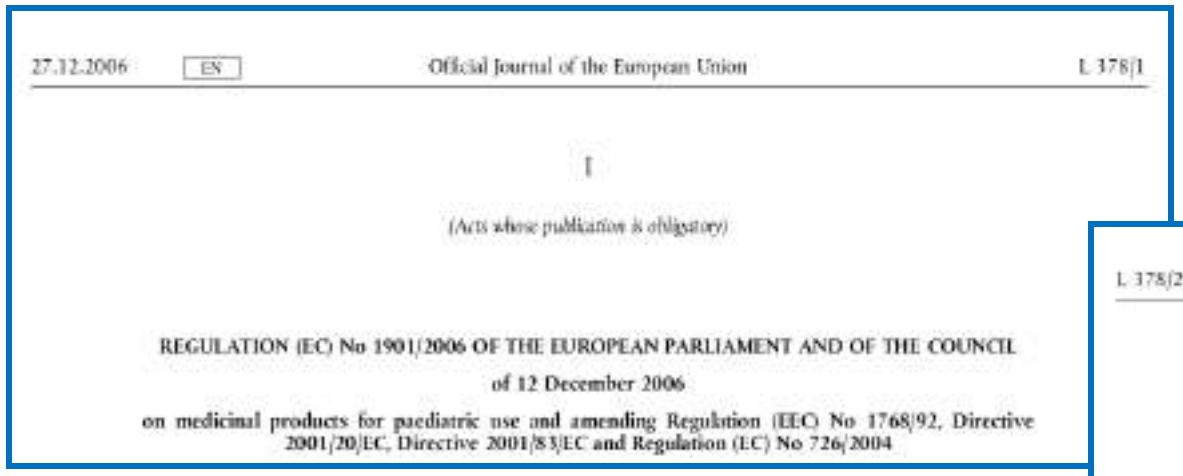
The EU Paediatric Regulation


27.12.2006 EN Official Journal of the European Union L 378/1

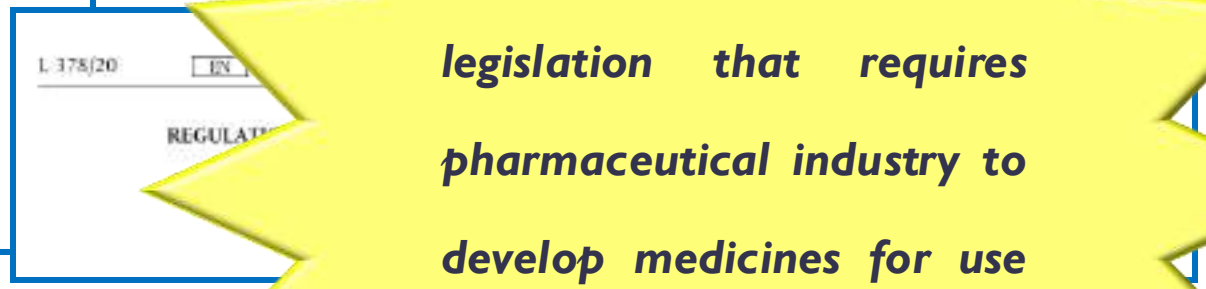
I

(Acts whose publication is obligatory)

REGULATION (EC) No 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 12 December 2006

on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004


L 378/20 EN

REGULA

The 1st piece of EU legislation that requires pharmaceutical industry to develop medicines for use in a particular subset of the patient population

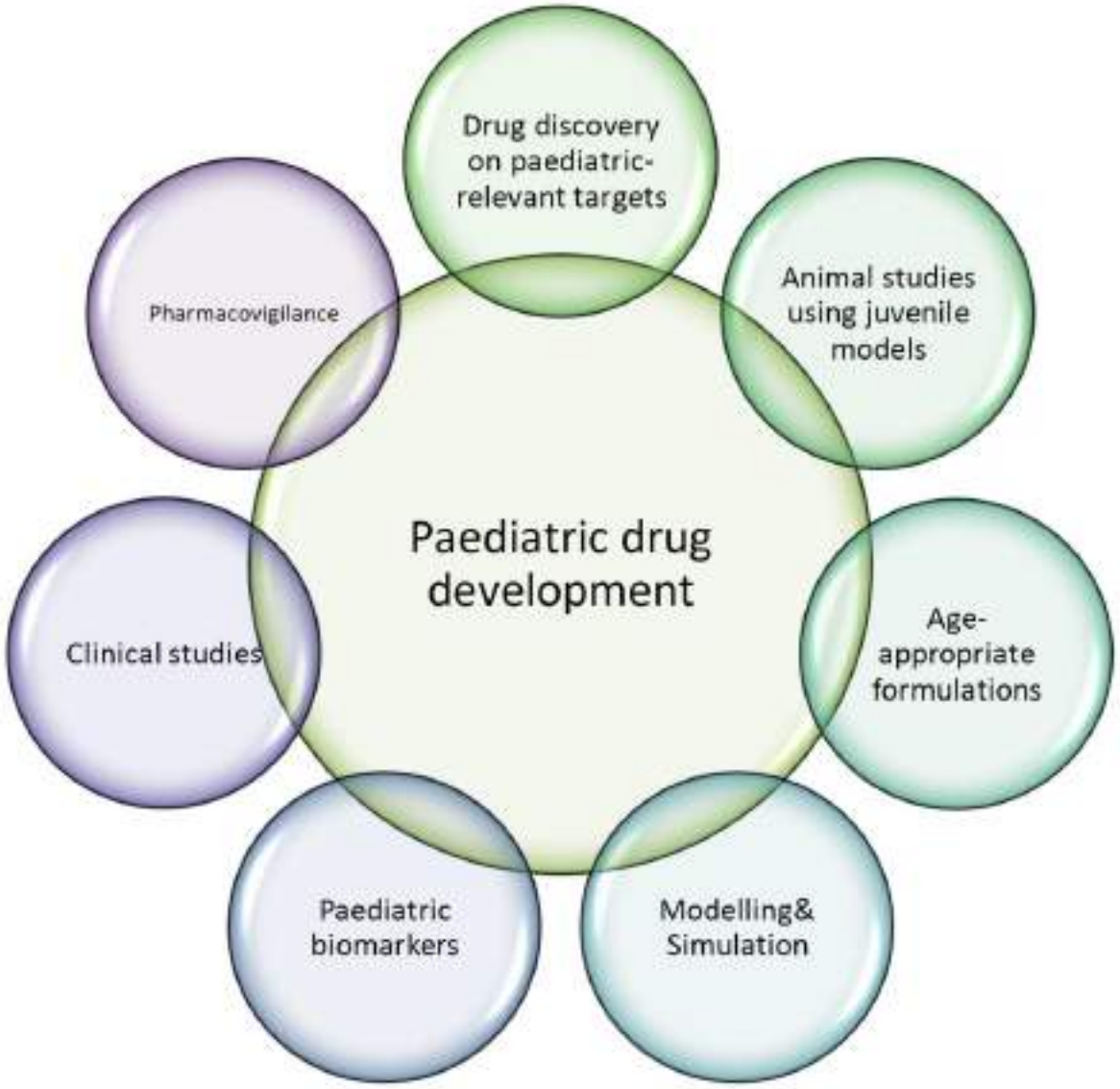
Entered into force in 2007 to facilitate R&D and ava ildren

- ensuring high quality research
- avoiding unnecessary studies
- not delaying the authorisation of medicines for adults

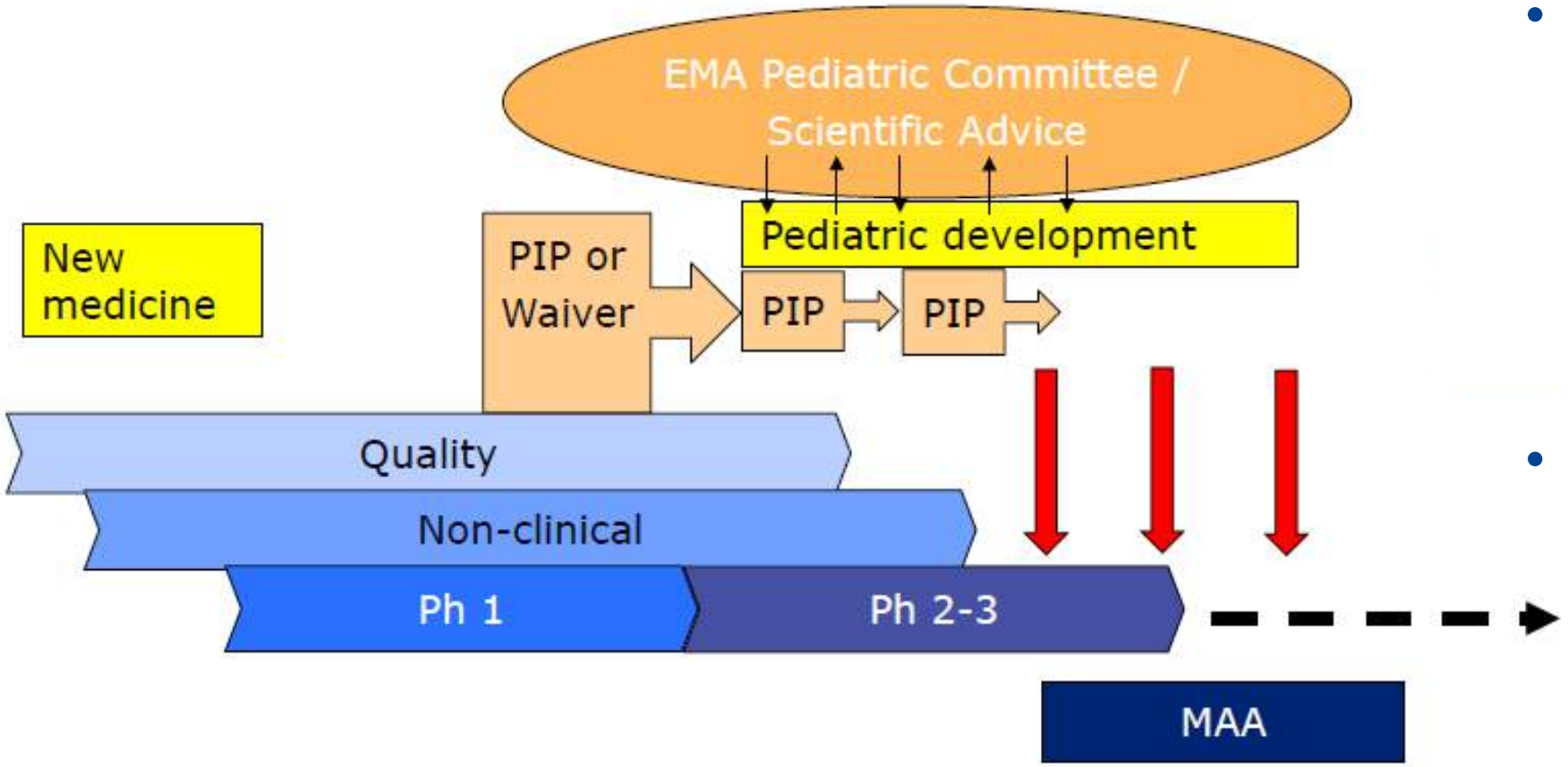
Paediatric Investigation Plan (PIP)

- **obligation to conduct the paediatric studies** in compliance with an approved PIP
- details of to demonstrate

  quality
  efficacy
  safety
  of the medicinal product for a therapeutic indication in the paediatric population



PIP within the R&D



- to be submitted **early** during product development (no later than adult phase II studies start – not after adults phase III)
- can also include **waivers** (to conduct paediatric studies) or **deferrals** (right to delay PIP completion)

Rewards and incentives

Unauthorised products

Obligation to submit results compliant with agreed PIP at the time of MAA

In-patent authorised products

Obligation to submit results compliant with agreed PIP at the time of application for new indication, route, formulation

6-month SPC* also in case of negative results

Off-patent products

Optional PIP covering paediatric indication and formulation

PUMA: 10-year data & market exclusivity

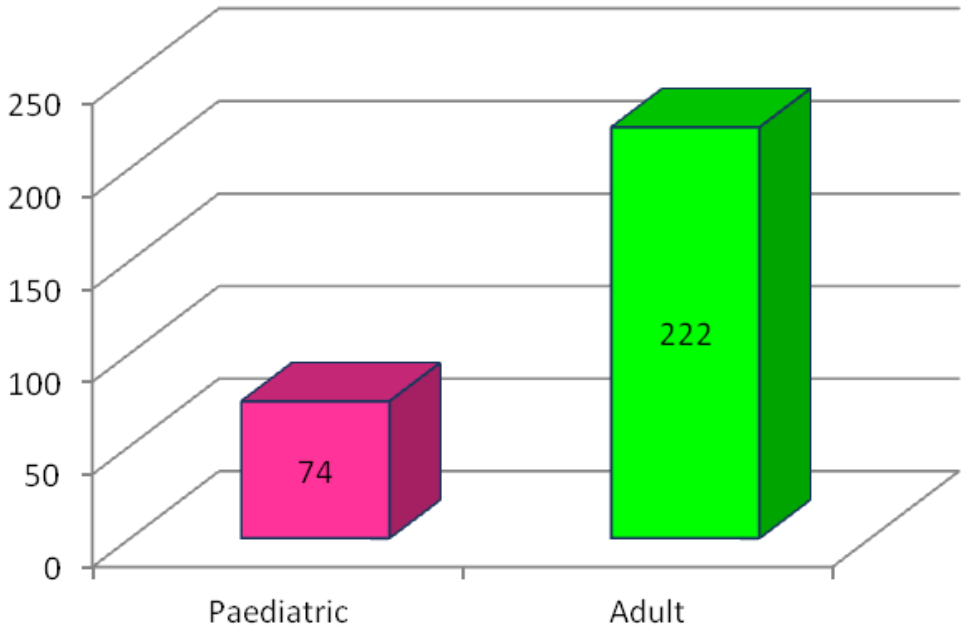
** Supplementary Protection Certificate*

Paediatric Regulation outcomes

- ⇧ paediatric medicines
- ⇧ agreed PIPs
- ⇩ paediatric trials

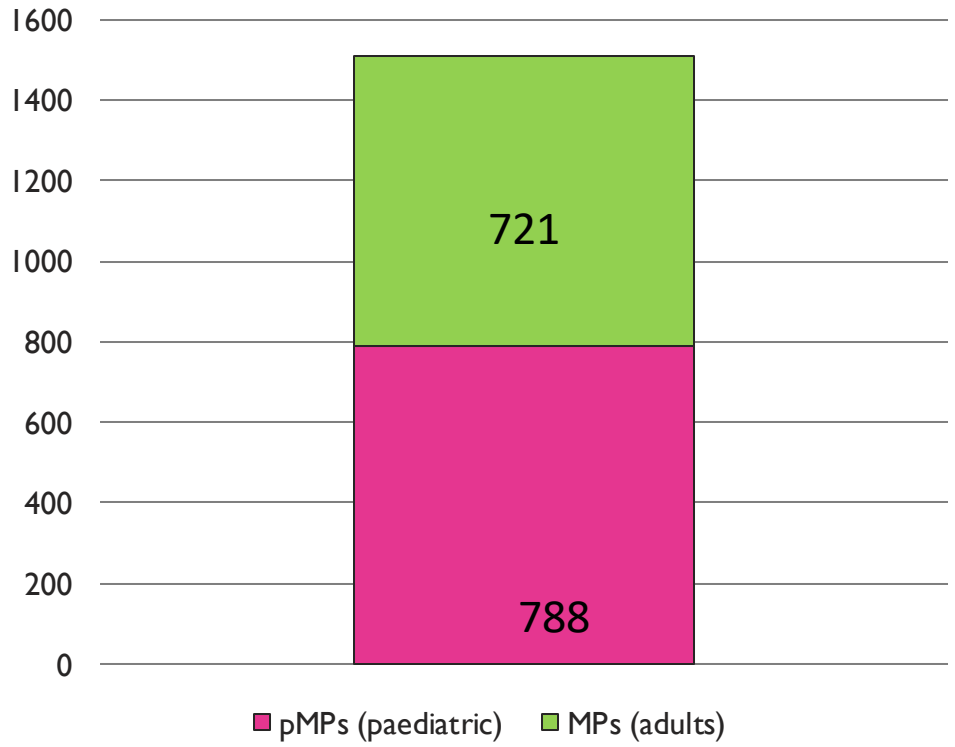
Number of authorised paediatric medicines

Centrally-approved medicines up to 2003



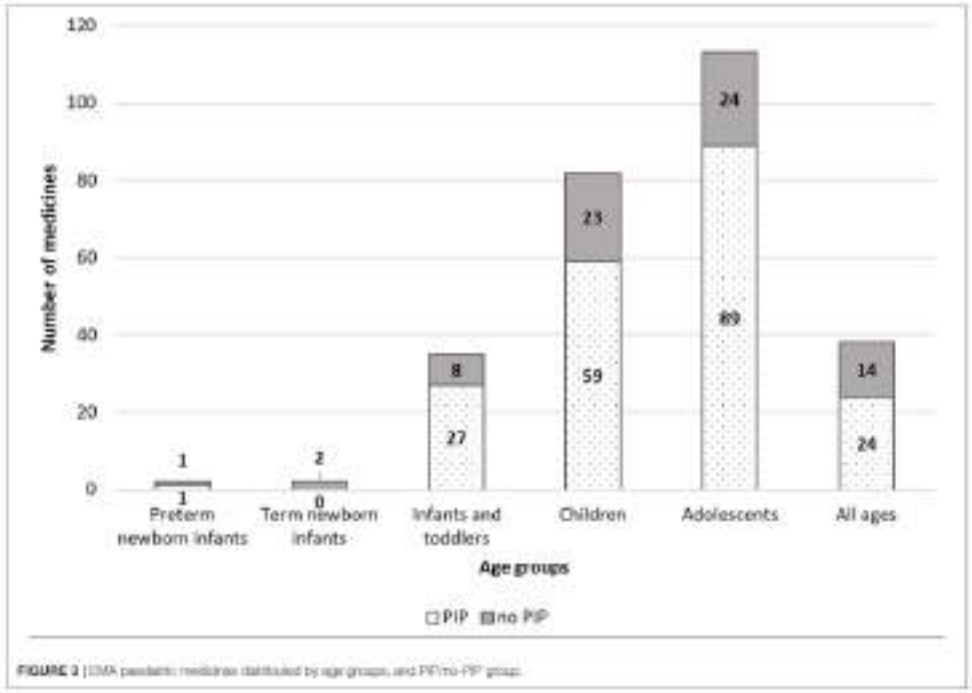
Ceci A. et al, EJCP 2006

Centrally-approved medicines up to 2025



Source: European Public Assessment Reports and TEDDY e-PMD

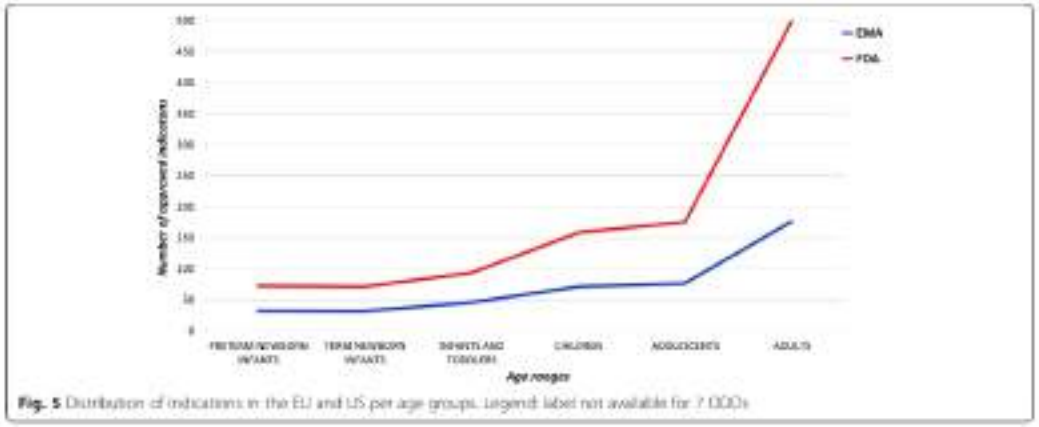
Paediatric unmet needs



Source: Toma et al, Front Med (Lausanne) 2020

- Part of unmet therapeutic needs still exists
- Many medicines not studied in children ⇨ off-label
- ~ 90% of rare diseases can begin in childhood ⇨ *'children are orphan two times'*

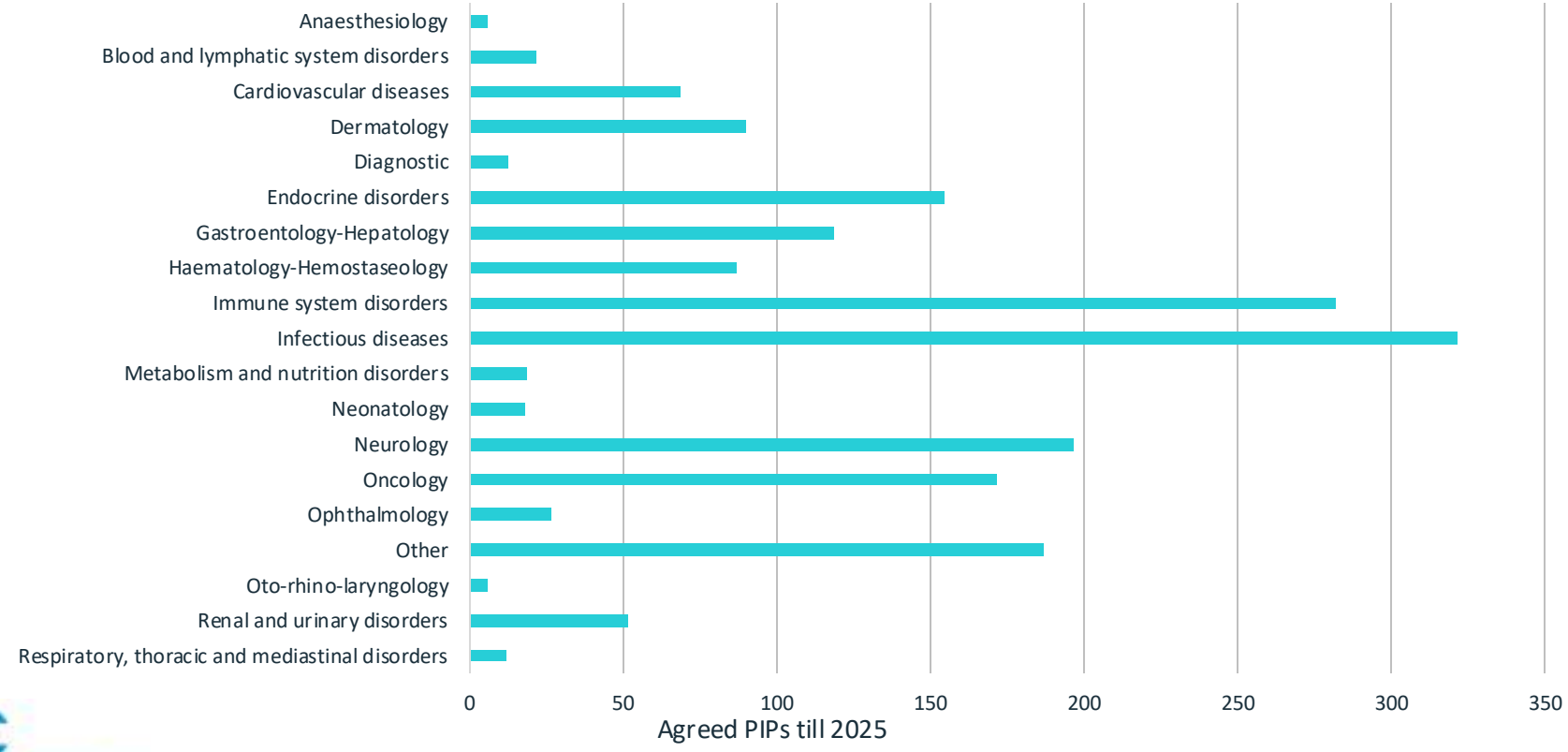
EC Joint Evaluation 2020 (SWD(2020) 163 final)



Source: Giannuzzi V et al. OJRD 2017

Number of PIPs

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	TOTAL
Full waiver granted	3	43	70	55	45	47	54	48	51	54	81	90	98	129	122	95	132	114	25	**1356**
PIPs agreed	0	22	41	116	46	45	53	58	66	84	69	65	82	130	145	203	267	293	70	**1855**



Source: EMA website

Number of PIPs and paediatric medicines

Paediatric Regulation

- PIP agreed by the PDCO
- (voluntary) PUMA

Directive 2001/83/EC

- NO PIP agreed by PDCO
- Results from pre-clinical or clinical studies to be provided

TABLE 4 | Paediatric studies characteristics.

Studies by MP	p-MPs in the PIP group (128–100%)	p-MPs in the no-PIP group (47–100%)	*p*-value*	p-OMPs in the PIP group** (41–100%)	p-OMPs in the no-PIP group** (16–100%)	*p*-value*
Study population including only children	77 (80%)	19 (40%)	0.020	24 (59%)	6 (38%)	0.153
All 3 phases studies	89 (70%)	16 (34%)	< 0.001	34 (83%)	4 (25%)	<0.001
No. of studies by approved drug	3.3	1.6	–	4.0	1.5	–

*Chi-square test; **p-OMPs have also been counted in the previous columns.

Toma M, et al, Frontiers 2021

Number of paediatric trials

In EU

- 2016: **631**/ 2880 (22% out of the total)
- 2025: **277**/ 2210 (12,5% out of the total)

Worldwide:

- 2016: **5111**/ 26471 (19%)
- 2025: **6629** / 38064 (17%)

Source: EU clinical trials register; CTIS, clinicaltrials.gov

EU research funds

- 18 agreed PIPs
- 3 PIPs completed -> 3 new PUMAs (hybrids for all paediatric ages)

Enalapril, Aqumeldi®

Paediatric formulation: orodispersible tablets

Hydrocortisone, Alkindi®

Paediatric formulation: granules

Dopamine, Neoatricon®

Paediatric formulation: new IV solution

Project	Active Substance(S)	Addressed paediatric indication(s)	Therapeutic area
TINN	Ciprofloxacin* / Fluconazole	treatment of infections in preterm and term newborns	
TINN2	Azithromycin	treatment of infections in preterm and term newborns	
NeoMero	Mer	treatment of late-onset sepsis in neonates and infants aged	
NeoVanc	Van		
NeoOpioid	Mo / Fe		
GAPP	Gabapentin	treatment of chronic pain	
Loulla & Philla	Methotrexate* / 6-Mercaptopurine*	treatment of Acute Lymphoblasti ia	Malignant neoplasms
03K	Cyclophosphamide / Temozolomide	treatment of paediatric cies	
EPOC	Doxorubicin*	treatment of childhood cancer	
HIP trial	Dopamine	management of hypotension in preterm newborns	Cardiology
NeoCirc	Dobutamine	treatment of systemic hypotension in infants	
LENA	Enalapril	cardiac failure in children	
NEMO	Bumetanide	treatment of neonatal seizures in babies with hypoxic ischemic encephalopathy	Neurology
KIEKIDS	Ethosuximide	treatment of absence and myoclonic epilepsy	
TAIN	Hydrocortisone*	treatment of adrenal insufficiency in neonates and infants	Endocrinology
METEIZZ	Metformin	treatment of polycystic ovary syndrome	
CloSed	Clonidine*	Sedation in intensive care	Intensive care/anaesthesiology
DEEP	Deferiprone*	treatment of chronic iron overload	Haematology
PERS	Risperidone	treatment of conduct disorder treatment of schizophrenia	Child & adolescent psychiatry
NEuroSIS	Budesonide*	prevention of bronchopulmonary dysplasia	Respiratory and cardiovascular disorders

* received an Orphan Drug designation (four in the same indication addressed by the project)

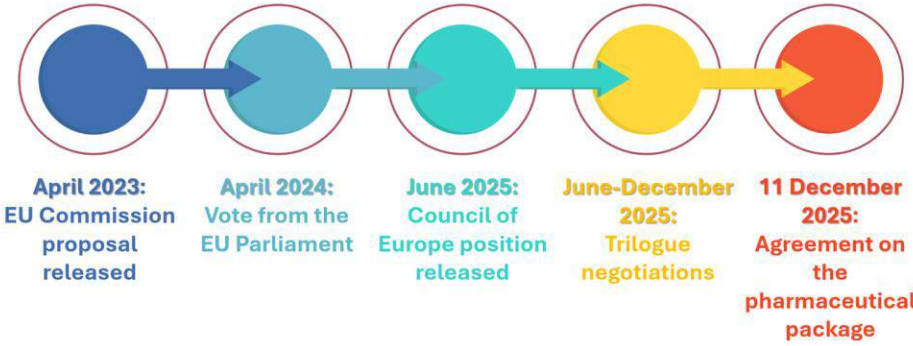
Ruggieri, Torretta et al., Front. Med. 2025

Current revision of the Regulation

What didn’t work?

- Paediatric unmet needs still relevant in certain areas e.g. paediatric-only diseases, neonates
- Administrative burden / complexity of the PIP procedure
- Delayed conduct of paediatric studies
- Interaction between PDCO and other EMA committees/working parties/groups
- Unattractive PUMA

Revision of Paediatric Regulation as part of the EU Pharma legislation revision



Timeline

December 2025
Political agreement on new pharmaceutical legislation

2026
Adopted acts of the new pharmaceutical legislation enter into force

2026-2028
Transition phase
-EU Member States update their national laws to reflect the new rules
-European Commission adopts implementing and delegated acts to help implement the new rules
-EMA and national competent authorities develop implementation guidance and adapt their procedures and IT systems

2028
New pharmaceutical legislation becomes applicable

The EU pharmaceutical system is undergoing major reform through a new Regulation and Directive redefining the authorisation of medicines

Source: EMA website

Upcoming rules

Reg (EC) 726/2004

Reg (EC) 141/2000

Reg (EC) 1901/2006

Dir. 2001/83/EC

Regulation

Directive

Council of the European Union

Brussels, 24 February 2026

Interinstitutional File: 2023/0131 (COD)

LIMITE

SAN 90
PHARM 14
MI 137
COMPET 169
VETER 21
ENV 130
RECH 68
CODEC 238
PI 21

NOTE

From:	General Secretariat of the Council
To:	Permanent Representatives Committee
Subject:	Regulation laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency - Analysis of the final compromise text with a view to agreement

Delegations will find in Annex the final compromise text of the Regulation laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency.

Council of the European Union

Brussels, 24 February 2026

Interinstitutional File: 2023/0132 (COD)

LIMITE

SAN 91
PHARM 15
MI 138
COMPET 186
ENV 131
PI 22
CODEC 237
IA 32
UK 21

NOTE

From:	General Secretariat of the Council
To:	Permanent Representatives Committee
Subject:	Directive on the Union code relating to medicinal products for human use - Analysis of the final compromise text with a view to agreement

Delegations will find in Annex the final compromise text of the Directive on the Union code relating to medicinal products for human use.

+ annexes

Upcoming rules

Reg (EC) 1901/2006

Regulation

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+ annexes

ANNEX VIII

CORRELATION TABLE *[TO BE UPDATED]*

Directive 2001/83 (EC)	Regulation (EC) No 1901/2006	This Directive
Art. 2(1)		Art. 1(1) and (2)
Art. 2(2)		Art. 1(4)
Art. 2(3)		Art. 1(3) and 142(1), second sentence
Art. 3(1), (2) and (3)		Art. 1(5), point (a), (b) and (c)

Paediatric Regulation to be repealed

ePTRI

THE CHILDREN'S

Modifications to Paediatric Regulation

- To simplify procedures
- To remove inconsistencies between opinions

COVINGTON

a working party with scientific expertise on paediatric medicinal products

CoE final compromise text of the Regulation

Modifications to Paediatric Regulation

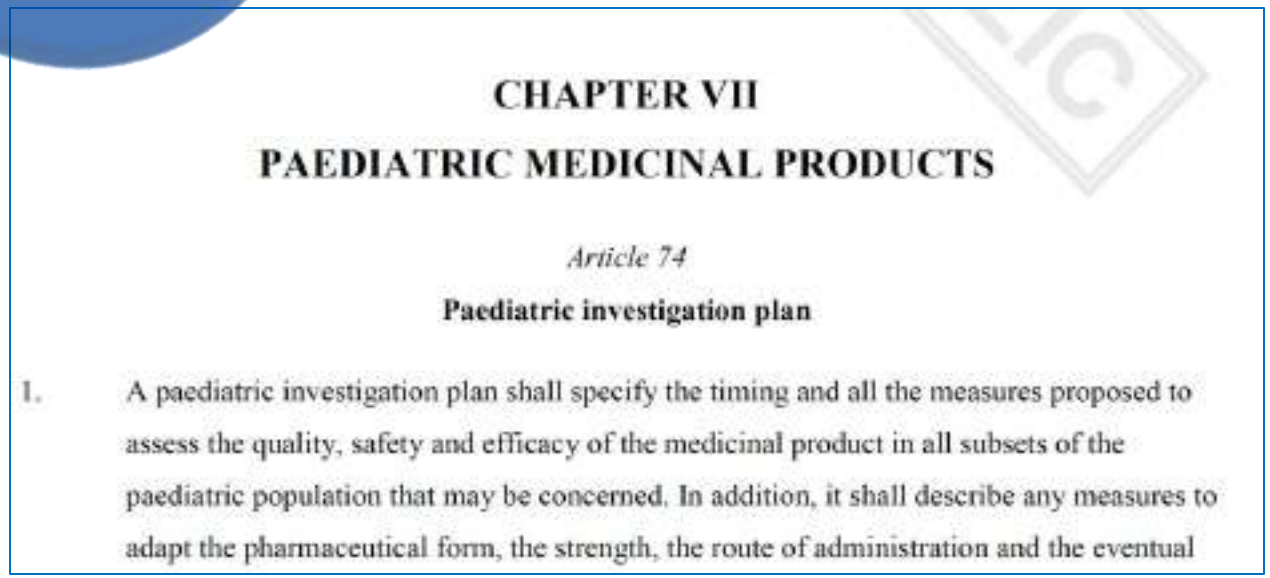
- Experts from national competent authorities (NCAs) -> *broadest possible geographical distribution*
- Minimum number of experts from NCAs -> *prioritised over external experts in a specific expertise area*
- Representatives of patients, healthcare professionals and academia as possible members
- NCAs not represented allowed attending meetings as observers
- Documents discussed accessible to all NCAs

a working party with scientific expertise on paediatric medicinal products

CoE final compromise text of the Regulation

Modifications to Paediatric Regulation

Regulation



CHAPTER VII

PAEDIATRIC MEDICINAL PRODUCTS

Article 74

Paediatric investigation plan

1. A paediatric investigation plan shall specify the timing and all the measures proposed to assess the quality, safety and efficacy of the medicinal product in all subsets of the paediatric population that may be concerned. In addition, it shall describe any measures to adapt the pharmaceutical form, the strength, the route of administration and the eventual

CoE final compromise text of the Regulation

- PIPs
- Waivers
- Validation
- Agreement
- Deferrals
- Modifications
- Compliance
- Decisions
- Discontinuation
- Scientific Advice
- Data from PIPs
- MA variations
- PUMA
- Paediatric trials information
- EU network
- Incentives
- Fees waivers
- Yearly reporting

Modifications to Paediatric Regulation

- Definitions

(37) 'paediatric investigation plan' means a research and development programme aimed at ensuring that the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population;

(38) 'paediatric population' means that part of the population aged between birth and ***under*** 18 years;

SECTION 7

SPECIFIC REQUIREMENTS FOR PAEDIATRIC MEDICINAL PRODUCTS

Article 48

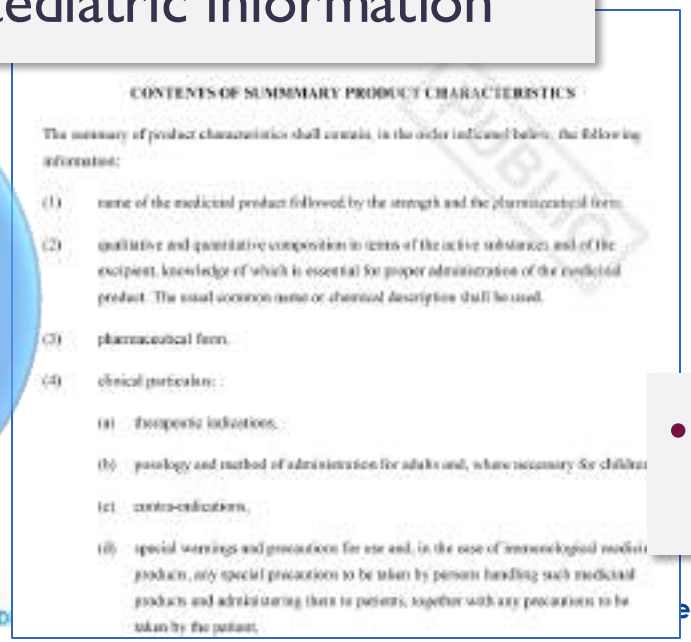
Compliance with the p

1. The competent authority of the Membc … ng authorisation or variation of a marketir … isions of this Chapter or of the Chapter VIII, sha … rements laid down in Article 6(5).

- PIP compliance
- Data from PIPs

in MSs

- Paediatric information



CONTENTS OF SUMMARY PRODUCT CHARACTERISTICS

The summary of product characteristics shall contain, in the order indicated below, the following information:

(1) name of the medicinal product followed by the strength and the pharmaceutical form;

(2) qualitative and quantitative composition in terms of the active substances and of the excipient, knowledge of which is essential for proper administration of the medicinal product. The usual common name or chemical description shall be used;

(3) pharmaceutical form;

(4) clinical particulars:

(a) therapeutic indications;

(b) posology and method of administration for adults and, where necessary for children;

(c) contra-indications;

(d) special warnings and precautions for use and, in the case of immunological medicinal products, any special precautions to be taken by persons handling such medicinal products and administering them to patients, together with any precautions to be taken by the patient;

Directive

NEW

Chapter VII

Regulatory protection, unmet medical needs and rewa… for paediatric medicinal products

- Rewards (+ 6month SPC or +1 year market protection for new indications bringing significant benefit)

CoE final compromise text of the Directive

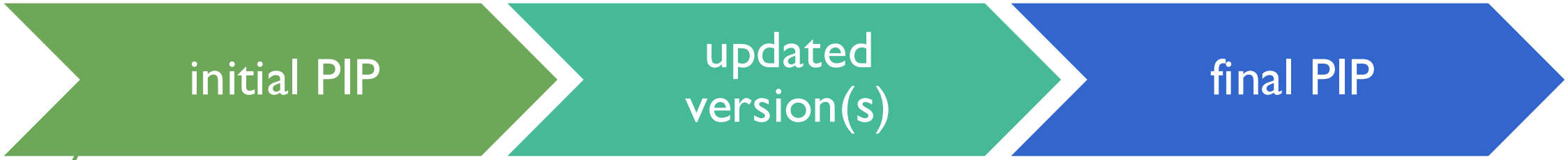
Modifications to PIP procedure

LENGTH OF DEFERRAL	capped to 5 years (prolonged in 'justified cases')
ASSESSMENT	EMA + CHMP consultation (+ WPs)
TIMELINES	~~60+60~~ ⇨ 90+90 days (70+70 for initial PIPs)
'INITIAL' PIP	only known details and timing of measures

Initial PIP

Criteria

- **active substance not yet authorised** in any medicine in EU and intended to diagnose/prevent/treat a **novel or** an **existing paediatric condition via a new mechanism of action**; or
- following acceptance by EMA of a duly justified request



- only details and timing of measures proposed to assess quality, safety and efficacy in all paediatric subsets concerned, **known** at the time of application
- precise timing of when updated versions and final PIP are expected to be submitted to EMA on the basis of scientifically justified reasons

New obligations and measures

- EMA may impose a **PIP based on the Mechanism of Action** (MoA) of the drug (action directed at a specific molecular target or biological pathway) relevant for a different disease in children **in the same therapeutic area**

- **PUMA** incentive: ~~**10 year ME**~~ ⇨ **same market protection of the other repurposed products** for off-patent paediatric products

New obligations and measures

- **Free of charge SA** also for in utero treatments

- Possible **temporary waiver** during **public health emergencies**

- A **dedicated section on medicines authorised in paediatrics** foreseen within the public EMA database of medicines

CoE final compromise text of the Regulation

Modifications to Paediatric Regulation

EMA shall develop a EU network of patient representatives, academics, medicines developers, investigators and centres with expertise in paediatric studies

- **to discuss priorities in clinical development of medicines for children, in particular in areas of unmet needs**
- **to coordinate studies relating to paediatric medicines**
- to build up the necessary scientific and administrative competences at EU level
- to avoid unnecessary duplication of paediatric studies

Enpr-EMA NETWORK

network of research networks, investigators and centres with expertise in paediatric studies

- sharing good practices
- promoting research into medicines for children
- building necessary competences at EU level
- dialoguing with ethics committees
- avoiding unnecessary duplication of studies

CoE final compromise text of the Regulation

Modifications impacting to paediatric medicines

Modifications impacting to paediatric medicines

PRODUCTS ADDRESSING 'UNMET MEDICAL NEEDS'

- Life threatening or severely debilitating disease AND
  - No medicinal product authorised in EU OR
  - Clinically relevant improvement of efficacy or safety

Nothing paediatric-specific….

~~*Lists of paediatric unmet needs*~~

CoE final compromise text of the Directive (art. 83)

Modifications impacting to paediatric medicines

REPURPOSING TO COVER UNMET NEEDS

- ☺ Not-for-profit entities may submit non-clinical or clinical evidence for a new therapeutic indication for unmet needs
- ☺ MAH can submit additional evidence
- ☺ Opinion favourable ⇨ MAH shall submit a variation to update the product information with the new therapeutic indication

A DEDICATED ARTICLE IN THE REGULATION!

CoE final compromise text of the Regulation, art 48

Other proposals: repurposing


frontiers | Frontiers in Medicine

TYPE: Perspective
PUBLISHED: 16 September 2024
DOI: 10.3389/fmed.2024.1456247

Check for updates

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Paediatric formulations—part of the repurposing concept?

Siri Wang[1]* and Viviana Giannuzzi[2]

[1]Norwegian Medical Products Agency, Oslo, Norway, [2]Fondazione per la Ricerca Farmacologica Gianni Benzi onlus, Research Department, Valenzano, Italy

- Paediatric- appropriate formulations are still lacking
- No definition/term currently stated by EU law…and still lacking in the proposed revision of legislation!

In our opinion, an age-appropriate formulation, targeting a relevant off-label use in children, even for a disease or condition already authorised in adults or older children, would qualify as 'reformulation' within the repurposing term

POSITION PAPER

The repeal of the EU Paediatric Regulation has raised concerns about possible impact on R&D and availability of paediatric medicines

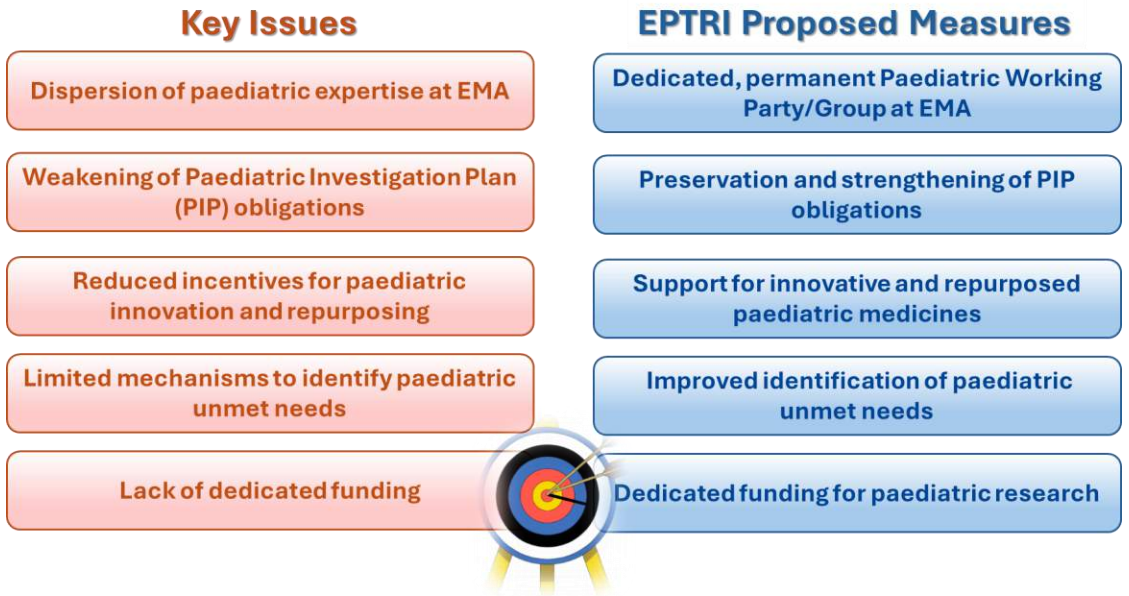

Figure 2. Key issues identified in the EU pharmaceutical reform and EPTRI proposed measures in 2023

Robust, mandatory paediatric regulatory pathways are essential to protect children's health.

Paediatric medicines call for dedicated expertise, strong obligations, and sustained investment, while the EU pharmaceutical legislation reform risks to leave children care behind

THE CHILDREN'S MEMORIAL HEALTH INSTITUTE

Wrap up & conclusions

Commitment to ensure robust, mandatory paediatric regulatory pathways and prioritisation of paediatric needs in the new EU legislation

Key players in regulatory and public health

- European Platform for Regulatory Science Research
- paediatric networks
- patient's organisations

Special thanks to
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Lucia Ruggieri
Maria Luisa Dalessandro

Viviana Giannuzzi

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PER LA RICERCA FARMACOLOGICA
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