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EUROPEAN PAEDIATRIC TRANSLATIONAL RESEARCH INFRASTRUCTURE

THE ETHICS AND REGULATORY SERVICE

Viviana Giannuzzi

EPTRI General Assembly– Bari –18 July 2024

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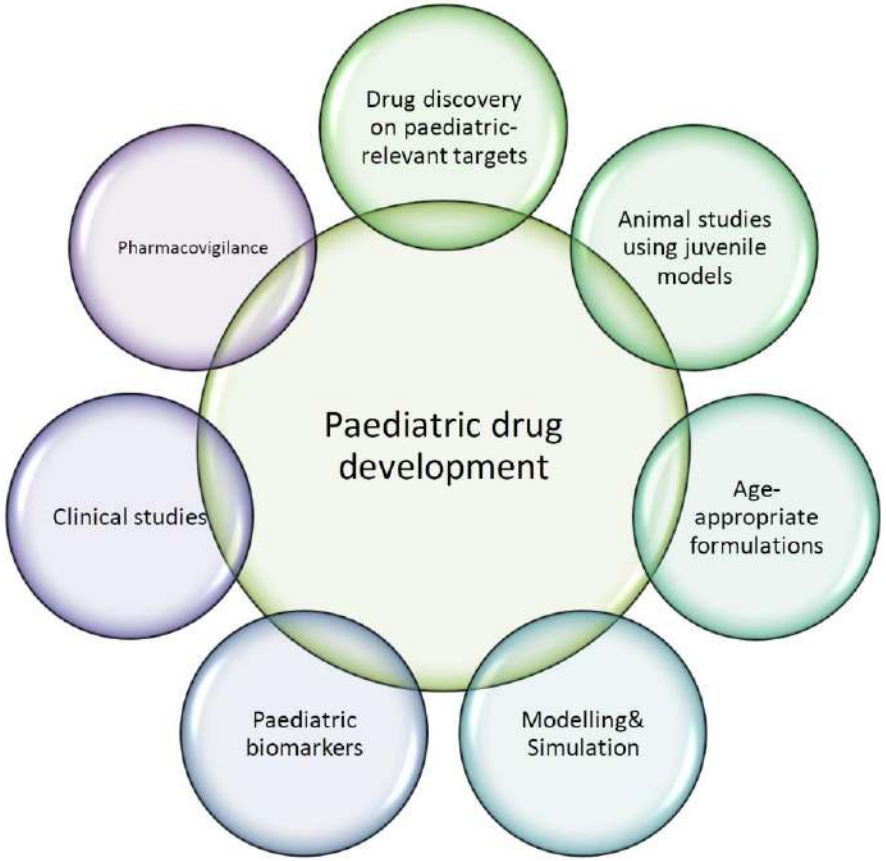
No financial disclosure to declare

Developing medicines for children



- Part of the population aged between birth and 18 years
- Subjects under the age of legal competence to give informed consent (according to the national law)

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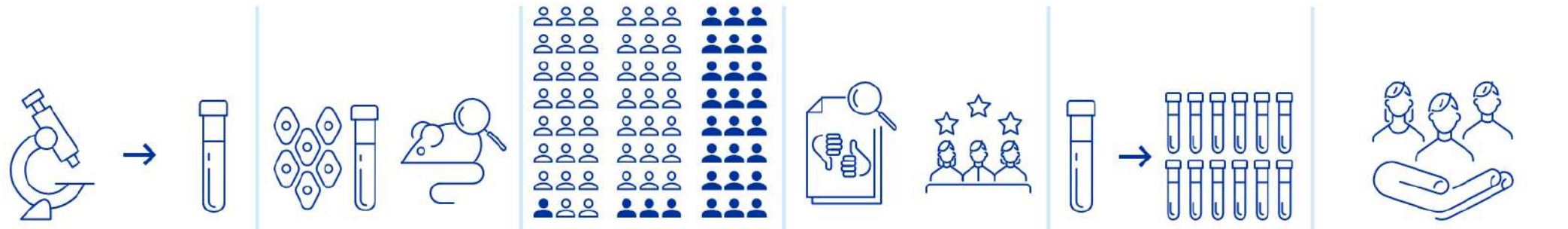
Developing medicines



small scale studies	in vitro	in vivo	I	II	III	EMA	EC	scale up production	safety studies
Pharmaceutical quality	**Non-clinical**		**Clinical trials**			**Evaluation & decision**		**Commercial manufacturing**	**Safety monitoring**

- **QUALITY**
- **SAFETY**
- **EFFICACY**

marketing authorisation
(centralised/non-centralised procedures*)

Academia more and more involved in R&D

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Source: EMA website

Rules to comply with: the same as adults

International Ethical Guidelines for Health-related Research Involving Humans

REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 5 April 2017
on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU
(Text with EEA relevance)

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 5 April 2017
on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC
(Text with EEA relevance)

COUNCIL OF EUROPE — Committee of Ministers

Recommendation CM/Rec(2016)6
of the Committee of Ministers to member States
on research on biological materials of human origin

ADDITIONAL PROTOCOL
TO THE CONVENTION
ON HUMAN RIGHTS
AND BIOMEDICINE,
CONCERNING BIOMEDICAL RESEARCH

Council of Europe Treaty Series - No. 195

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25.11.2014 EN Official Journal of the European Union L 337/1

II
(Non-legislative acts)

REGULATIONS

COMMISSION DELEGATED REGULATION (EU) No 1252/2014
of 28 May 2014
supplementing Directive 2001/83/EC of the European Parliament and of the Council with regard to principles and guidelines of good manufacturing practice for active substances for medicinal products for human use
(Text with EEA relevance)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 July 2021
EMA/CHMP/QWP/BWP/259165/2019
Committee for Medicinal Products for Human Use (CHMP)

Guideline on quality documentation for medicinal products when used with a medical device

(Legislative acts)

REGULATIONS

REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 16 April 2014
on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC
(Text with EEA relevance)

1 December 2016
EMA/CHMP/ICH/135/1995
Committee for Human Medicinal Products

Guideline for good clinical practice E6(R2)
Step 5

L 119/1

(Legislative acts)

REGULATIONS

REGULATION (EU) 2016/679 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 27 April 2016
on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)

2001L0083 — EN — 30.12.2008 — 006.001 — 1

This document is meant purely as a documentation tool and the institutions do not assume any liability for its contents

▶B DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 6 November 2001
on the Community code relating to medicinal products for human use
(OJ L 311, 28.11.2001, p. 67)

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Rules to comply with: the same as adults *+ further more*


European Medicines Agency

London, 24 January 2008
Doc. Ref. EMEA/CHMP/SWP/169215/2005

COMMITTEE FOR HUMAN MEDICINAL PRODUCTS (CHMP)

GUIDELINE ON THE NEED FOR NON-CLINICAL TESTING IN JUVENILE

Non-clinical studies


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 September 2017
EMA/CPMP/ICH/2711/
Committee for Human

ICH E11(R1)
medicinal pr
Step 5

INTERNATIONAL COUNCIL ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

ADDENDUM TO ICH E11: CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION

E11 (R1)

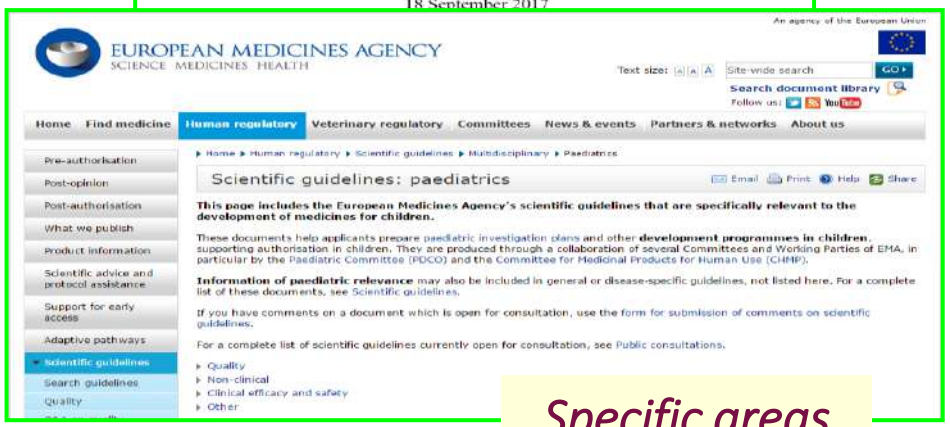
Clinical trials


Ethical considerations for clinical trials on medicinal products conducted with minors

Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use

18 September 2017

Ethical Recommendations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SCIENCE MEDICINES HEALTH

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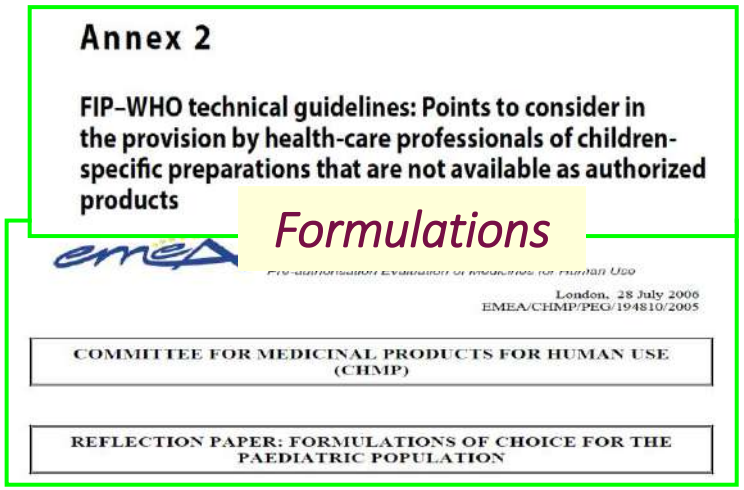
Scientific guidelines: paediatrics

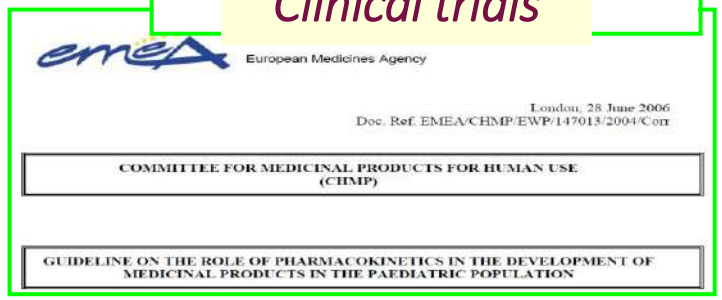
This page includes the European Medicines Agency's scientific guidelines that are specifically relevant to the development of medicines for children.

Specific areas


Annex 2

FIP–WHO technical guidelines: Points to consider in the provision by health-care professionals of children-specific preparations that are not available as authorized products

Formulations


European Medicines Agency

London, 28 June 2006
Doc. Ref. EMEA/CHMP/EWP/147013/2004/Corr

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE ROLE OF PHARMACOKINETICS IN THE DEVELOPMENT OF MEDICINAL PRODUCTS IN THE PAEDIATRIC POPULATION

London, 28 July 2006
EMEA/CHMP/PEG/194810/2005

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

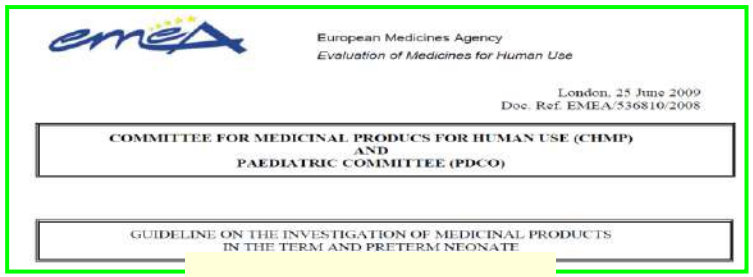
REFLECTION PAPER: FORMULATIONS OF CHOICE FOR THE PAEDIATRIC POPULATION


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 August 2013
EMA/CHMP/QWP/805880/2012 Rev. 2
Committee for Medicinal Products for Human Use (CHMP)
Paediatric Committee (PDCO)

Guideline on pharmaceutical development of medicines for paediatric use

Pharmaceutical development


European Medicines Agency
Evaluation of Medicines for Human Use

London, 25 June 2009
Doc. Ref. EMEA/536810/2008

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)
AND
PAEDIATRIC COMMITTEE (PDCO)

GUIDELINE ON THE INVESTIGATION OF MEDICINAL PRODUCTS IN THE TERM AND PRETERM NEONATE

Neonates

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Ethics issues in biomedical research

1. Human embryos & foetuses
2. Human beings
3. Human cells or tissues
4. Personal data
5. Animals
6. Non-EU countries
7. Environment, health & safety
8. Artificial Intelligence
9. Other ethics issues

Paediatric ethical requirements to be fulfilled

- Involvement of minors in the informed consent process according their age and mental maturity
- Separate documents for adults and children
- Assent & agreement
- Trials with female adolescents - *information and inclusion with the use of contraception*
- Insurance contracts not limiting the liability period to consider long-term effects


Ethical considerations for clinical trials on medicinal products conducted with minors

Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use

Revision 1

18 September 2017

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How EPTRI can provide ethics and regulatory support?

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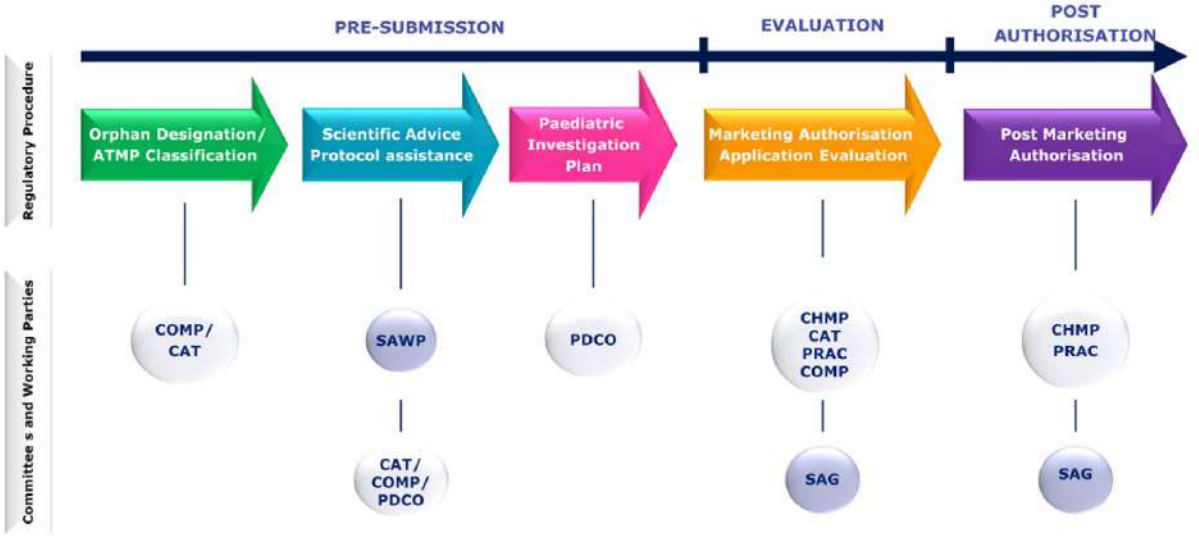
1. EMA regulatory procedures for medicines of paediatric interest

Preparation of

- Paediatric Investigational Plan
- Orphan Designation
- Scientific Advice/Protocol Assistance including the Qualification procedure
- other EMA voluntary procedures
- Paediatric Marketing Authorisation Application



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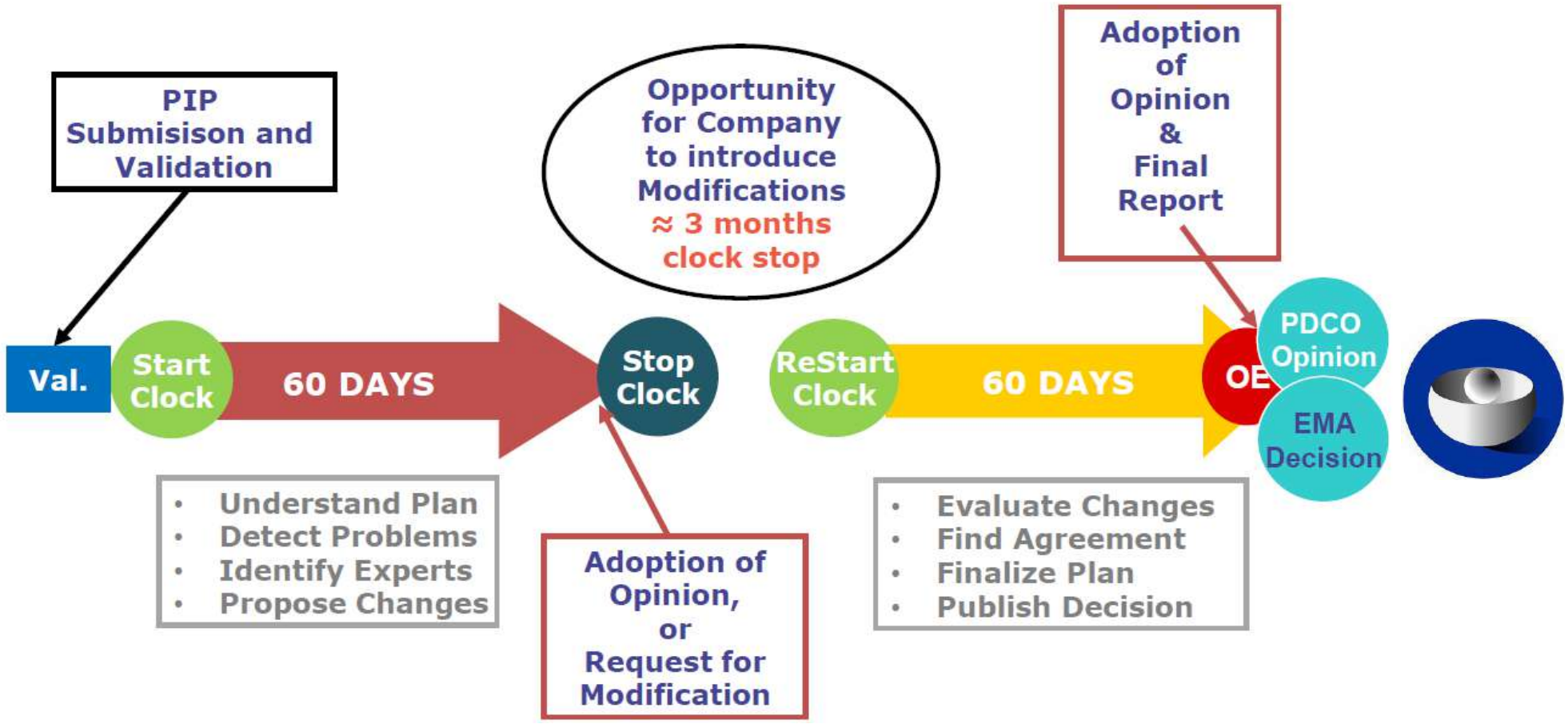
Source EMA website

Paediatric Investigation Plans (PIPs)

studies and analyses providing evidence on the use of medicines in all paediatric ages



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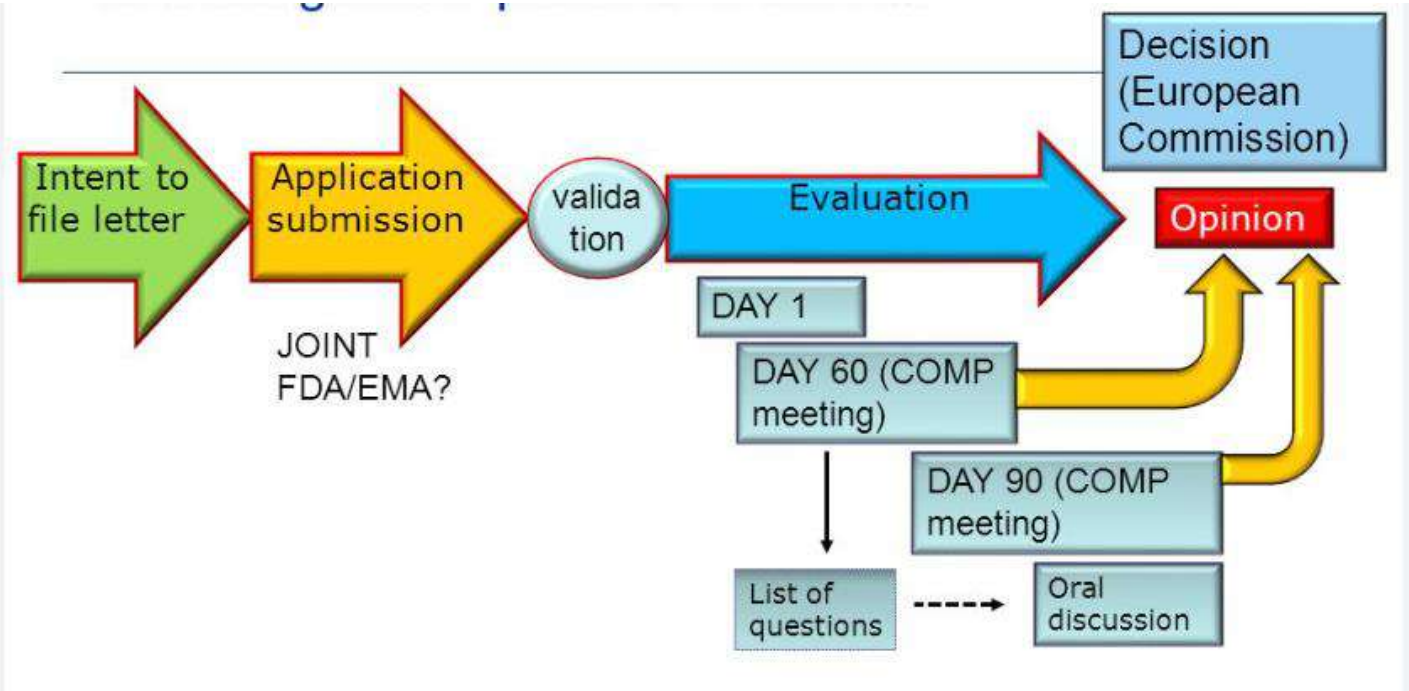
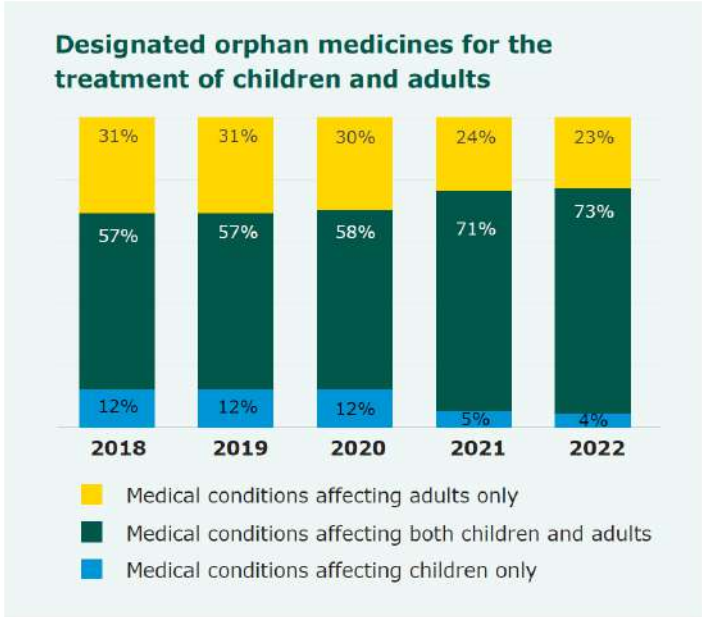
Orphan Designations





EMA Annual Report 2022

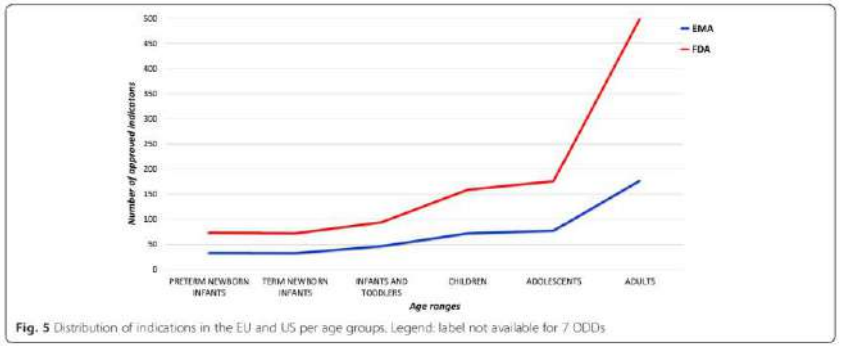


Fig. 5 Distribution of indications in the EU and US per age groups. Legend: label not available for 7 ODDs

Giannuzzi V et al. OJRD 2017

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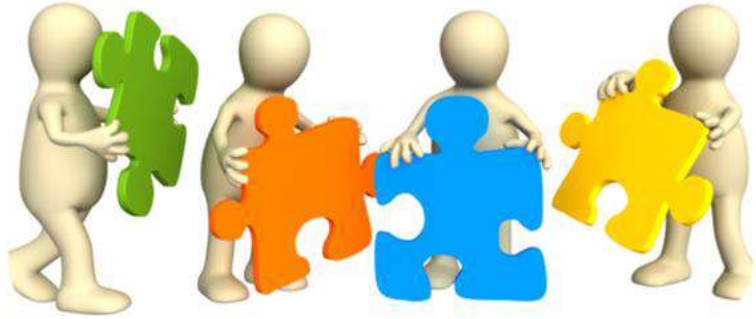
Scientific Advice/Protocol Assistance

- Guidance on the best methods and study designs (clinical aspects, methodological issues)
- Responding to specific questions
- For orphan medicines ⇨ protocol assistance

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10 November 2014
EMA/CHMP/SAWP/72894/2008
Revision 1: January 2012[1]
Revision 2: January 2014[2]
Revision 3: November 2014[3]
Revision 4: October 2020[4]
Scientific Advice Working Party of CHMP

Qualification of novel methodologies for drug development: guidance to applicants

- Acceptability of specific use of proposed innovative methods/tools not yet integrated in medicines R&D and clinical management, based on assessment of submitted data

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EMA website

Lots of things to do…

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 28 March 2024
DOI 10.3389/fmed.2024.1369547

OPEN ACCESS

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RECEIVED 12 January 2024
ACCEPTED 13 March 2024

Innovative research methodologies in the EU regulatory framework: an analysis of EMA qualification procedures from a pediatric perspective

Viviana Giannuzzi[1*], Arianna Bertolani[2,3], Silvia Torretta[3], Giorgio Reggiardo[2], Eleonora Toich[2], Donato Bonifazi[2,3] and Adriana Ceci[1,3] on behalf of the European Paediatric Translational Research Infrastructure (EPTRI)

Paediatric interest

Disease or medicinal product addressed in a PIP

Methodology already applied/used in paediatric studies *(clinicaltrials.gov, literature)*

<u>70%</u> qualified methodologies (19/27) potentially of interest for paediatric patients

<u>Only 6</u> (22%) had paediatric data in the submission dossier

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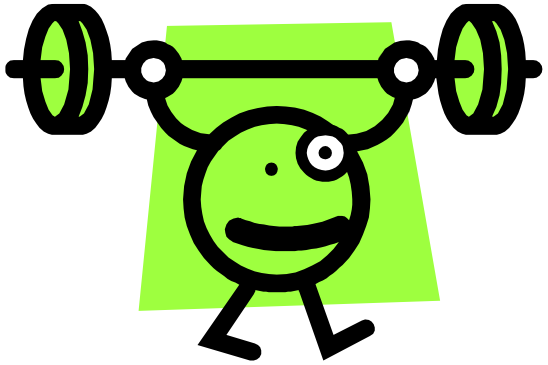
EMA applications for innovative medicines & unmet needs

- **Innovation Task Force (ITF) briefing meetings:** early dialogue with applicants (SMEs, academics, researchers) on innovative aspects in medicines development ⇨ informal exchange of information and guidance
- **PRIME**: priority medicines designation for early and proactive support to SMEs and academia to develop medicines targeting conditions with unmet medical needs



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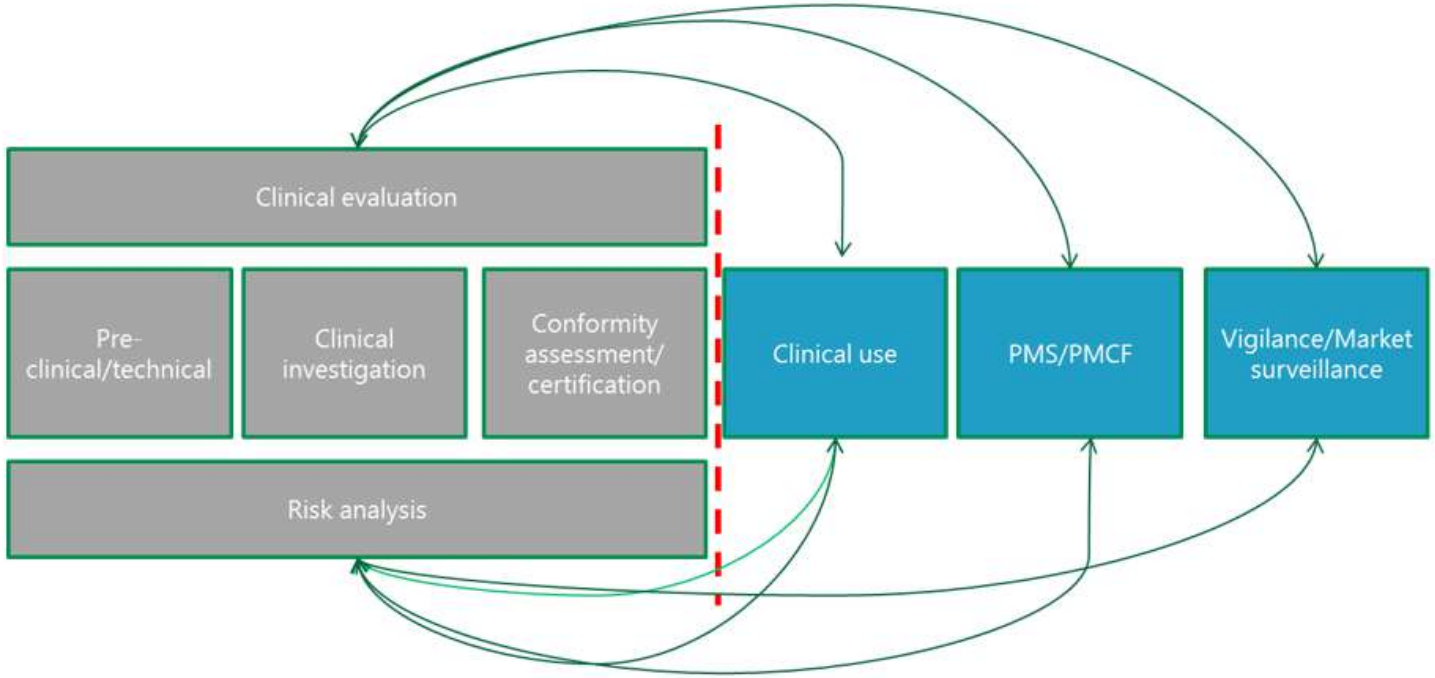
2. Advice on regulatory procedures for medical devices of paediatric interest

Preparation and submission of documents for

- clinical study
- CE mark
- medical devices classification
- MA

applications



Source: Training of members of Commission's expert panels on medical devices and in vitro diagnostic devices (EXPAMED), 2020

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3. Support for the implementation of ethical requirements

- Ethics revision of paediatric clinical study protocols
- Preparation of documents for informed consent and assent
- Advice on the implementation of GDPR provisions

- implement the proper ethical requirements to perform paediatric research
- compliant with EU internationally-agreed provisions

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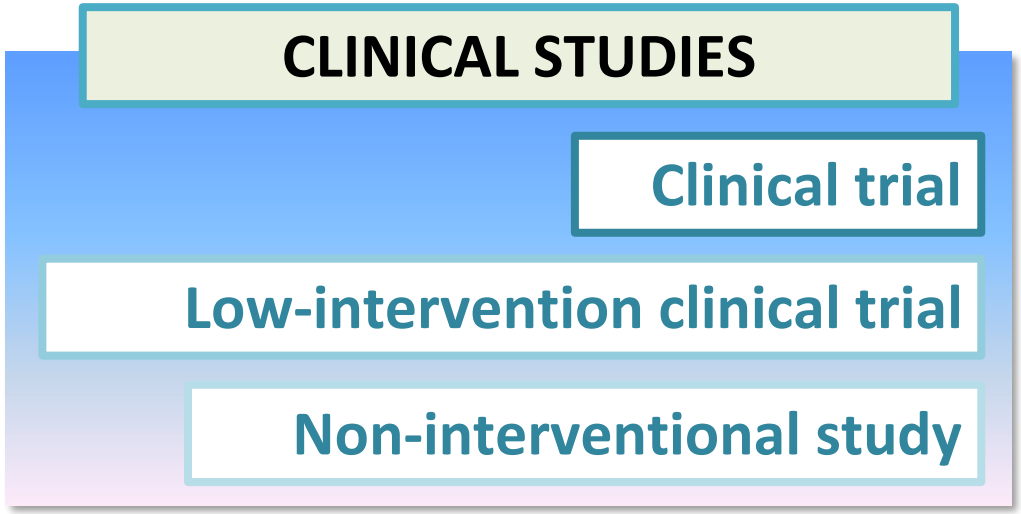
Preparing paediatric study protocol

- Non-clinical and clinical data supporting a paediatric use
- Design feasibility
- Use of placebo under stricter conditions
- Balance of expected benefit versus risks
- Evidence of direct benefit for child/group
- Age-appropriate scales or measures of endpoints
- Study risks, pain, fear and discomfort
- Appropriate pharmacovigilance procedures



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- EU Ethical Recommendations, EC 2017; ICH Topic E11 Guideline -

Preparing material for informed consent

- Information sheet + consent form
- 2 separate information and signatures for:

Genetic tests

Personal data processing

Signed and dated by legally designated representative(s) and study personnel performing the interview and giving study information

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Reg (EU) 536/2014; Reg (EU) 2016/679; EC Ethical Recommendations, 2017; CIOMS WHO guidelines 2016

Preparing material for informed assent

- Tailored for age groups
- Appropriate language and format

Assent/informed consent guidance

Symbol	Description
✖	Does not have to be included in the assent/agreement/informed consent process for this age group
✔	Should be included and discussed during the assent/agreement/ informed consent process for this age group
◎	May be included/optional to include in the assent/agreement/informed consent process for this age group

Trial specific information for informed consent and assent (agreements)

Age group in years				Legal representative(s)	Elements to consider/information which must be included into the assent/consent document	Questions to be addressed	Notes and example methods/texts to be used
0–2	2–5	6–9	10–18				
✖	◎	✔	✔	✔	**Title/topic of the trial/introduction/purpose of the trial/size of the trial (how many patients/participants, how many sites)**	▶ What is the purpose of this trial? ▶ Why is this trial needed? ▶ Is there information about this trial available somewhere?	NOTE: EUCTR number and trial protocol code must be added. The trial must be registered in the official Trial Registry (EudraCT) before the start of the trial. Additionally, in other registries or websites according to national requirements.
✖	✖	✖	✔	✔	**Possible future effects (infertility, birth defects, miscarriage)**	▶ Can the trial medication or treatments have some effect on the fetus via mother or father, in case of the child/adolescent's pregnancy/ child/adolescent's girlfriend's pregnancy? ▶ What happens if this situation occurs? ▶ Who will be told about this?	NOTE: Information about the potential teratogenic risks during pregnancy/ fertility (both females and males) should be discussed, and also the possibility to use contraception, and what type of contraception should be used if it is required. Explain what should happen if pregnancy arises during the trial.
✖	✔	✔	✔	✔	**Participation/recruitment/child/adolescent selection**	▶ Why has the child/adolescent been invited to participate in this trial?	

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EMA website; Lepola, Kindred, Giannuzzi et al, Arch Dis Child 2021

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FONDAZIONE
PER LA RICERCA FARMACOLOGICA
GIANNI BENZI
ONLUS

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