Evaluation of PIPs & ethical aspects of the design of paediatric trials proposed in the PIPs.

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DISCLAIMER

- The views expressed during the presentation are the personal view of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the PDCO or/and the EMA.

Marek Migdal – personal profile

- Paediatrician, pulmonologist > 30 years of experience in the field of paediatrics, respiratory medicine and paediatric intensive care
- External expert > since 1995 Polish NCA, since 2007 member of the PDCO, EMA
- Former member of the EC, CMHI, Warsaw
- Pharma industry > Boehringer Ingelheim, 1990-1994 (consultant, Medical Director, Director of the BI Branch Office in Poland)

Points to be discussed during the presentation

- Objectives of the Paediatric Regulation
- Evaluation of PIPs – role of the EMA/the PDCO
- Current experience
- What is known & what is unknown on ethical issues during the PIP assessment
- Future changes

Paediatric Regulation (EC) (1901/2006)

- The Paediatric Regulation has 3 objectives :
  - to facilitate the development and accessibility of medicinal products for use in the paediatric population;
  - to ensure that medicinal products used to treat the paediatric population are subject to research of high quality and are appropriately authorised for use in the paediatric population;
  - to improve the information available on the use of medicinal products in the various paediatric populations.

- These objectives, to be achieved:
  - without subjecting the paediatric population to unnecessary clinical trials
  - without delaying the authorisation of medicinal products for other age populations

What is PIP?

24.9.2008 EN Official Journal of the European Union C 243/1

II

(Information)

INFORMATION FROM EUROPEAN UNION INSTITUTIONS AND BODIES

COMMISSION

Communication from the Commission — 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

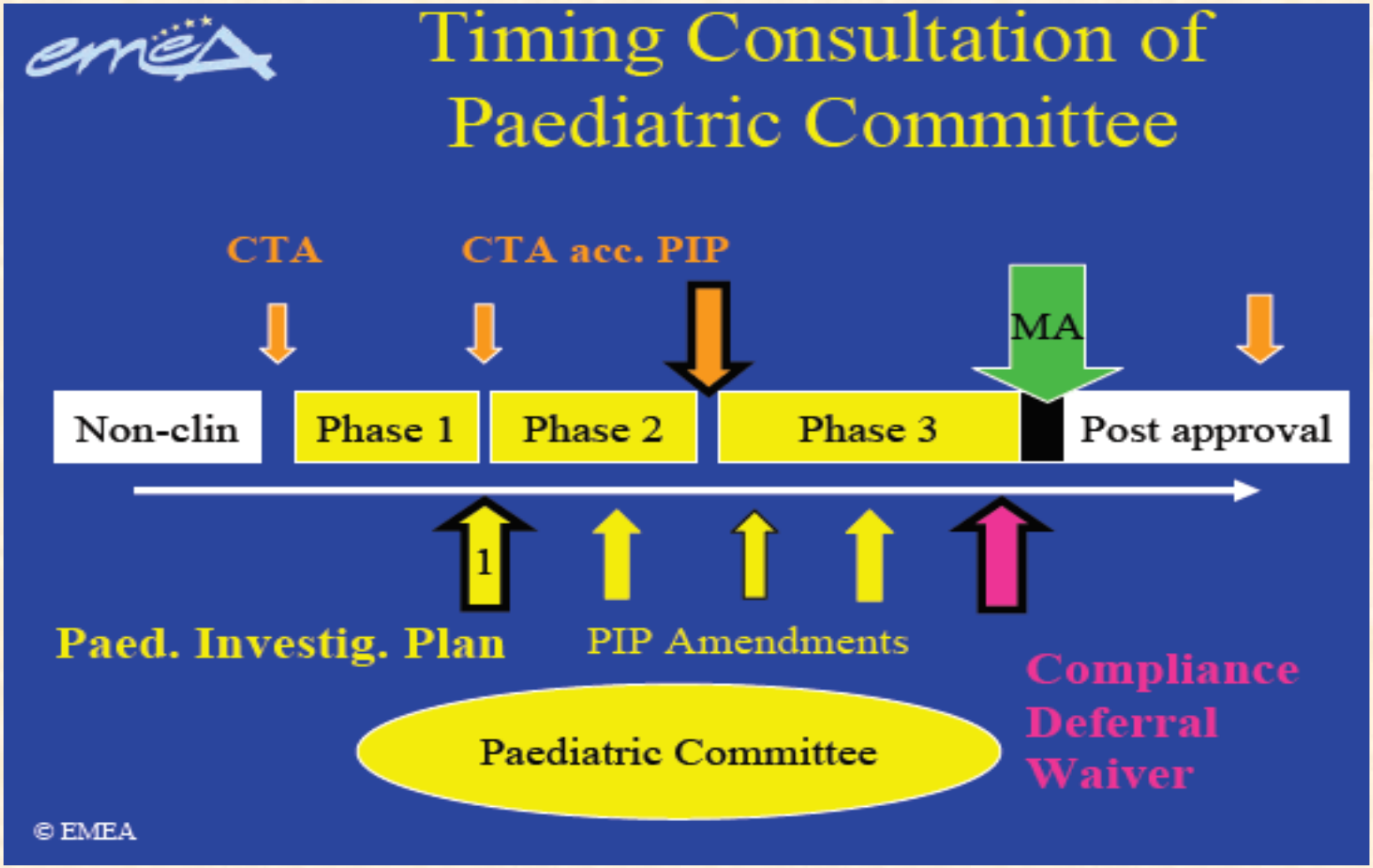
(2008/C 243/01)

Basic definitions

- **Paediatric investigation plan** - “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”

- **The PIP** - “the document upon which the development and authorization of medicinal products for the paediatric population should be based”

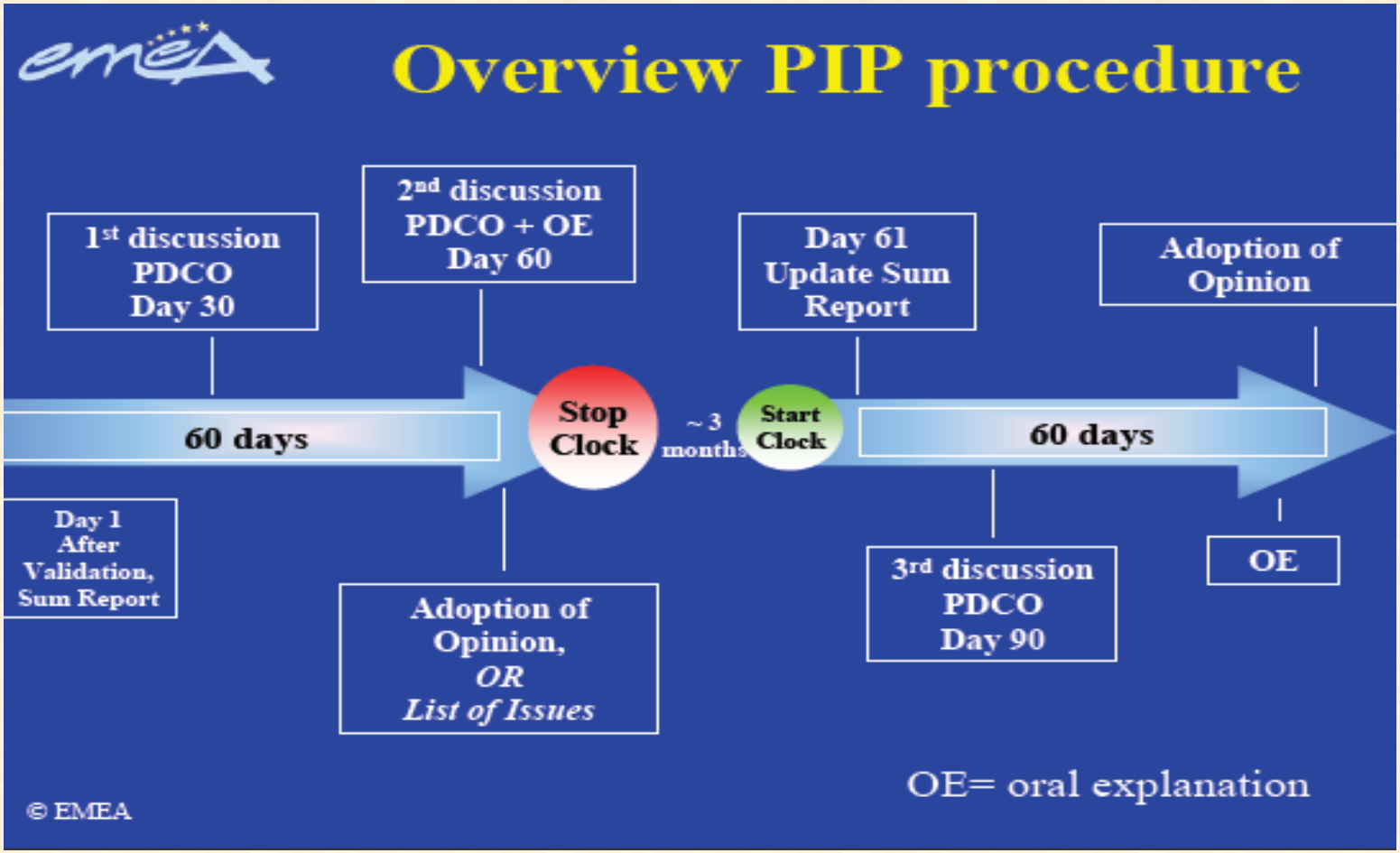
When the PIP should be submitted?



Structure of a PIP application

- Part A: Administrative and product information;
- Part B: Overall development of the medicinal product including information on the conditions;
- Part C: Applications for product specific waivers;
- Part D: Paediatric investigation plan;
- Part E: Applications for deferrals;
- Part F: Annexes.

PIP assessment – timelines



PIP evaluation - PDCO

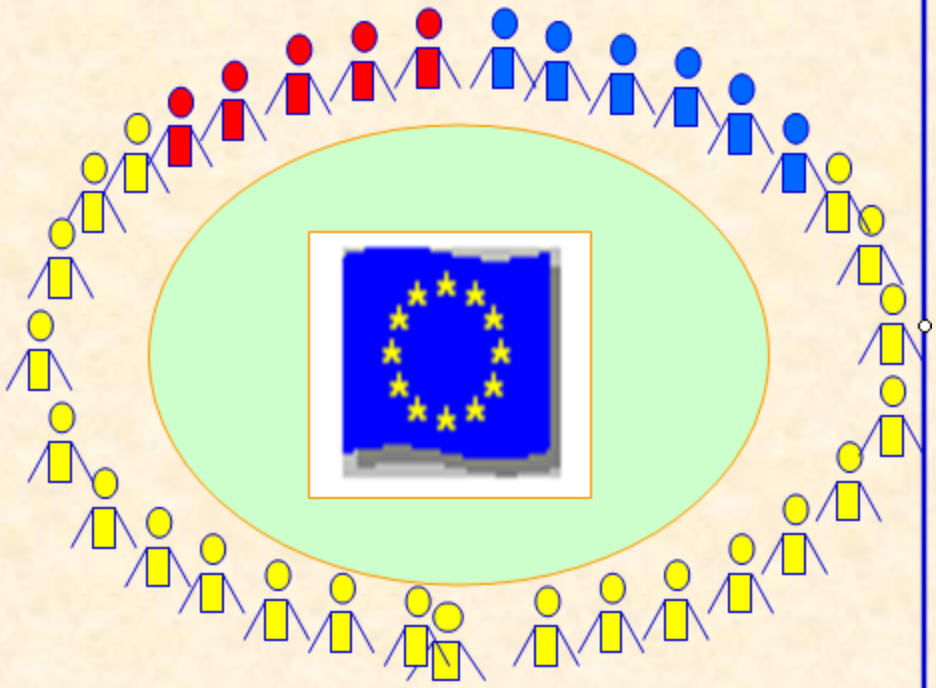
27 Members (plus alternates)

including 5 from Approval Committee (CHMP)

3 HealthCare Professionals

3 Patients representatives

2 from Norway, Iceland



Structure of a PIP application – part B

- B.1: Discussion on similarities and differences of the disease/condition between populations
  - details on similarities and differences between adult and paediatric population
  - important to assess the possibility and extent of extrapolation between populations (adult and various children age subsets)
  - earliest age of onset of the diseases/conditions – important for age cut-off for waiver

Structure of a PIP application – part B

- B.2: Current methods of diagnosis, prevention or treatment in paediatric population
  - discussion should be focused on the relationship with the proposed development
  - proper diagnosis
  - position of the product > prevention or treatment

Structure of a PIP application – part B

- B.3: Significant therapeutic benefit and/or fulfilment of therapeutic need
  - comparison with the current methods discussed in B2 (safety, efficacy, ease of use, improved quality of life etc)
  - if significant benefit cannot be anticipated ⇨ deferral or waiver
  - if the therapeutic need is included in the inventory – reference should be made

List of paediatric needs

List of paediatric needs (established by the former Paediatric Working Party)

The first exercise to establish paediatric needs was carried out between 2001 and 2007 by the Paediatric Working Party (PEG) — a temporary working party of the CHMP, established prior to implementation of the Paediatric Regulation.

Please refer to EMA/PEG procedure for identifying paediatric needs (EMEA/175192/2004/rev2) before reviewing any of the documents in the table below.

Table of contents

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 July 2010
EMA/480197/2010
Rev. 2010 – update 17/11/2010*
Human Medicines Development and Evaluation

Revised priority list for studies into off-patent paediatric medicinal products

for the 5th Call 2011 of the 7th Framework Programme of the European Commission

Structure of a PIP application – part C

Grounds for waiver:

- **a product-specific waiver**
  - based on lack of efficacy or safety
  - based on the disease or condition not occurring in the specified paediatric subset
  - based on lack of significant therapeutic benefit
- **Class waiver** - no product-specific waiver necessary, if therapeutic indication and the subset of the paediatric population are already covered by a class waiver

Class waiver

Short table of the European Medicines Agency Class Waivers:

Class of medicinal products	Condition	Decision date
	Treatment of chronic lymphocytic leukaemia	21/04/2008
	Treatment of chronic obstructive pulmonary disease (COPD) (excluding chronic lung diseases associated with long-term airflow limitation, such as asthma, bronchopulmonary dysplasia, primary cilia dyskinesia, obstructive lung disease related to graft-versus-host disease after (bone-marrow) transplantation).	03/12/2007
	Treatment of climacteric symptoms associated with decreased oestrogen levels, as occurring at menopause	03/04/2009

Structure of a PIP application – part D

- Existing data and overall strategy proposed for the paediatric development
- PIP indication & selected paediatric subsets
- Information on the existing quality, non-clinical and clinical data
- Strategy in relation to quality aspects, non-clinical aspects & clinical aspects
- table of all planned and/or ongoing non-clinical studies as well as of all planned and/or ongoing clinical studies
- Synopsis/outline of protocol of each of the planned and/or ongoing clinical studies

Structure of a PIP application – part D

- Formulations:
  - age-appropriate formulations and strengths necessary
  - route and frequency of administration
  - choice of excipients
  - palatability and ways of investigating it
  - rate of infusion,
  - reconstitution or dilution procedures (volume to be administered)

Structure of a PIP application – part D

- Clinical aspects:
  - type of study and design vary widely depending on condition, product characteristics, clinical experience in children etc.
  - one or more of the following:
    - BE of the age-appropriate oral formulation to the existing adult formulation (in healthy adult volunteers)
    - PK and safety study
    - Safety study
    - PK, safety and efficacy study

Agreed PIP – an example

Opinion of the Paediatric Committee on the agreement of a Paediatric Investigation Plan and a deferral and a waiver

EMEA-000782-PIP01-09

Scope of the application

Active substance(s):

Recombinant human monoclonal antibody to human interleukin-13

Condition(s):

Treatment of asthma

Pharmaceutical form(s):

Solution for injection

Route(s) of administration:

Subcutaneous use

Name/corporate name of the PIP applicant:

MedImmune Ltd

Agreed PIP – an example

2. Waiver

2.1. Condition

Treatment of asthma

The waiver applies to:

- the paediatric population from birth to less than 6 years of age,
- for solution for injection, subcutaneous use,
- on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments.

Agreed PIP – an example

3. Paediatric Investigation Plan

3.1. Condition to be investigated

Treatment of asthma

3.1.1. Indication targeted by the PIP

Treatment of uncontrolled asthma despite the daily use of medium or high dose inhaled corticosteroid and long-acting beta-2-agonist.

3.1.2. Subset(s) of the paediatric population concerned by the paediatric development

From 6 to less than 18 years of age.

Agreed PIP – an example

3.1.4. Studies

Area	Number of studies	Description
Quality	0	Not applicable.
Non-clinical	0	Not applicable.
Clinical	6	1. Single-dose, open-label, parallel-group study to evaluate the safety, tolerability, and pharmacokinetics (PK) of subcutaneous (SC) CAT-354 in adolescents (12 to less than 18 years) and adults with uncontrolled

Agreed PIP – an example

Area	Number of studies	Description
		asthma. 2. Multicentre, randomised, double blind, placebo controlled, add-on study to standard therapy to evaluate the efficacy and safety of subcutaneous CAT-354 in adults and adolescent subjects with uncontrolled asthma. 3. Multicentre, randomised double blind placebo controlled add-on study to standard therapy to evaluate the efficacy and safety of subcutaneous CAT-354 in adults and adolescent subjects with uncontrolled asthma. 4. Open label, single ascending-dose study to evaluate the safety, tolerability, efficacy, PK and immunogenicity of subcutaneous CAT-354 in children (6 to less than 12 years) with uncontrolled asthma. 5. Multicentre, randomised, double-blind, placebo controlled, parallel-arm, dose-ranging add-on study to standard therapy to evaluate the efficacy and safety of CAT-354 in children aged 6 to less than 12 years with uncontrolled asthma and determine an appropriate dose for the subsequent pivotal study in children 6 to less than 12 years. 6. Multicentre, randomised double blind placebo controlled add-on study to standard therapy in order to evaluate the efficacy and safety of subcutaneous CAT-354 in children aged 6 to less than 12 years with uncontrolled asthma.

Agreed PIP – an example

4. Follow-up, completion and deferral of PIP

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 December 2022
Deferral for one or more studies contained in the paediatric investigation plan:	Yes

PDCO – activities
2007- until October, 2011

Total number of PIP/waiver applications 1173

- according to article 7 789 73%
- according to article 8 259 24%
- according to article 30 26 3%

Cumulative experience on PIPs

Eur J Clin Pharmacol
DOI 10.1007/s00228-011-0997-4

SPECIAL ARTICLE

Three years of paediatric regulation in the European Union

Thorsten M. Olski · Simona F. Lampus ·
Giulia Gherarducci · Agnes Saint Raymond

- August 2007 – December 2009 > 528 valid applications for PIPs and 136 for full waivers
- 166 opinions on PIPs and 91 on full waivers given
- Details of 62 phase II/III CTs analysed

Cumulative experience on PIPs

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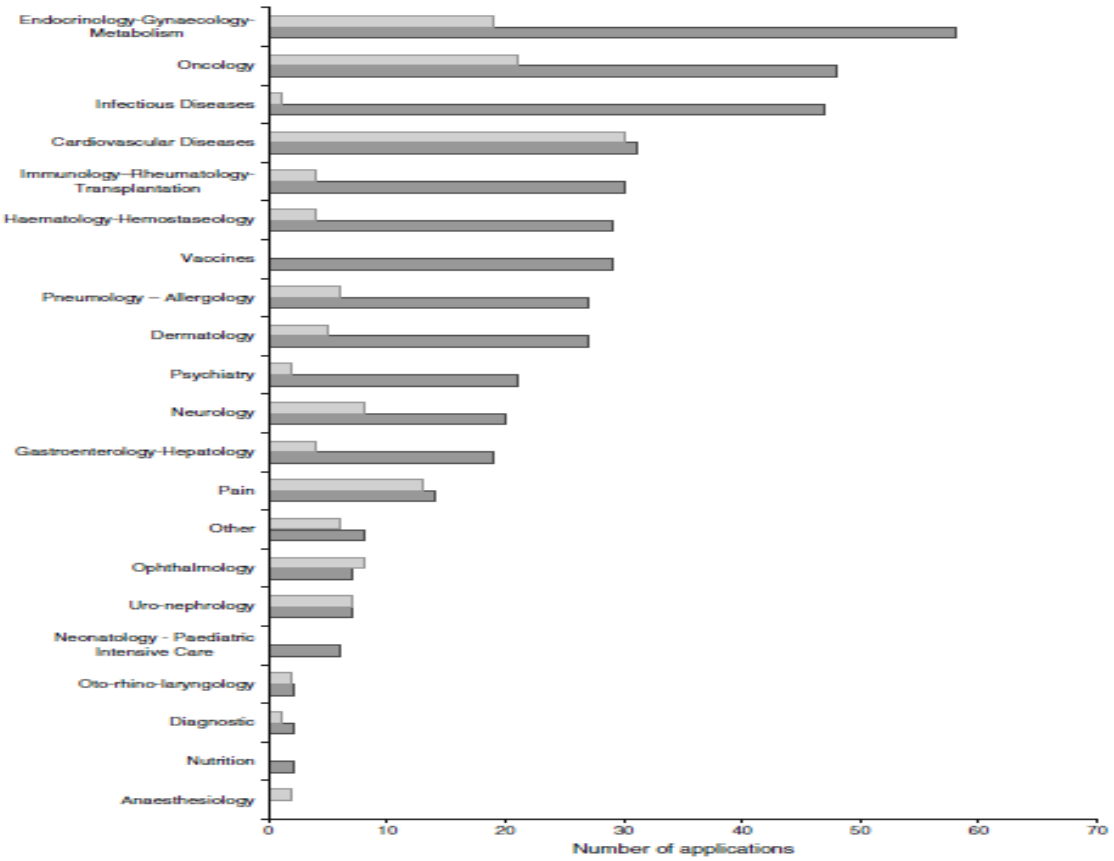
Eur J Clin Pharmacol

Fig. 2 Number of applications for PIPs (*dark-grey bars*) and full waivers (*light-grey bars*) submitted to the EMA by therapeutic area



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Clinical trial design parameters	Proposed	Accepted by PDCO	Requested by PDCO	Total
Number of trials	62 (100%)	61	23 (100%)	85 (100%)
Randomised trials	50 (81%)	50	18 (78%)	68 (80%)
Double-blind	33 (53%)	32	11 (47.8%)	44 (52%)
Placebo controlled	12 (19%)	12	12 (52.2%)	24 (28%)
Active controlled	35 (57%)	35	6 (26.1%)	41 (48%)[a]
Active+placebo	4 (7%)	4	0	4 (5%)

Cumulative experience on PIPs

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Investigation plans covering these age groups	Proposed	Accepted by PDCO	Requested by PDCO	Covering these age groups after requests by PDCO
12–18 years	76% (41/54)	37	7[a]	81% (44/54)
6–11 years	67% (36/54)	33	7	74% (40/54)
2–5 years	46% (25/54)	24	5	54% (29/54)
Partial coverage	9% (5/54)	4	3	13% (7/54)
28 days–23 months	28% (15/54)	12	7[b]	35% (19/54)
Partial coverage	17% (9/54)	6	3	17% (9/54)
0–27 days	15% (8/54)	7	7	26% (14/54)
Following a staggered approach	11% (6/54)	6	5	20% (11/54)

Cumulative experience on PIPs

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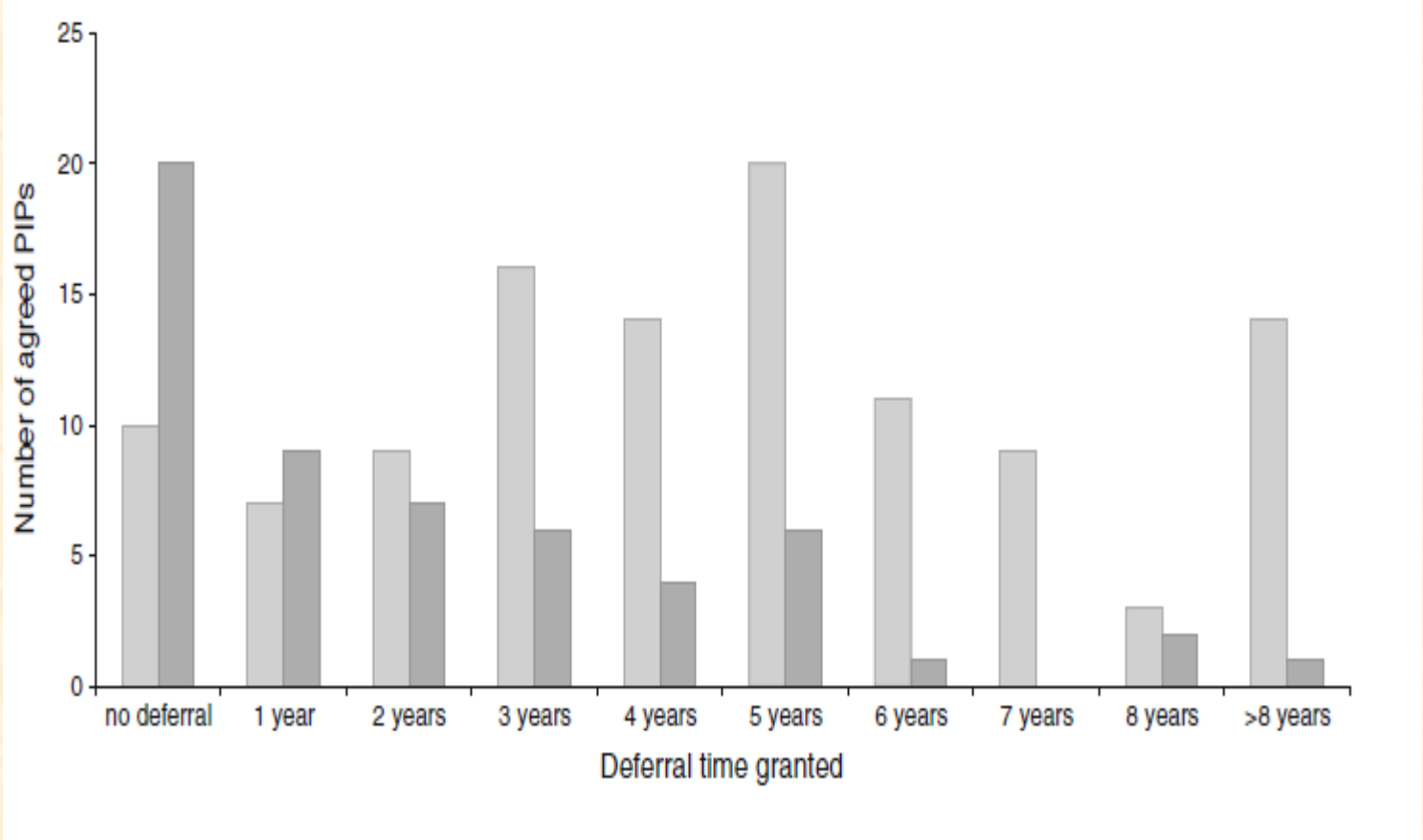

Frequently asked questions during PIP evaluation

- Is there a paediatric need for a medicinal product which is planned to be developed?
- What are currently drugs used for the indication?
- Potential advantages of a proposed medicinal product over currently use drugs?
- Differences between adult and paediatric patients?
- Existing guidance on the condition /type of treatment (scientific or EMA/NCA guidelines, registries, formularies)

Frequently asked questions during PIP evaluation

- Is there a need to run clinical trials in paediatric population – what data are needed
  - PK?, safety? , efficacy/safety?
- Design of studies (active comparators, placebo, placebo add on standard therapy, appropriate (validated) PEs and SEs, sample size (properly calculated), popPK
- Advices received from any regulatory authority relevant to the development of the medicinal product for paediatric population

Frequently asked questions during PIP evaluation

- Are there enough paediatric patients to be included in the trials in the same therapeutic area?
- Role of extrapolation, simulation?
- How to minimalised potential risk/harm for children enrolled to CTs
- Use of a DSMB
- Need for long term follow-up of potential safety issues > what should be a period of observation

Ethical aspects - what is unknown at the time of PIP evaluation

- Impact of changing enviroment (medical knowledge, new diagnosic/therapeutic oportunitis) within approved timelines (years !!!)
- Exact information on investigators/ centres in terms of experise on specific paediatric problems
- Full documentation of the CT (approved protocol, information for patients/parents and informed consent forms)

Conclusions

- Common task for all stakeholders (EMA/PDCO, investigators, ECs, patients/parents, industry) is to actively participate in the process ensuring that medicinal products for use in children are of high quality, being ethically researched and finally authorised appropriately.
- Current results of the Paediatric Regulation implemantation into the law of all UE MS are promising.
- Meetings like today's should stimulate further improvement.

Thank you