

AGAH

Workshop

PAEDIATRIC INVESTIGATION PLAN

How to Adapt Clinical Development to the Particularities of Paediatrics?

13. -14. 01. 2009

Bonn

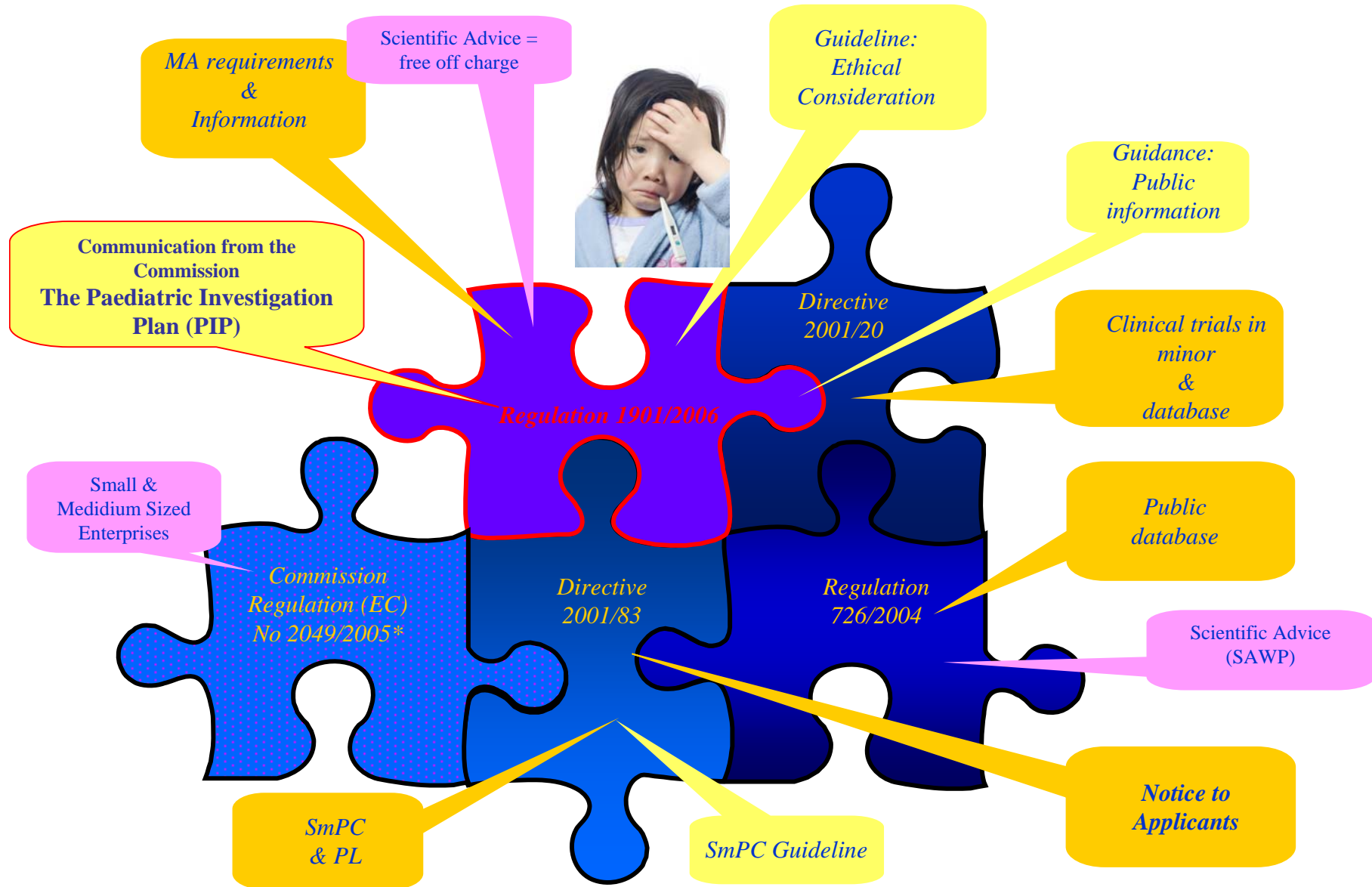
Birka Lehmann

Medicinal Products

New requirements for marketing authorisation & Information and Transparency



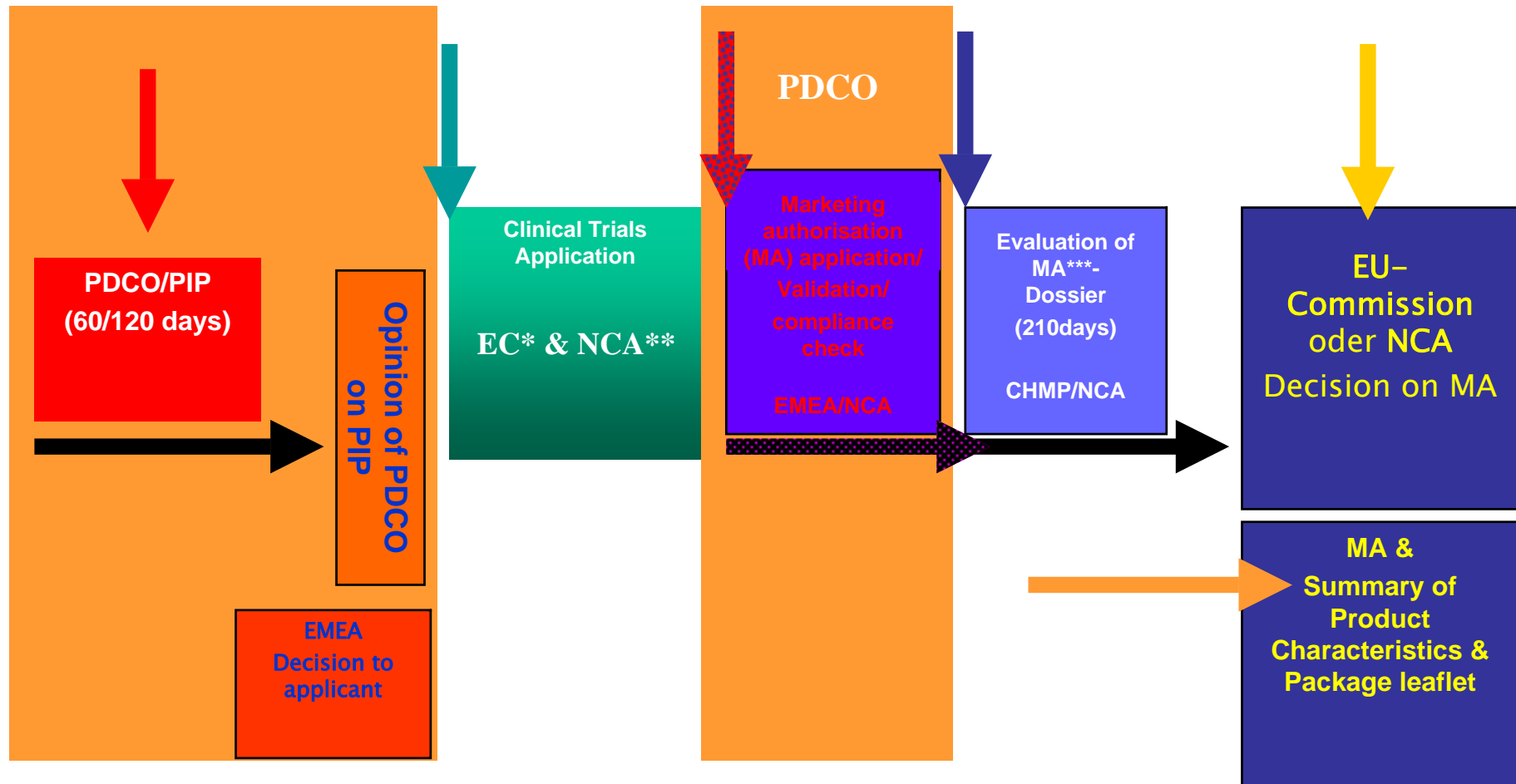
Regulation (EC) No 1901/2006



- EMEA's/PDCO's expectations and experiences with submitted PIPs,
- Regulatory requirements for PIPs with
 - new drugs,
 - marketed and
 - out-of-patent drugs
- New paediatric formulations

PIP and Consequences

- Clinical trials application: Ethics Committees & national competent authority
- Validation of MA application – COMPLIANCE CHECK
- MA with SmPC & PL



*Ethics Committee & **national competent authority

The Paediatric Investigation Plan (PIP)

D.1.2 Selected age group(s)

...should cover all subsets of the paediatric population, including neonates, which are not covered by a waiver

D.4: Strategy in relation to clinical aspects (PIP indications and age subsets)

Efficacy

Safety

Dose/dosage

Age appropriate formulation



Pre-term Infant	Term Newborn	Infant/Toddler	Child	Adolescent
< 36 weeks gestation	0-27 days	28 days -23 months	2 - 11 years	12 - end of 17 years
Survival	Adaptation	Growth	Training	Maturation

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Reg. 1901/2006

12 December 2006

Art 2(2) Paediatric investigation plan indication – condition

New: CommComm PIP

24 September 2008

,Condition‘

,Paediatric investigation plan indication‘

,proposed therapeutic indication‘

Condition – vs – definition of waiver request

The specific medicinal product or class of medicinal products is likely to be ineffective or unsafe in part or all of the paediatric population

The disease or condition for which the specific medicinal product or class is intended occurs only in adult populations

The specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients

Based on the provisions set out in Article 11–13 of the Paediatric Regulation, the PDCO proposes to grant a class waiver for the following indications (condition)
→ publication 21 April 2008

Reg. 1901/2006

12 December 2006

Art 2(2) Paediatric investigation plan indication – condition

New: CommComm PIP

24 September 2008

,Condition‘

,Paediatric investigation plan indication‘

,proposed therapeutic indication‘

➔ Condition – vs – definition of waiver request

➔ Content of PDCO opinion/EMA decision

➔ Information in cover letter

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Regulation (EEC) No 1901/2006

CORE: Paediatric Investigation Plan (PIP)

Application for marketing authorisation for medicinal products

➤ Article 7

26.07.2008 = application of new medicinal products with PIP and results of studies according to PIP

➤ Article 8

26.01.2009 = Line-Extensions (with Supplementary Protection Certificate/Patent)

➤ Article 30

Paediatric Use Marketing Authorisation (PUMA) – off patent medicinal products

New: Communication from the Commission **The Paediatric Investigation Plan (PIP)**

24 September 2008

SECTION 1 – FORMAT AND CONTENT OF APPLICATIONS FOR AGREEMENT OR MODIFICATION OF A PAEDIATRIC INVESTIGATION PLAN AND REQUESTS FOR WAIVERS OR DEFERRALS

2.1 – GENERAL PRINCIPLES AND FORMAT

The **same application form** (see the Annex to this guideline) should be used whether requesting agreement to a paediatric investigation plan, a waiver, a deferral or a combination thereof. **Different parts (Part A to Part F)** of the application are provided to fulfil the different types of request.

Part C: Application for product **specific waivers**

Part E: Application for **deferrals**

New: The Paediatric Investigation Plan (PIP)

D.5.4: Synopsis/outline of protocol of each of the planned and/or ongoing clinical studies or trials

- type of study,
- study design,
- type of control (placebo or active control with dose to be used) and justification,
- location (regions),
- test(s) products; dosage regimen; route of administration,
- objective(s) of the study,
- number of subjects (M/F), ages, number per ICH age groups or other relevant age group,
- duration of treatment including the duration of post-treatment observation,
- main inclusion/exclusion criteria,
- parameters or endpoints (primary, secondary),
- sample size (more or less detailed as appropriate),
- power calculation: describe effect size expected,
- options in case of recruitment issues, interim analyses and stopping rules,
- statistical methods (Statistical methods used to compare groups for primary outcome, and for additional analyses if relevant).

Paediatric Investigation Plan (PIP)

Design of clinical trials



Feasibility of the trial to be performed

Size of trial

Ethnic groups (genetic characteristics)

Blinded/un-blinded



Use of placebo (not withholding effective treatment)
Comparator (unlicensed??)



Pain, distress and fear minimisation

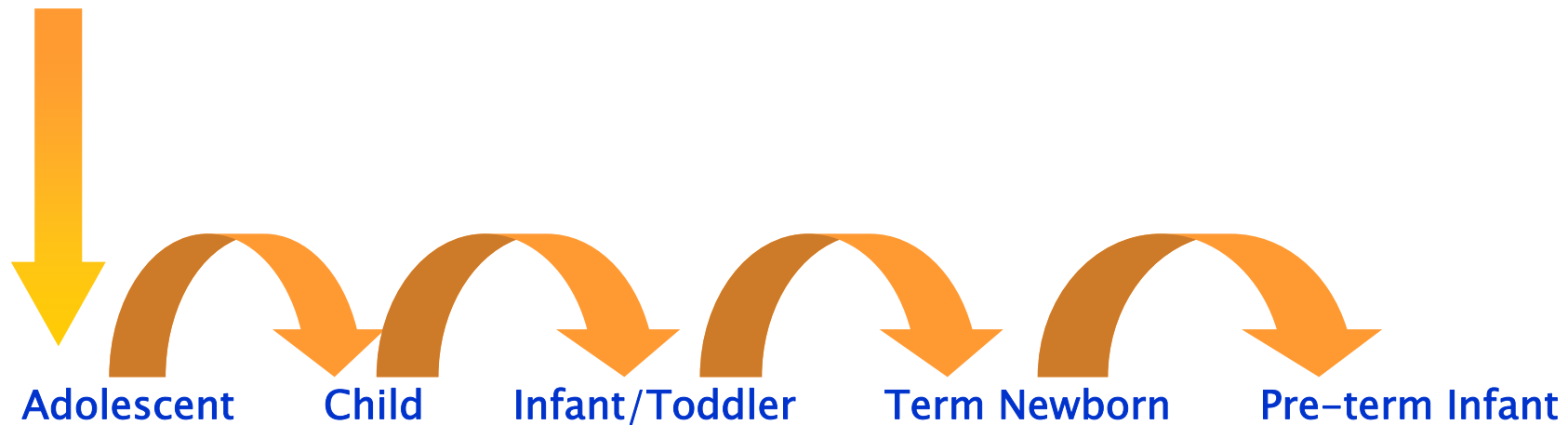
Risk assessment and monitoring

Benefit and measures of benefit

The Paediatric Investigation Plan (PIP)

Extrapolation: ?Efficacy – Safety?

Adult



Guidelines on indication/conditions

Addendum (Annex) for paediatric population

Why?

- Diagnostic
- Endpoints – measurement/monitoring
- Monitoring

Development of a CHMP Guideline on the Clinical Investigations of Medicinal Products for the treatment of Pulmonary Hypertension

Up-date of guidelines

EXAMPLE

Addendum for paediatric population

Why?

- **Endpoints**

The suitability of **6–Minutes Walk Test** as a primary endpoint should be discussed considering it is influenced by **age**, and degree of **motivation**

- Other endpoints could include functional tests

(e.g. cardiopulmonary exercise testing, shuttle walk test), biomarkers, or the development of a PAH–specific quality of life questionnaire.

(Possible) Recommendation

- **Endpoints? Pulmonary vascular resistance**

Invasive (right cardiac catheterization) / non–invasiv
(echocardiography/Doppler) for children under (6?) years of age – correlation
clinical score

New: The Paediatric Investigation Plan (PIP)

Part E: Applications **deferrals**

Pursuant to Article 20(1) of the paediatric regulation, 'a request may be made for deferral of the initiation or completion of some or all of the measures'.

With reference to the timelines stated in Section D.5.1, and to which

- indication,
- route of administration
- pharmaceutical form.
- The application should specify the age group to which it applies.

For timelines, specific months and years should be given also in relation to the development in adults.

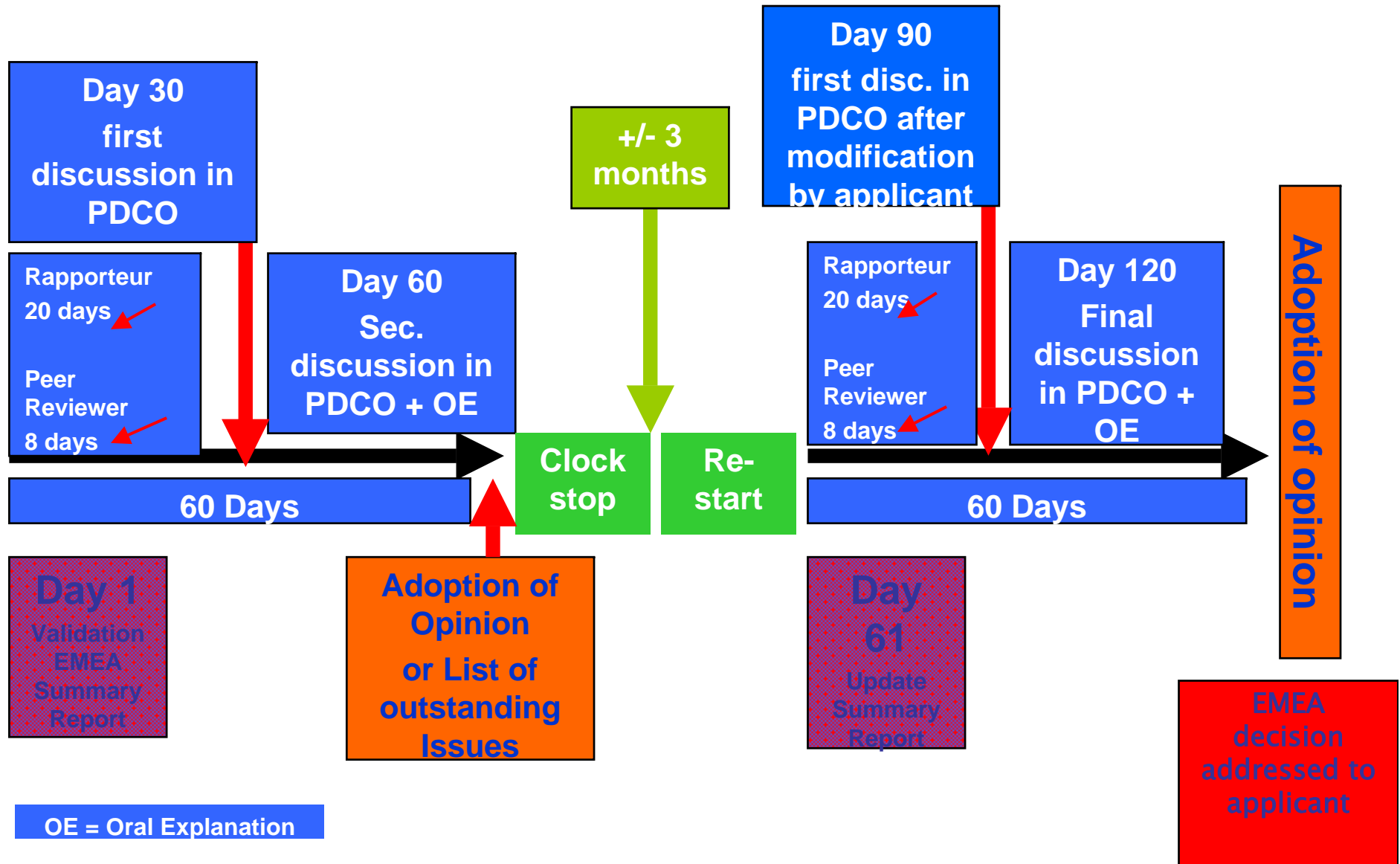
Requests for deferrals should be justified on scientific and technical grounds or on grounds related to public health and the paediatric regulation requires that a deferral be granted when:

- it is appropriate to conduct studies in adults prior to initiating studies in the paediatric population,
- studies in the paediatric population will take longer to conduct than studies in adults.

Other examples of scientific and technical justification for a deferral may include when **additional non-clinical data** are considered necessary or when **major quality problems** currently prevent development of the relevant formulation(s).

Timelines PIP

Request of Agreement: Article 15 – 19 & 25 Regulation (EC) No 1901 /2006



Article 7 & 8 & 30 – Studies according to Paediatric Investigation Plan

Annex to the monthly PDCO press release, 10-12 December 2008

OVERVIEW OF PAEDIATRIC INVESTIGATION PLAN/WAIVER APPLICATIONS

	2007 (August to December)	2008 (January to December)	Cumulative Total
Total number of validated PIP / waiver applications	85	271 ¹	356 ²
Applications submitted for a product not yet authorised (<i>Article 7³</i>)	39	186	225 (63%)
Applications submitted for a product already authorised still under patent in view of a submission of a variation/extension for a new indication, pharmaceutical form or route of administration (<i>Article 8³</i>)	45	75	120 (34%)
Applications submitted for an off-patent product developed specifically for children with an age-appropriate formulation (<i>Article 30³</i>)	1	10	11 (3%)
PIPs and full waiver indications covered by these applications	202	395	597

Number of Paediatric Committee (PDCO) opinions	2007	2008	Cumulative Total
Positive on full waiver	10	48	58
Positive on PIPs including potential deferral	2	81	83
Negative opinions adopted	0	4	4
Positive opinions adopted on modification of the PIP	0	8	8
Positive opinion on compliance with PIP	0	5	5

Compliance
Check

Regulation (EEC) No 1901/2006

CORE: data collection and verification



Article 45
finalised studies

Paediatric Worksharing

Chemical = 980

Natural Products = 8*/ 456

Vaccines = 192

Radiopharmaceutical = 72



Article 46
submission 6 months after
finalisation

* High priority

Change (?) in
Summary of Product
Characteristics
& Patient
Information

- EMEA's/PDCO's expectations and experiences with submitted PIPs,
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- **New paediatric formulations**

New paediatric formulations – the challenges



Dosages according to weight (1 kg – xx kg)?

Dermal: Hydration of skin?

Oral: Dosing by mixture with food?

Parenteral: i.v. – volume/needle

Formulation

- preservatives?
- colourants?
- sweetner?



Rejection: taste and/or smell

New paediatric formulations the challenges



REFLECTION PAPER: FORMULATIONS
OF CHOICE FOR THE PAEDIATRIC
POPULATION
(EMA/CHMP/PEG/194810/2005)

- ➔ Expert working group at EMA/PDCO
- ➔ New guideline(s)?

Thank you very much for your attention

