EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Key concepts of the paediatric regulation and latest developments

Paolo Tomasi, M.D. Ph.D.
Head of Paediatric Medicines
European Medicines Agency

Presented by: Paolo Tomasi

The EU Paediatric Regulation

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

(Text with EEA relevance)

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

Paediatric development is now mandatory in the EU

- Unless a product-specific **waiver** or a class waiver is granted
  (which applies only for specific conditions and dosage forms)
- **Deferrals** can also be granted
  (studies in children can be initiated and/or completed after applying for marketing authorisation in adults)

Pillars of the Paediatric Regulation

- A system of OBLIGATIONS and REWARDS
- Paediatric Committee
- Paediatric Investigation Plan (PIP)
- Transparency / information measures
- Other measures

EU Paediatric Regulation: obligations versus incentives

Type of MP	Obligation	Incentive	Comments
New Medicinal product	Paediatric Investigation Plan or Waiver	6 months extension of SPC (patent) *	Necessary for **validation** of application
On Patent and authorized Medicine	Paediatric Investigation Plan or Waiver	6 months extension of SPC (patent)*	When new indication or new route or new pharmaceutical form: necessary for **validation**
Orphan Medicine	Paediatric Investigation Plan or Waiver	2 additional years of market exclusivity*	In addition to 10 years
Off patent Medicine	None (voluntary PIP possible for PUMA)	10 years of data protection	Research funds Paed. Use MA (PUMA)

**if compliance with PIP, information, approval EU-wide*

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

	US BPCA	US PREA	EU
Development	Optional	Mandatory	Mandatory *(optional for off-patent)*
Instrument	Written Request	-	Paediatric Investigation Plan
Waiver	N/A	3 grounds	3 grounds
Timing	End of phase 2	End of phase 2	End of phase 1
Reward	6 months exclusivity	-	Main: 6 months SPC extension (patent)
New drugs (section 505)	Yes With exclusivity	Yes	Yes
Biologicals (most)	Yes	All	All
Orphan	Included	Excluded	Included
Decision	FDA	FDA	EMA (Opinion: Committee)

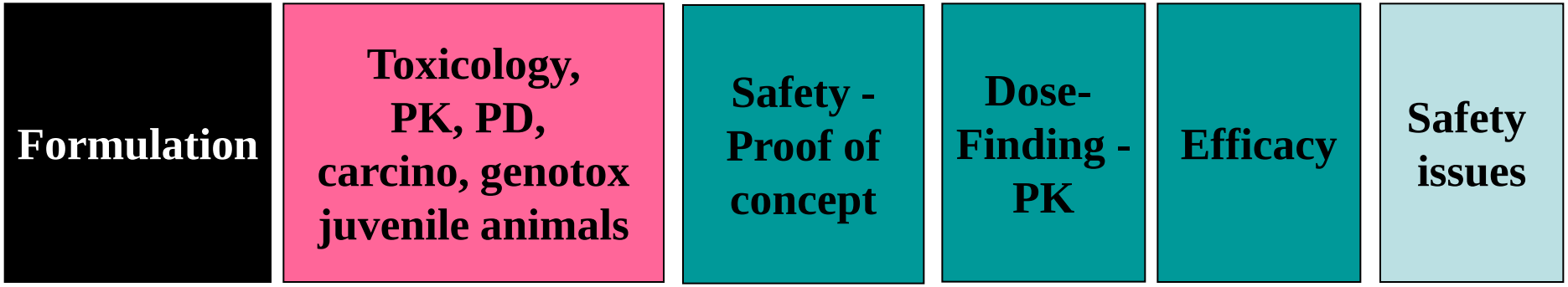
What is a PIP?

From the Paediatric Regulation (art. 2.2):

‘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

Paediatric Investigation Plan

- Data on efficacy, safety and age-appropriate formulation are needed
- Timelines for start and completion of each study
- *In practice: discussion on each condition/indication and formulation, for each paediatric subset (not only age groups).*



Enabling SMEs to agree PIPs/waivers smoothly

Information on already agreed PIPs/waivers and on existing paediatric data

Or:

What can the EMA do for you?

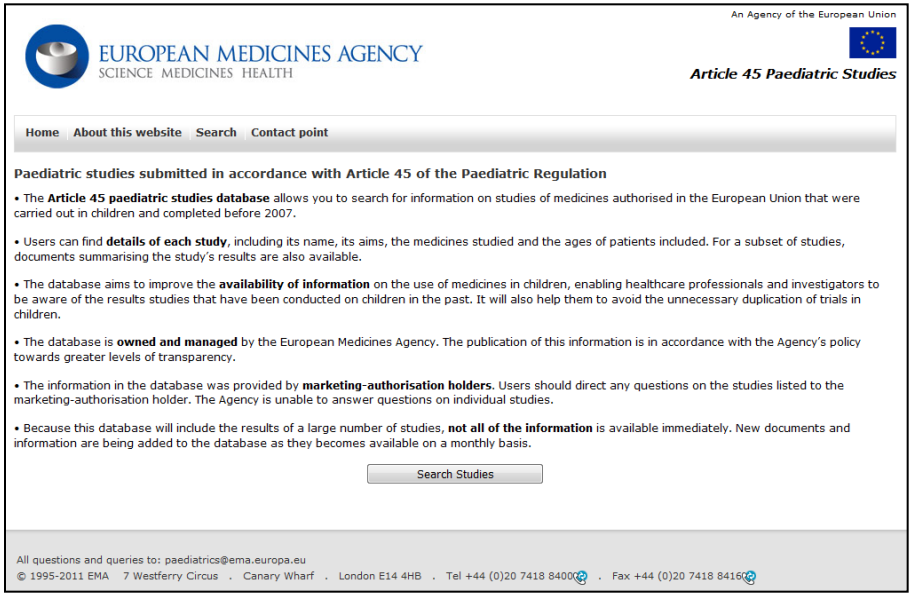
Transparency / provision of information

EMA decisions on Paediatric Investigation Plans

- On EMA homepage (www.ema.europa.eu), and searchable
- Contains paediatric trials agreed between EMA and company (+dosage form and non-clinical studies)
- From 2013 will include "key elements" of each trial (short summary)

Database of all paediatric clinical trials performed before 2008 and not otherwise submitted to reg. authorities (authorised products)

- Art. 45: all **existing** paediatric studies to EMEA/NCAs by 26/1/2008
  - appr. 17,000 names of studies received
  - appr. 3,200 results of studies published on EMA website (http://bit.ly/10BPba7)
  - Appr. 3,200 results of studies received, still to be published
  - Evaluation ongoing (national products)



Paediatric clinical trials in EU-CTR

clinicaltrialsregister.eu /

- All clinical trials and of other trials submitted to National Authorities (protocol-related information)
- Third countries trials linked to a PIP
- Results will be added in EudraCT (Q4 2013)
- Access possible via WHO portal

- **Public access to paediatric information for authorised products** (EudraPharm)

Proceedings from Expert groups at EMA

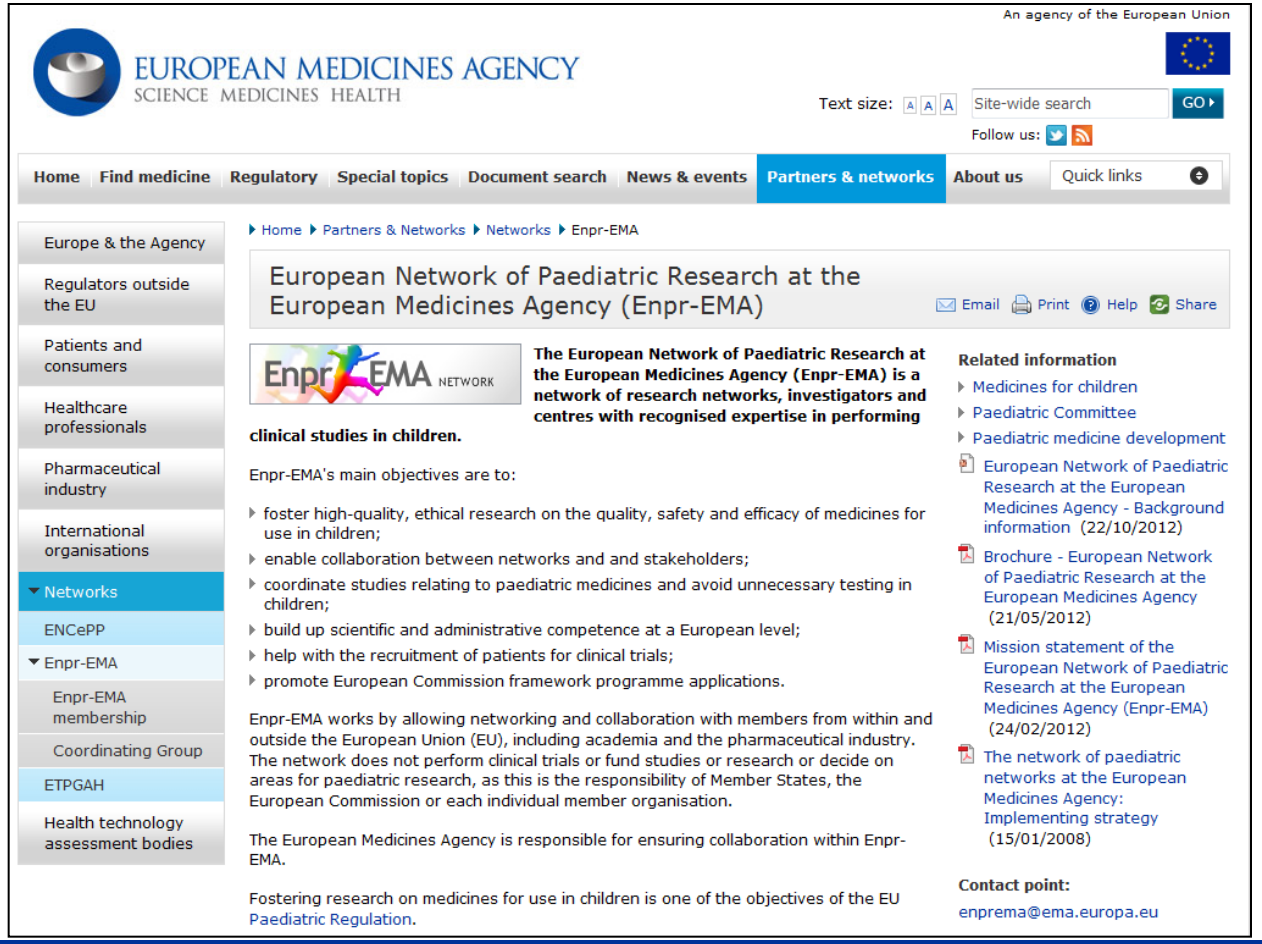
(http://tinyurl.com/PaedExpGroups)

Not binding for PDCO, but provide general guidance for PIP development

European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA)

- Network of research networks
- EU and extra-EU
- EMA implementing strategy of the European network
- Stimulation of quality research in EU

- Annual workshop, meeting with industry



An agency of the European Union

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Text size: A A A Site-wide search GO

Follow us:

Home | Find medicine | Regulatory | Special topics | Document search | News & events | Partners & networks | About us | Quick links

- Europe & the Agency
- Regulators outside the EU
- Patients and consumers
- Healthcare professionals
- Pharmaceutical industry
- International organisations
- Networks
  - ENCePP
  - Enpr-EMA
    - Enpr-EMA membership
    - Coordinating Group
  - ETPGAH
- Health technology assessment bodies

Home ▸ Partners & Networks ▸ Networks ▸ Enpr-EMA

European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA)

Email Print Help Share

The European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) is a network of research networks, investigators and centres with recognised expertise in performing clinical studies in children.

Enpr-EMA's main objectives are to:

- foster high-quality, ethical research on the quality, safety and efficacy of medicines for use in children;
- enable collaboration between networks and and stakeholders;
- coordinate studies relating to paediatric medicines and avoid unnecessary testing in children;
- build up scientific and administrative competence at a European level;
- help with the recruitment of patients for clinical trials;
- promote European Commission framework programme applications.

Enpr-EMA works by allowing networking and collaboration with members from within and outside the European Union (EU), including academia and the pharmaceutical industry. The network does not perform clinical trials or fund studies or research or decide on areas for paediatric research, as this is the responsibility of Member States, the European Commission or each individual member organisation.

The European Medicines Agency is responsible for ensuring collaboration within Enpr-EMA.

Fostering research on medicines for use in children is one of the objectives of the EU Paediatric Regulation.

Related information

- Medicines for children
- Paediatric Committee
- Paediatric medicine development
- European Network of Paediatric Research at the European Medicines Agency - Background information (22/10/2012)
- Brochure - European Network of Paediatric Research at the European Medicines Agency (21/05/2012)
- Mission statement of the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) (24/02/2012)
- The network of paediatric networks at the European Medicines Agency: Implementing strategy (15/01/2008)

Contact point:

enprema@ema.europa.eu

PIP/waiver presubmission meetings

- To be requested with sufficient advance (at time of Letter of Intent)
- Draft PIP application needed for discussion
- PDCO Rapporteur and Peer Reviewer always invited
- Scope is facilitation of validation and smooth procedure

Ultra-short course on how to prepare a PIP application

or: what has the Agency done to simplify life to applicants?

1) simplified forms (key elements) and opinions
2) New scientific document template (B-E)
3) predictable identification of the right condition (scope of the PIP)
4) How to claim the reward earlier (changing the scope of the PIP)

What to do first

Read the basics – do your homework!

- **Paediatric Regulation** http://bit.ly/tth2CD
- **EC Guideline on Format and Content of PIP applications** http://tinyurl.com/ECGuidancePIP
- **EMA Procedural Advice** http://tinyurl.com/PIPQ-A
- Other documents/guidelines

Other documents: Additional EMA Procedural Guidance

- All Templates and Deadlines for applications http://tinyurl.com/PaedTemplatesDates
- Q&A on PUMAs http://tinyurl.com/PUMAQ-A, published in September 2011
- Q&A on Compliance Check,http://tinyurl.com/CC-Guidance updated 2012
- Guidance (2012) on:
  - Defining the scope of the PIP (“condition and indication”);
  - Changing the scope of PIPs (“merging” and “splitting” PIP decisions)

SIX CORE QUESTIONS

1. Is there a need for the candidate medicinal product in children?
2. If there is a need for paediatric development, what is the condition(s) in which paediatric development should occur, considering the proposed indication(s) in adults?
3. In which age group(s)/paediatric subsets should the development take place?
4. Should there be an adapted formulation and a specific non-clinical package?
5. What clinical measures should the paediatric investigation plan contain?
6. Should measures in the PIP (mainly clinical trials in children) be deferred or not?

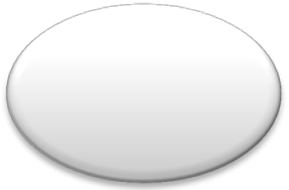
Defining the scope of the PIP

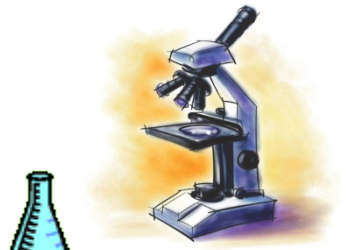
(adult indication and relevant PIP condition)

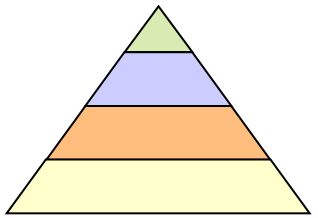
http://bit.ly/Z9Oza9

How to identify the condition of potential paediatric need (scope of the PIP)

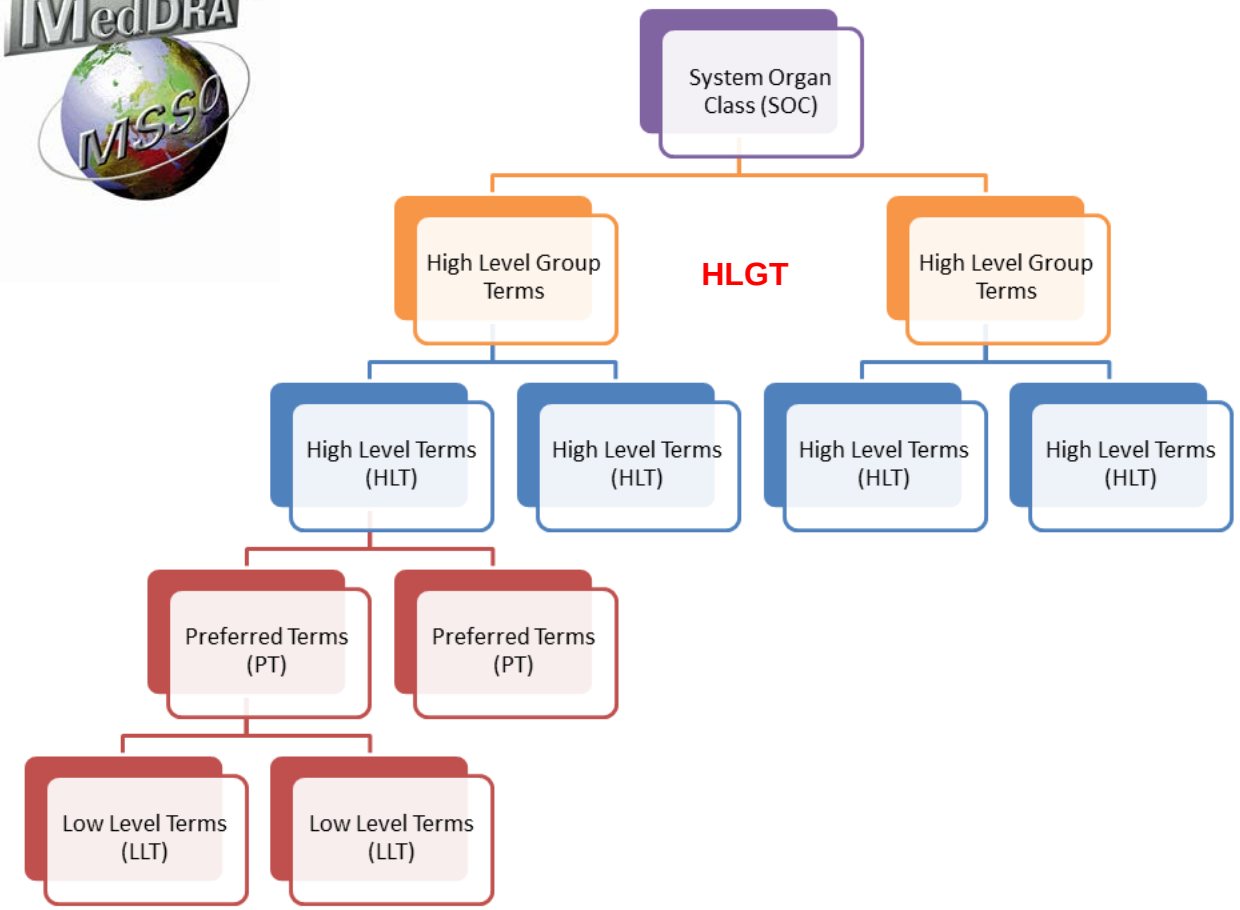
- **Systematic approach based on 3 pillars**:
  - **proposed indication(s) and therapeutic area in adults**
  - **characteristics of the product (mechanism of action)**
  - **hierarchical classification of diseases/conditions**







MedDRA hierarchical structure

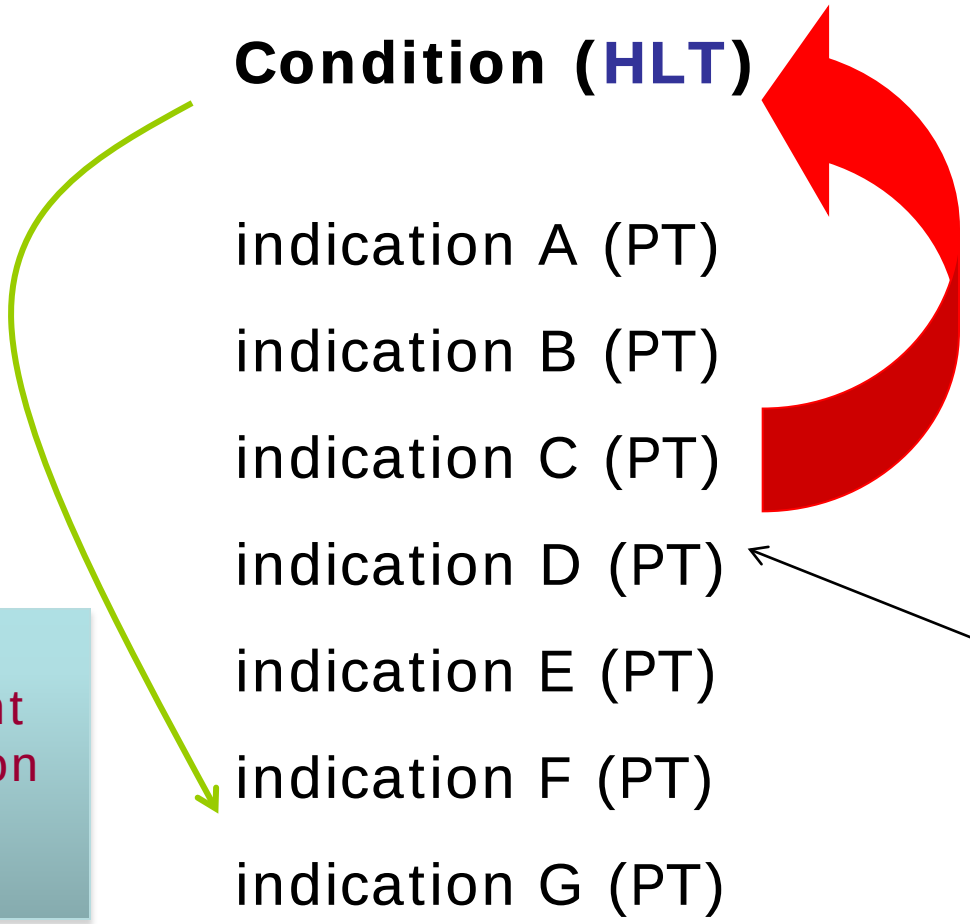


(therapeutic areas)

(conditions)

(indications)

Principle: overarching HLT identified



Step 2: PDCO / Applicant identify HLT as condition of reference (MoA)

Step 1: Applicant proposes indication C in adults

Step 3: PDCO / Applicant identify indication F as best paed indication

Principal Steps

1. Analysis of proposed condition/indication / MOA
2. Determination of HLT *(HLGT or PT exceptionally)*
3. Discussion of Conditions (PTs) included under HLT
4. **Determination of indication to be studied in PIP: 1 PT**
   - Mechanism of action
   - Paediatric use / need
   - As close as possible to indication/condition targeted by applicant
5. **PIP-opinion = HLT, automatically covering all PTs below HLT without further waiver(s) needed**

Structure of the PIP application

(simplification of opinions)

- Section A: Product and Regulatory information

PDF form

- Section B : Targeted conditions / indications and needs General pharmacology, Clinical need by age groups/subsets (with prevalence), Benefit of the product versus alternatives
- Section C : Waiver request
- Section D: Summary of existing data and Development plan Quality, Non-clinical, Clinical (±Risk management Plan), synopses of proposed non-clinical and clinical studies
- Section E: Timelines, deferral request

Word document, free format

- Key elements form: applicant's proposal for opinion

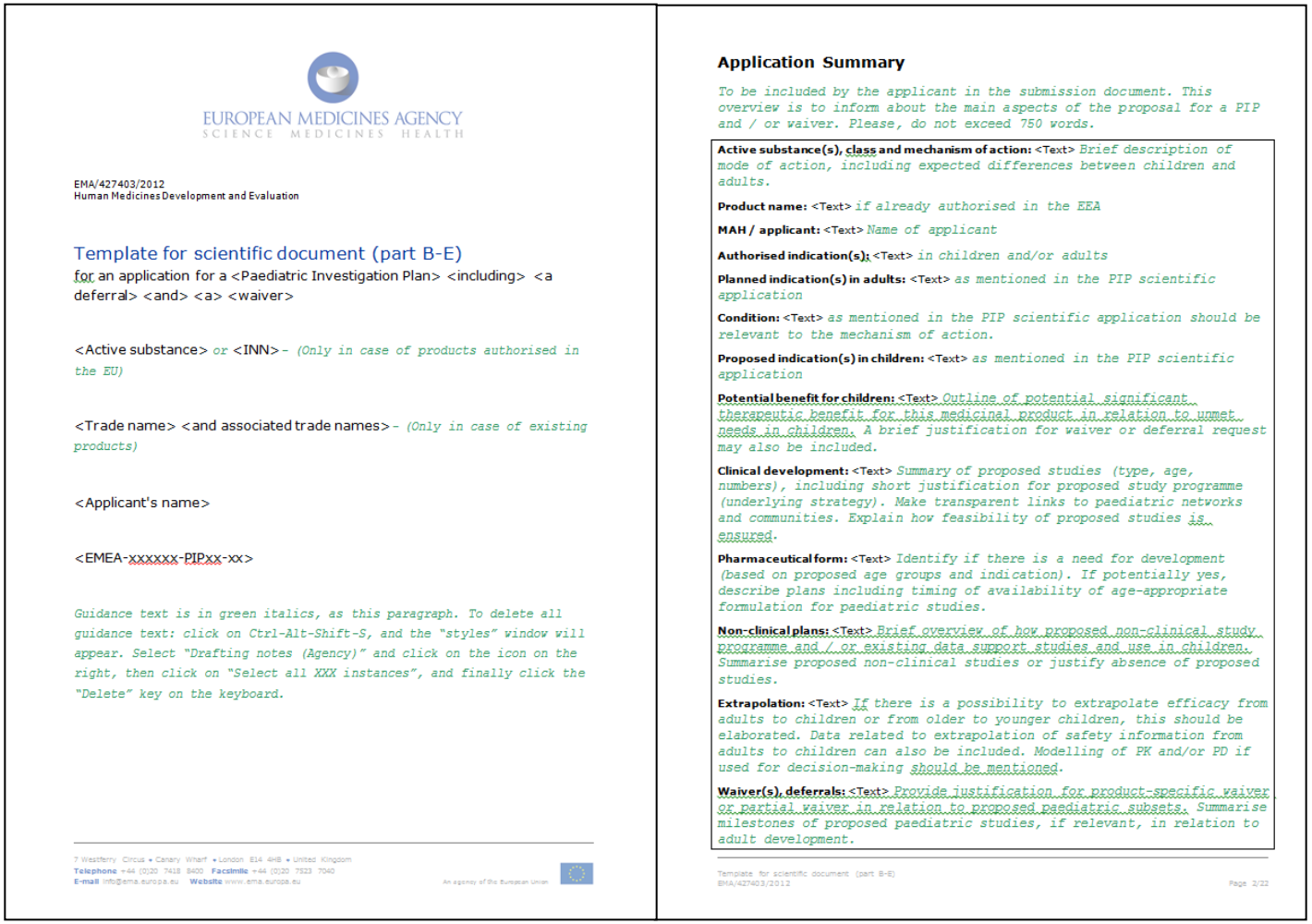
PDF form

Studies: what to put where

- Study synopses/outlines must be provided in PIP application for ALL studies of paediatric relevance, including pharmaceutical and nonclinical studies – AND DEFERRED STUDIES!
- Not (necessarily) a traditional full study protocol.
- From Feb 2013:
- Put **synopses/outline of studies/measures** in the Scientific Document (parts B-E). New template available (http://bit.ly/12821Ox)
- Put **proposed key elements** for the PIP opinion in the new “Key elements” PDF form ()

New template for scientific document (parts B-E)
http://bit.ly/12821Ox

The template does not include tables for quality, non-clinical and clinical studies (applicant is free to use any format)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/427403/2012
Human Medicines Development and Evaluation

Template for scientific document (part B-E)
for an application for a <Paediatric Investigation Plan> <including> <a deferral> <and> <a> <waiver>

<Active substance> *or* <INN> *- (Only in case of products authorised in the EU)*

<Trade name> <and associated trade names> *- (Only in case of existing products)*

<Applicant's name>

<EMEA-xxxxxx-PIPxx-xx>

Guidance text is in green italics, as this paragraph. To delete all guidance text: click on Ctrl-Alt-Shift-S, and the "styles" window will appear. Select "Drafting notes (Agency)" and click on the icon on the right, then click on "Select all XXX instances", and finally click the "Delete" key on the keyboard.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 Facsimile +44 (0)20 7523 7040
E-mail info@ema.europa.eu Website www.ema.europa.eu
An agency of the European Union

Application Summary

To be included by the applicant in the submission document. This overview is to inform about the main aspects of the proposal for a PIP and / or waiver. Please, do not exceed 750 words.

Active substance(s), class and mechanism of action: <Text> *Brief description of mode of action, including expected differences between children and adults.*

Product name: <Text> *if already authorised in the EEA*

MAH / applicant: <Text> *Name of applicant*

Authorised indication(s): <Text> *in children and/or adults*

Planned indication(s) in adults: <Text> *as mentioned in the PIP scientific application*

Condition: <Text> *as mentioned in the PIP scientific application should be relevant to the mechanism of action.*

Proposed indication(s) in children: <Text> *as mentioned in the PIP scientific application*

Potential benefit for children: <Text> *Outline of potential significant therapeutic benefit for this medicinal product in relation to unmet needs in children. A brief justification for waiver or deferral request may also be included.*

Clinical development: <Text> *Summary of proposed studies (type, age, numbers), including short justification for proposed study programme (underlying strategy). Make transparent links to paediatric networks and communities. Explain how feasibility of proposed studies is ensured.*

Pharmaceutical form: <Text> *Identify if there is a need for development (based on proposed age groups and indication). If potentially yes, describe plans including timing of availability of age-appropriate formulation for paediatric studies.*

Non-clinical plans: <Text> *Brief overview of how proposed non-clinical study programme and / or existing data support studies and use in children. Summarise proposed non-clinical studies or justify absence of proposed studies.*

Extrapolation: <Text> *If there is a possibility to extrapolate efficacy from adults to children or from older to younger children, this should be elaborated. Data related to extrapolation of safety information from adults to children can also be included. Modelling of PK and/or PD if used for decision-making should be mentioned.*

Waiver(s), deferrals: <Text> *Provide justification for product-specific waiver or partial waiver in relation to proposed paediatric subsets. Summarise milestones of proposed paediatric studies, if relevant, in relation to adult development.*

New template for scientific document (parts B-E)
http://bit.ly/12821Ox

The template however includes tables for modelling and simulation studies and for extrapolation studies, to guide on the level of detail

modelling and simulation

If modelling and simulation studies are planned as a substantial (or exclusive) part of the PIP, use the following format in this document. In the Key elements form (PDF file), please, list the key elements of substantial M/S studies using the clinical study table.

Modelling and simulation study name	*Insert here a descriptive name for the study*
Model Objective	*Model objective/s must be specified. Choose from: Study optimisation, Data analysis, Dose finding, Decision making.*
Model Description	*Type of model must be specified:* *-Population PK /(PD) model,* *-Physiologically based PK /(PD) model,* *-Mechanistic model,* *-Exposure response model,*
Data to be used to Build Model	*This must describe the type of data used to build the model. This includes data from: Literature, In vitro, Non-clinical, Adult and Paediatric data.* *Studies and literature references must be listed with the following format:* *Type of data (e.g. PK, PD, Clinical efficacy, Safety)* *Age subsets providing data,* *Number of patients/participants,* *Sampling time-points (model could employ random sampling points).* *Number of samples per patient,*
Model Building Methodology & Software	*This must describe the approach used to build model. Choose from:* *-Step up (Physiologically based)* *-Step down (Population based)* *Software used must be detailed.*
Covariates	*Provide a discussion on covariates. These must include at least: Age, Body Surface Area, and Weight.*
Model Qualification	*This must describe both the internal and external qualification used to validate the model assumptions and make adjustments.*
Date of completion of study	*Provide month and year; a date is always necessary.*

extrapolation

<Text>

If an extrapolation study is planned as a substantial (or exclusive) part of the PIP, use the following format in this document. In the Key elements form (PDF file) list the key elements of substantial extrapolation studies using the clinical study table.

Study identifier(s)	Measure to extrapolate efficacy to the paediatric population	Comments
Type of study, study design	Analysis of existing in house and literature data on <medicine / mechanism of action / class of medicines> and on concerned conditions	
Study objective(s)	• To provide / support efficacy assumptions in the paediatric population based on extrapolation <perhaps add some specificities, e.g. from (source population)> • Target population: Children aged from birth to less than 18 years of age	
Methodology	• To present data supporting the assumption that the outcome of treatment is likely to be similar in paediatric subsets by age and by any other relevant characteristics compared to adults • To model and to evaluate pharmacokinetic, pharmacodynamic, response and efficacy data in adults and pharmacokinetic data in children <as well as data on the maturational profile of these parameters and using results from a physiology-based model>	
Study population and subset definition (incl. stratification)	• <disease / population description, studies done, registries, data sources in adults> • <as above with "children" in case any paediatric data should also be used>	
Number of study participants by paediatric subset (e.g., age, sex, stratum)	<"quantity" of data in adults, number of patients etc. >	
Date of initiation		
Date of completion (last patient, last visit)		

Comments:

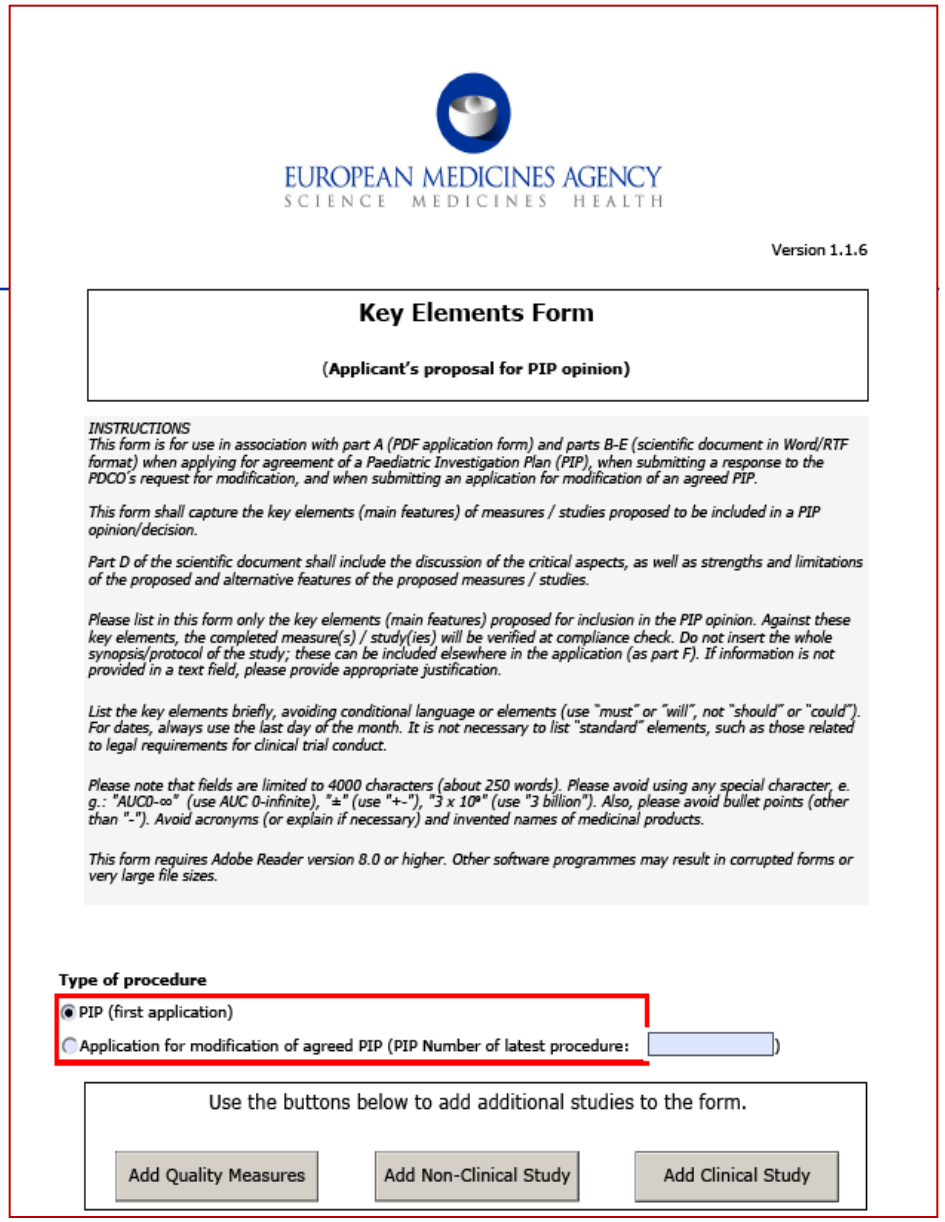
Paediatric Co-ordinator:

<Text>

Rapporteur:

Key elements form

- **Applicants should list here what their proposal is for the key elements of the opinion**
- **EMA/PDCO will use the proposal in the preparation and draft of the PDCO opinion**



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Version 1.1.6

Key Elements Form

(Applicant's proposal for PIP opinion)

INSTRUCTIONS
This form is for use in association with part A (PDF application form) and parts B-E (scientific document in Word/RTF format) when applying for agreement of a Paediatric Investigation Plan (PIP), when submitting a response to the PDCO's request for modification, and when submitting an application for modification of an agreed PIP.

This form shall capture the key elements (main features) of measures / studies proposed to be included in a PIP opinion/decision.

Part D of the scientific document shall include the discussion of the critical aspects, as well as strengths and limitations of the proposed and alternative features of the proposed measures / studies.

Please list in this form only the key elements (main features) proposed for inclusion in the PIP opinion. Against these key elements, the completed measure(s) / study(ies) will be verified at compliance check. Do not insert the whole synopsis/protocol of the study; these can be included elsewhere in the application (as part F). If information is not provided in a text field, please provide appropriate justification.

List the key elements briefly, avoiding conditional language or elements (use "must" or "will", not "should" or "could"). For dates, always use the last day of the month. It is not necessary to list "standard" elements, such as those related to legal requirements for clinical trial conduct.

Please note that fields are limited to 4000 characters (about 250 words). Please avoid using any special character, e. g.: "AUC0-∞" (use AUC 0-infinite), "±" (use "+-"), "3 x 10⁹" (use "3 billion"). Also, please avoid bullet points (other than "-"). Avoid acronyms (or explain if necessary) and invented names of medicinal products.

This form requires Adobe Reader version 8.0 or higher. Other software programmes may result in corrupted forms or very large file sizes.

Type of procedure

◉ PIP (first application)
○ Application for modification of agreed PIP (PIP Number of latest procedure:)

Use the buttons below to add additional studies to the form.

Add Quality Measures | Add Non-Clinical Study | Add Clinical Study

Key elements form Clinical measure (trial)

Clinical studies (currently 1 study)

Summary of proposed clinical study, to be included in the PIP

Remove this study ▲
Insert study below ▼

PIP study number
1361906420718

Study Identifier (for referencing older studies)

Study is
Type of study
Design
Type of control
Objective
Randomisation
Blinding
Minimum number of paediatric participants

Main study design features and objectives

Study population and subset definition

Number of study participants by paediatric subset

Study duration for participants

Dosage, treatment regimen, route of administration

Control(s)

Primary endpoint(s) with time(s) of assessment

Main secondary endpoint(s) with time(s) of assessment

Statistical plan including study conduct and analysis

Other

Plan for specific follow-up

External Data Safety Monitoring Board (yes / no)

Date of initiation
Additional dependencies:

Deferral for initiation requested? ○ Yes ○ No

Date of completion
Additional requirements:

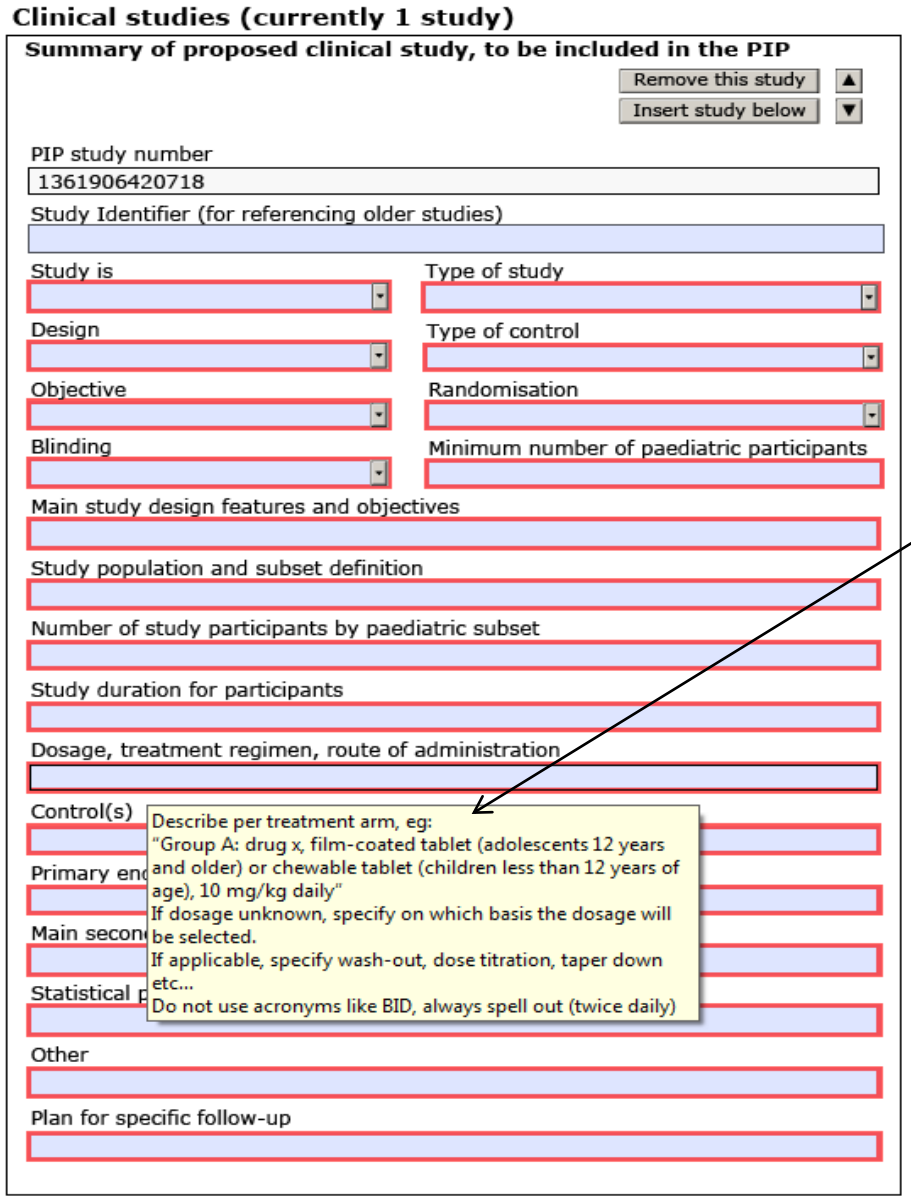
Deferral for completion requested? ○ Yes ○ No

Use the buttons below to add additional studies to the form.

Add Quality Measures | Add Non-Clinical Study | Add Clinical Study

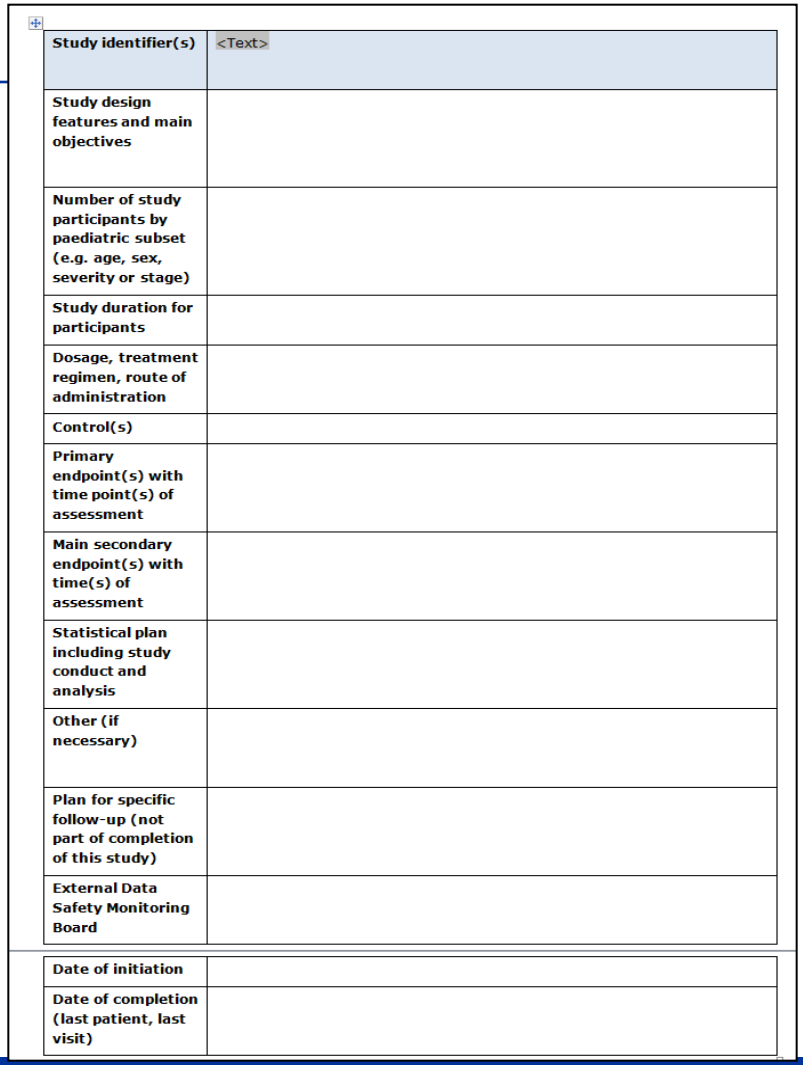
Key elements form Clinical measure (trial)

- Hovering with the mouse over a field shows specific guidance



The PDCO will then adopt an opinion using the simplified template

- Already in use since December 2012
- Reduced number of fields and simplification of details
- The website has the old version – to be updated soon
- The template for clinical studies key elements has only 13 fields



Study identifier(s)	<Text>
Study design features and main objectives	
Number of study participants by paediatric subset (e.g. age, sex, severity or stage)	
Study duration for participants	
Dosage, treatment regimen, route of administration	
Control(s)	
Primary endpoint(s) with time point(s) of assessment	
Main secondary endpoint(s) with time(s) of assessment	
Statistical plan including study conduct and analysis	
Other (if necessary)	
Plan for specific follow-up (not part of completion of this study)	
External Data Safety Monitoring Board	
Date of initiation	
Date of completion (last patient, last visit)	

Changing the scope of the PIP
("merging" and "splitting" PIP decisions for condition)
http://bit.ly/R2UERw

When is “merging” / “splitting” PIP decisions indicated?

- **“Merging”:** may be compulsory if regulatory application involves 2 or more conditions (routes, ph. forms) that are dealt in separate PIPs
  - ✓ To comply with art 7/8 at MA/variation/LE application
- **“Splitting”:** always optional. Needed if company wants to (potentially) benefit from an earlier reward, for completing the PIP only for one condition (route, ph form), when the original agreed PIP included 2 or more
- In both cases: procedure of modification of agreed PIP necessary

Principle on requirement for single PIP decision ("merging" PIP decisions

- The EMA will not accept in a regulatory application (or applications submitted at the same time) the submission of independent PIP Decisions (i.e. without cross-reference), as the tracking of such situations would be impossible to manage by the EMA or national competent authority.
- Multiple PIPs:
  - ✓ are possible
  - ✓ they may allow an earlier reward, but:
  - ✓ May not satisfy the requirement of art. 8 (PIP decision has to address existing and new indications, routes and ph. forms).

"Merging" PIP decisions

- Done via a procedure of modification of an agreed PIP (any of the existing ones) – but will be specified in the decision
- Other PIP decision still valid
- The "modified" PIP opinion does not change (unless modifications also for the existing PIP)
- Decision has new sentence:

  This agreed PIP covers all conditions, indications, pharmaceutical forms, routes of administration, measures, timelines, waivers and deferrals, as agreed in PIP EMEA-XXXXXX-PIPYY-ZZZZ(-M0X) (decision P/XX/20YY) including subsequent modifications thereof.

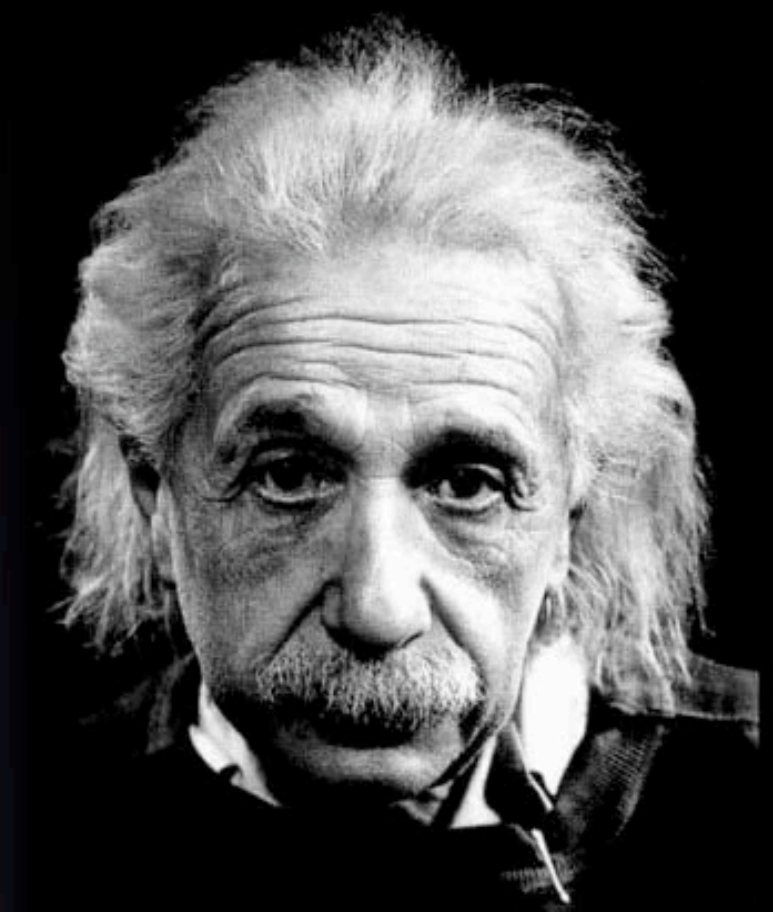
“Splitting” PIP decisions

- **PIP eligible for the reward (“reward PIP”)**: the PIP which is triggered by the first regulatory procedure submitted by the applicant (after the first PIP is agreed)
- PIP 1 containing conditions A and B: modification procedure needed to remove either A or B from PIP
- If development is continuing for both (albeit not simultaneously): applicant to request new PIP for removed condition at the same time

Conclusion

"Everything should be made as simple as possible, but not simpler."

Albert Einstein



Still uncertain?

- Call or write to your Paediatric Coordinator (EMA Scientific Administrator assigned to the procedure), or:
- Write to paediatrics@ema.europa.eu
- The friendly Paediatric Medicines team will answer

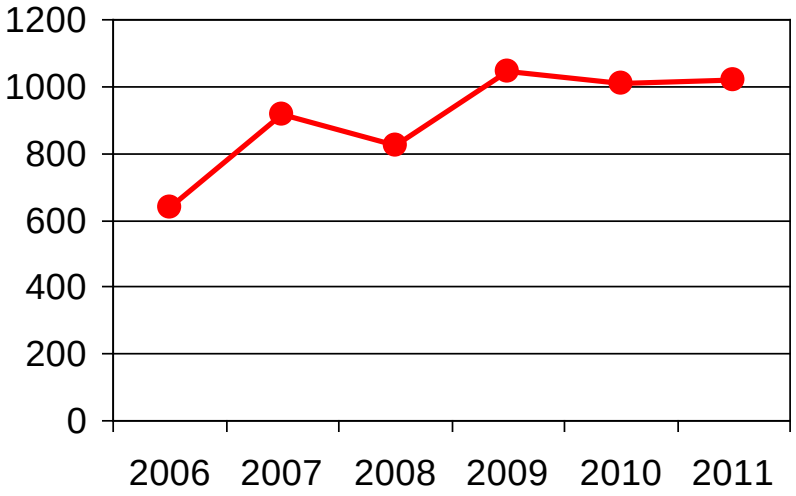
Backup slides

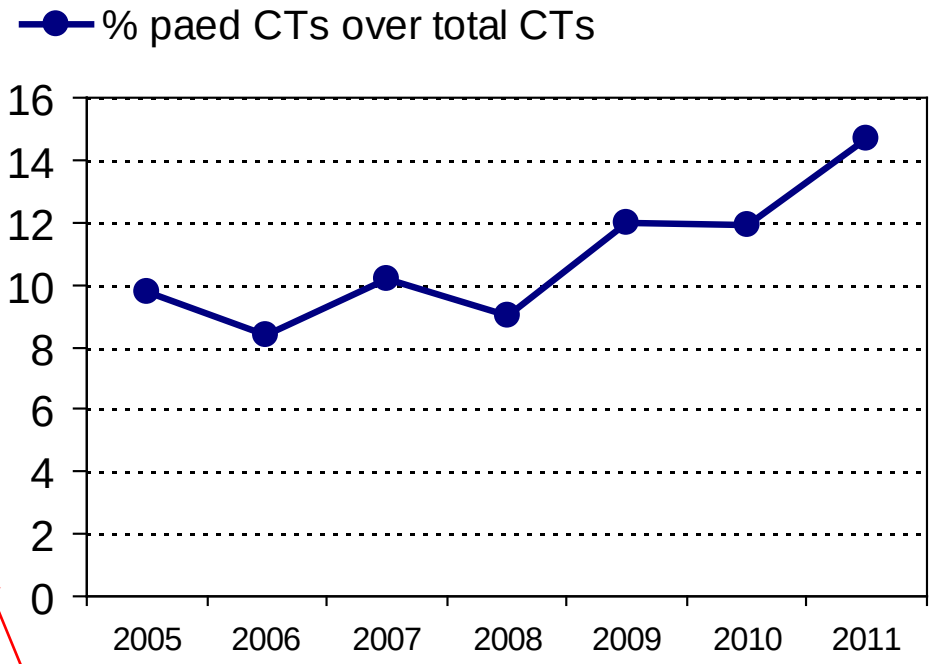
Bridging adults → children: "complete" vs. "partial" extrapolation

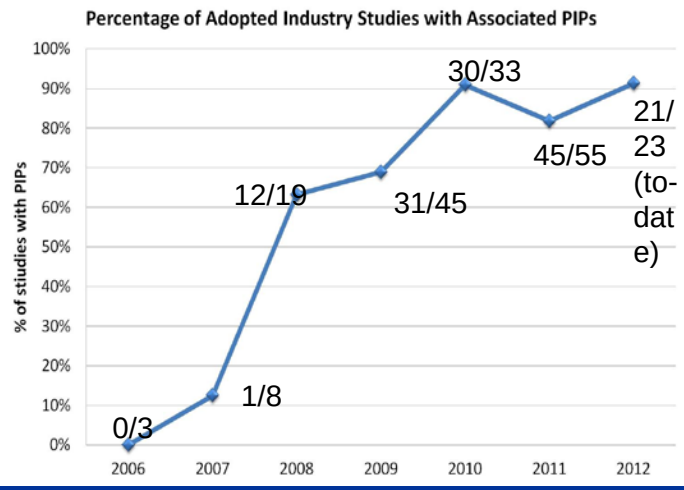
- Extreme view: anything less than 2 fully powered confirmatory trials is extrapolation
- "partial" extrapolation is highly prevalent, albeit unacknowledged. Examples:
  - One-sided vs. two-sided significance tests and/or higher p values allowed in specific situations
  - Bayesian methods
  - One confirmatory study only
  - No confirmatory study (orphan conditions)
  - Registration after failed superiority vs placebo (but superiority vs active comparator demonstrated)

5-year results of Paediatric regulation

More studies in children







%CTs including children in EudraCT

N. of CTs incl. children in EudraCT

% of paediatric CTs that are in PIPs (MCRN UK)

5-year results of Paediatric regulation

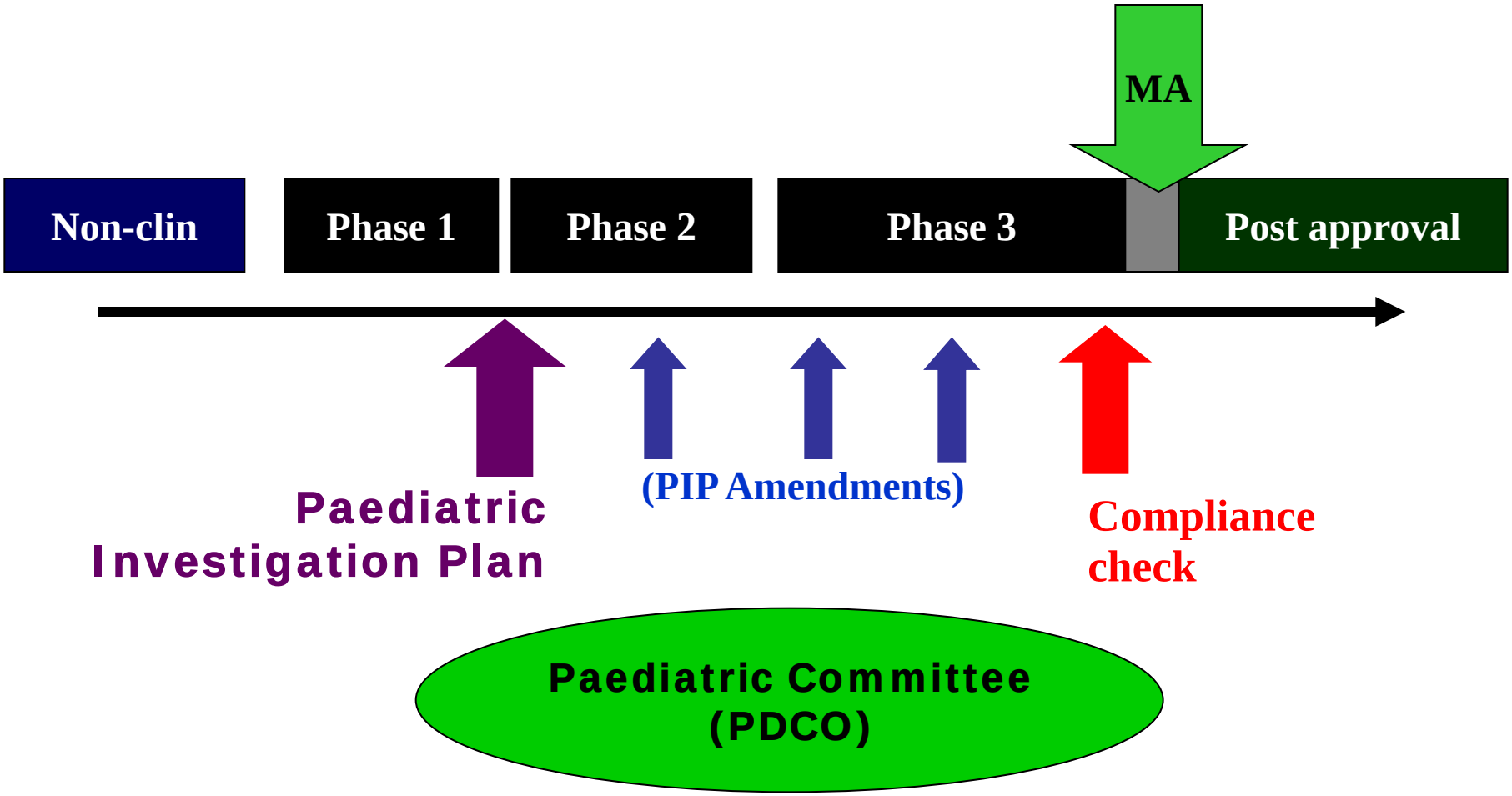
More medicines for children

- **Linked to Paediatric Regulation (centrally / nationally):**
  - **13 new medicines for paediatric use (10 / 3)**
  - **30 new paediatric indications (18 / 12)**
  - **9 new pharmaceutical forms relevant for children (3 / 6)**
- **Incentives:**
  - **Supplementary protection certificates extended in 16 Member States concerning 11 medicines**
  - **1 PUMA only (1 ongoing)**
- **PIPs are progressing without reported issues in >50%**
- **Good overlap between agreed PIPs and off-label use (survey)**

Main roles of PDCO

- To adopt opinions on PIP/waivers (decision signed by EMA Executive Director, not by EU Commission)
- To provide advice on any question relating to paediatric medicines (at the request of the Agency's Executive Director or the European Commission)
- To assess data generated in accordance with agreed PIP, to adopt opinions on the quality, safety or efficacy of any medicine for use in the paediatric population (at the request of the CHMP or a national competent authority)

When should the PIP be requested?



Deferral(s):

Instrument to avoid delaying marketing authorisation in adults

"Deferred" means Marketing Authorisation Application for adults is possible before initiation/completion of one or more measures in the PIP

- **Given by study/measure** (cfr US PREA: "total" deferral)
- **For initiation and/or completion of study/measure:** completion of a clinical trial may be deferred, but initiation may not be!
- **Completion dates established**

Paediatric Use Marketing Authorisation

- New dedicated type of Marketing Authorisation application (MAA) for exclusive paediatric use
- Intended for off-patent medicinal products:
- Incentives:
  - 10 year marketing protection (compliance with agreed PIP necessary) on data contained in the PUMA
  - Fee reductions for Marketing Authorisation

- Studies funded by European Commission (Framework Programme), chosen from a priority list of off-patent drawn by EMA (public private partnership, 75 m€ so far)

PUMA

- Results so far rather disappointing
- 25 to 35 PIP applications for possible PUMA

  (difficult to say as PIP application for new product + possible PUMA not identifiable)
- 3 PUMA applications so far
- Incentive is weak (data protection + market protection) and limited to the paediatric data