The New Paediatric Regulation - Establishment and Role of the Paediatric Committee (PDCO)

DGRA.e.V Bonn
June 2007

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CHMP Chair / EMEA

Plan

- Legislative Process
- Paediatric Committee (PDCO)
- Paediatric Investigation Plan (PIP)
- Interactions

Plan

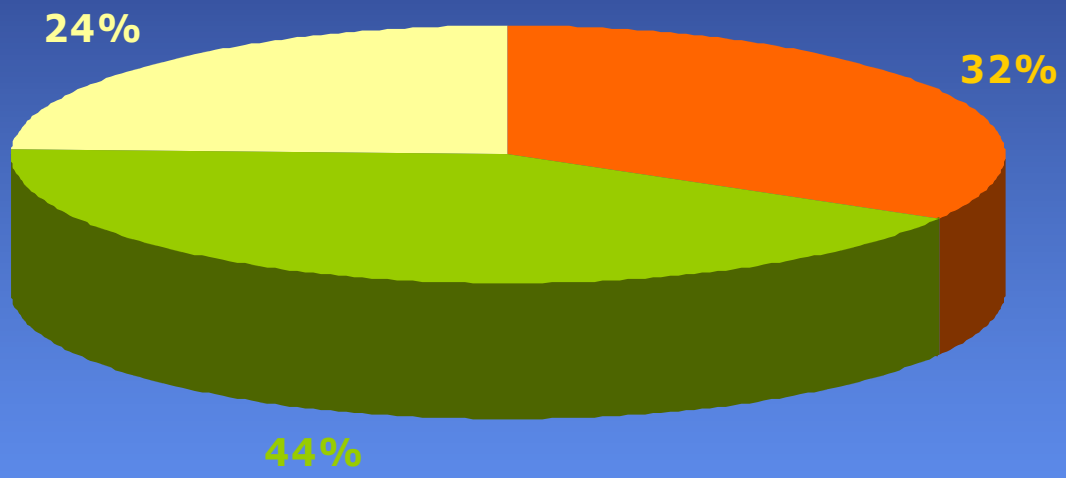
- **Legislative Process**
- **Paediatric Committee (PDCO)**
- **Paediatric Investigation Plan (PIP)**
- **Interactions**

Legislative Initiative

- First European publications in the 80's
- European Commission Round Table, EMEA, December 1997
- European Council Resolution in Dec 2000
- Consultation and Extended Impact Assessment 2000-2004
- Adoption of Draft Regulation by European Commissioners in September 2004

Paediatric Medicines Were Still not Studied

Number of active substances: 258 (1995 - January 2006)



EMEA data

Legislative Process

- First readings in European Parliament and Council 2004-5
- Second readings in European Parliament and Council, December 2005 to June 2006
- Vote in European Parliament, 1 June 2006
- Final steps in Council and Parliament Oct-Nov 2006

- Publication of Regulation expected December 2006
- Entry into force January 2007 but staggered implementation

Objectives of the 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 authorisation for adults**

Main Pillars

- Creation of a Paediatric Committee at EMEA
- Measures for patented medicinal products
- Measures for off-patent medicinal product

For yet Unauthorised Products

Patent-protected products

- **Obligation to submit results of agreed Paediatric Investigation Plan at time of marketing authorisation, or variation (i.e. new indication, route of administration, or pharmaceutical form)**

- **Reward**
  - 6 months extension of the Supplementary Protection Certificate (= patent protection)

For 'Old' Products

Off-patent products not covered by a patent or supplementary protection certificate

- **Optional procedure**
- **Paediatric Use Marketing Authorisation (PUMA)**
  - **Paediatric Investigation Plan needed**
  - **Formulation + paediatric indication(s) only**

Old products (2)

Incentive

- 10 years data protection/exclusivity (as for new products)
- Possible use of existing brand name (brand recognition)

Orphan Drugs

- 15-20% of rare diseases affect children only, 55% affect adults and children

- **Reward**

  2 years of market exclusivity added to existing 10 years, if development in accordance with Paediatric Investigation Plan

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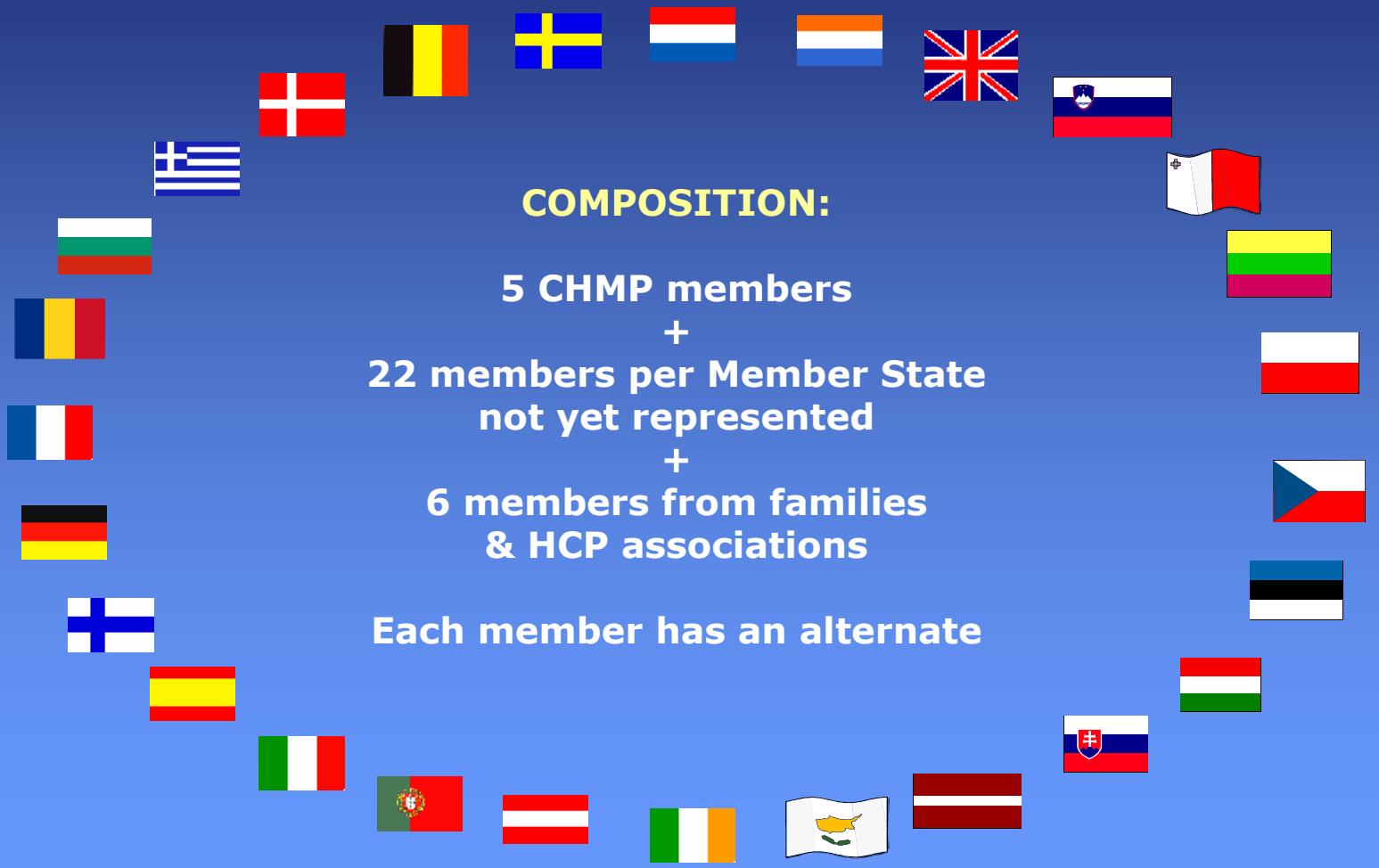
PDCO



COMPOSITION:

5 CHMP members
+
22 members per Member State not yet represented
+
6 members from families & HCP associations

Each member has an alternate

Paediatric Committee

- 6 months to establish (i.e. before July 2007)
- Expertise in all aspects related to medicines for children
  - Pharmaceutical development
  - Paediatric medicine
  - General practitioners
  - Paediatric pharmacy
  - Paediatric pharmacology
  - Paediatric research
  - Pharmacovigilance
  - Ethics and public health

Tasks of PDCO (1)

- **Paediatric Investigation Plans (more than 200 announced in 2007)**
  - **Assessment (on basis of EMEA summary report)**
  - **Deferrals**
  - **Modifications**

- **Waivers (more than 80 announced in 2007)**
  - **Product and condition (severity?)**
  - **Public list of waivers**

  About 300 procedures from questionnaire to EMEA MAH/MAA, but likely to be more as not all companies have understood the scope

- **Compliance checks**

Tasks of PDCO (2)

Use as Expert Group by and for CHMP

- **Scientific Advice (158 announced in 2007)**
  - **No paediatric expertise in SAWP**
  - **Duplication of expertise to be avoided**
  - ***Use of PEG has proved useful but limited number of experts for areas covered, and workload***

- **'SAG' or expert source for marketing authorisation applications (60-70% of new products with paediatric interest)**

Tasks of PDCO (3)

- Paediatric Needs Inventory: Criteria for survey of use (off label) by Member State
- Support and Advice on the European Network establishment
- Experts for DG Research? (FP7 funding)

Tasks of PDCO (4)

- Advice on "communication of arrangements available for conducting research into medicinal products for paediatric use", which corresponds to Eur. Parliament's wish for PDCO to promote participation in /educate on clinical research
- Advice to Commission, or to EMEA Executive Director on an ad-hoc basis
- Opinion on symbol for paediatric products

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- Paediatric Investigation Plan (PIP)
  - Submission
  - Timing
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Paediatric Investigation Plan

- **Basis for the development and authorisation of a medicinal product for the paediatric population subsets**
- **Include details of the timing and the measures proposed to demonstrate**
  - **Quality**
  - **Safety**
  - **Efficacy**

Marketing Authorisation Criteria

+ Any proposed adaptation of the medicinal product

Version January 2007

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

Comments should be e-mailed as word documents using the template to Peter Arlett at the European Commission (peter.arlett@ec.europa.eu)

Definitions

Paediatric Investigation Plan (PIP) indication:

- **The proposed indication(s) in the paediatric population for the purpose of a PIP and at time of PIP submission**
- **It should specify if the medicinal product is intended for diagnosis, prevention or treatment of a condition**

Definitions

***Proposed* therapeutic indication:**
The therapeutic indication in adults and/or paediatric populations as proposed by the PIP applicant at the time of submission of the PIP.

***Granted* therapeutic indication:**
The therapeutic indication in adults and/or paediatric populations that is included in the MA. This will be the result of the assessment of the Q/S/E data submitted with the MA application.

Definitions

ICH E11

- **Birth - 27 days: pre-term and term neonate**
- **1 month (28 days) - 23 months: infant**
- **2 years - 11 years: child**
- **12 years - 17 years: adolescent up to 18th birthday**

Subsets

- Can differ, but the use to be justified

Principles

1. Same application (form) for PIP/Waiver/Deferral/ Combination
2. Applications to cover all subsets of the paediatric population
3. Applications (Article 8) to cover all existing and new indications but in *one* PIP
4. All relevant information (+ or – to the product) to be included in the dossier, in particular incomplete/discontinued pharmaco-toxicological test/CT
5. The assessment of
   - Significant therapeutic benefit
   - Fulfilment of therapeutic needs

   to be assessed in the light of any other relevant information

Administrative and Product Information (1)

Part A

1. Name, address of the applicant (contact person)
2. Name of manufacturer (of active substance/ medicinal product)
3. Name of active substance (INN)
4. Type of product (chemical, biological, vaccine… / target, mechanism of action)
5. Details (strength, form, route of administration…)

Administrative and Product Information (2)

Part A

6. Regulatory status in the EU
   - MA status (including refusals)
   - Authorised indications/routes/dosage forms
   - Information on CTs within EU
   - Scientific advices (SAWP – National)
   - Restrictions (in any EEA…)
7. Regulatory status outside EU (including refusals)
   - Worldwide
   - Adult/Paediatric
   - Any third advice of any type in third countries on paediatric development

Administrative and Product Information (3)

Part A

8. Conditions according to ICD – IO
9. Proposed therapeutic indication (+ATC code)

Overall Development

Information on Target Diseases/Conditions

Part B

1. Discussion on similarities/differences between ***populations*** (adults versus paediatric [subsets])
2. Discussion on anticipated similarities/differences on ***the effect*** of the product (adults versus paediatric [subsets])
3. Prevalence/incidence in the paediatric population
4. Current methods of diagnosis/prevention/treatment in the paediatric population (including [unauthorized] standard of care)
5. Significant therapeutic benefit, fulfilment of therapeutic need (decision to go for a PIP/waiver)

Basis for Significant Therapeutic Benefit

a) Improved efficacy upon the existing
b) Substantial improved safety profile
c) Better dosing scheme/method of administration
d) Availability of relevant age-appropriate formulation
e) New/relevant clinical knowledge of better use
f) Different mechanism of action

- At this (early) stage of development, such claims could be based on 'well justified' and plausible assumptions
- If not, consider waiver/deferral
- Refer to the inventory when appropriate

Applications for Waivers

Part C

1. Scope
   - Age range/subsets
   - Pharmaceutical form
   - Route of administration
2. Grounds
   - Based on efficacy/safety (justify lack of E/S risks)
   - Based on condition/disease (in adults 'only'!?)
   - Based on lack of significant therapeutic benefit

PIP

Part D1

Overall strategy proposed by the applicant:

- **Indication**
- **Selected age groups**
- **Outline of the quality/(non)-clinical data**
- **Extrapolation/interrelation between adult/paediatric**
- **Existing paediatric information**
- **Significant therapeutic/fulfilment of therapeutic need**

Strategy in Relation to Quality

Part D2

- Need for a specific formulation/dosage form in relation to age group
- Availability/timeframe of the formulation/ dosage form
- Appropriateness to age subsets (device, food…) (suitability)

Strategy in Relation to Non-clinical Aspects (S)

Part D3

- **Pharmacology**
  - **Proof of concept**
  - **PD studies**
  - **Safety pharmacology**
- **PK**
  - **Juvenile animals**
- **Toxicology**
  - **Juvenile animals (species)**
  - **Specific endpoints (neuro-, nephro-, tox…)**
  - **Local tolerance (topical…)**

Strategy in Relation to Clinical Aspects (E)

Part D4

Appropriateness of clinical endpoints

- **PD**
  - Difference adults/paediatrics
  - Extrapolations
  - Need for specific studies
  - Biomarkers(?) for PK(?) , for PD(?)
- **PK**
  - Extrapolations from adults/older groups
  - Bridging studies (adults/older groups)
  - Need for specific studies
  - Population PK
  - Interactions (?) possibility to extrapolate, effects of pharmacogenetics

Strategy in Relation to Clinical Aspects (E)

Part D4

Appropriateness of clinical endpoints

- **Efficacy/safety studies**
  - **Dose finding studies**
  - **Relevance of age-appropriate endpoints**
  - **Use of surrogate markers**
  - **Need short/long term safety studies**
  - **Need for studies in the post-authorisation phase**
- **Technicalities**
  - **Less invasive techniques**
  - **SMB**
  - **Recruitment**

Planning for Development

Part D5

1. Overall summary table (all studies)
2. Outline of each study/steps in development
3. Synopsis of protocols of non-clinical
4. Synopsis of protocols of clinical
   - Type of study/control
   - Design
   - Location
   - Test product/regimen/route
   - Number of subjects
   - Duration of treatment
   - Main in-ex/clusion criteria
   - Endpoints
   - Sample size/power calculations
   - Recruitment issues, interim analyses…
   - Statistical methods

Timeline of Measures in PIP

Part D6

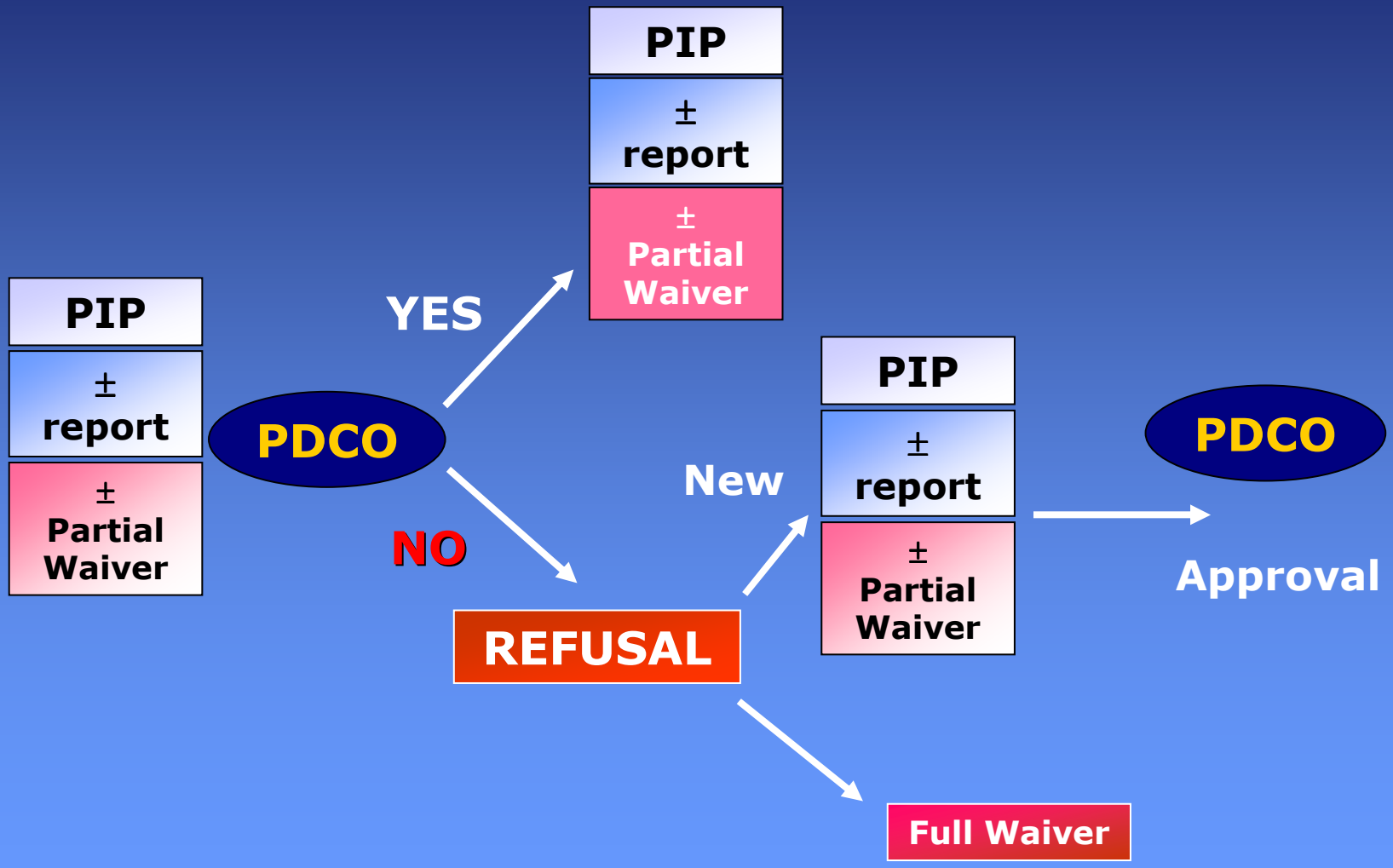
- Detailed timelines
- Compared to the adult development
- Predicted timing of applications
- Timelines of initiation/completion of each measure

Deferrals

Part E

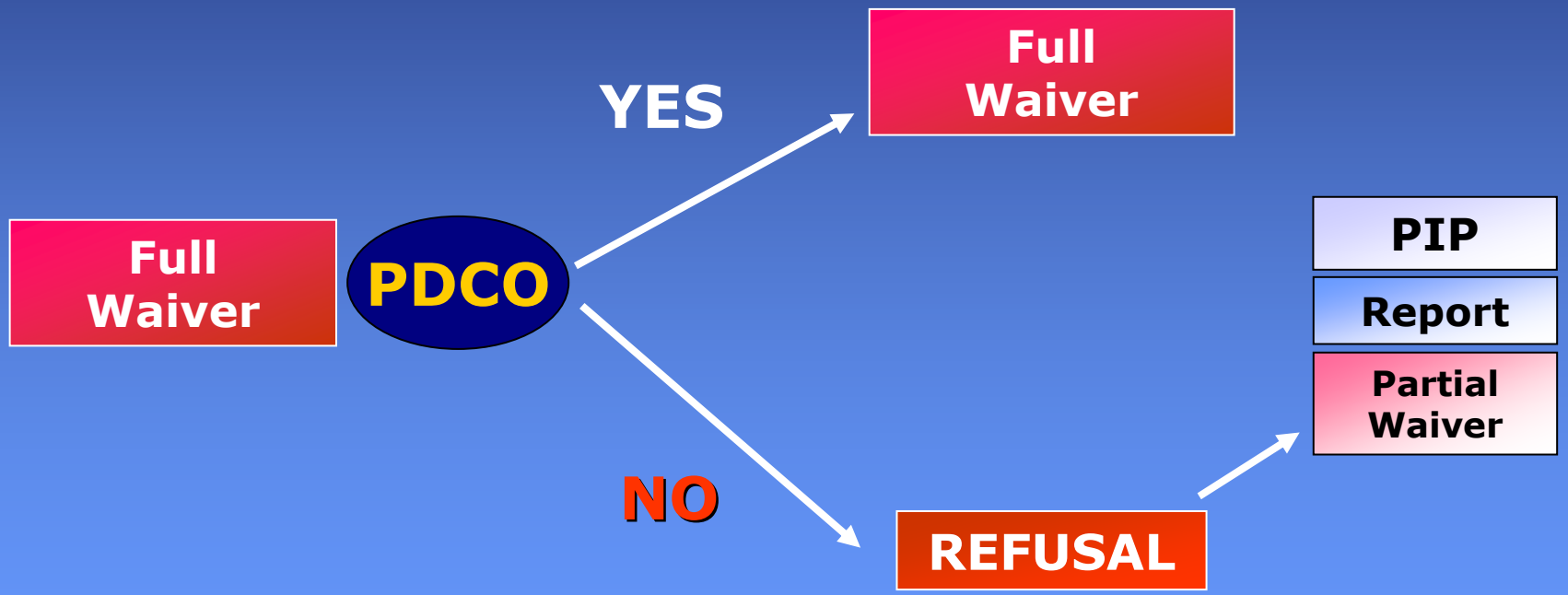
- Specify indication/route/form
- Specify age group to which it applies
- Justify
  - Conduct in adults prior to the paediatric population
  - Longer duration in paediatric populations
  - Need for additional non-clinical data
  - Difficulties to develop timely a relevant formulation

Request of PIP



Full waiver = no reward

Request for Waiver



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Annexes

Part F

- References of published literature
- Investigation brochure
- Previous opinions on competent authorities
- Information of an authorised product

Amendments of PIP

The same template to followed, mentioning the changes in the relevant sections.

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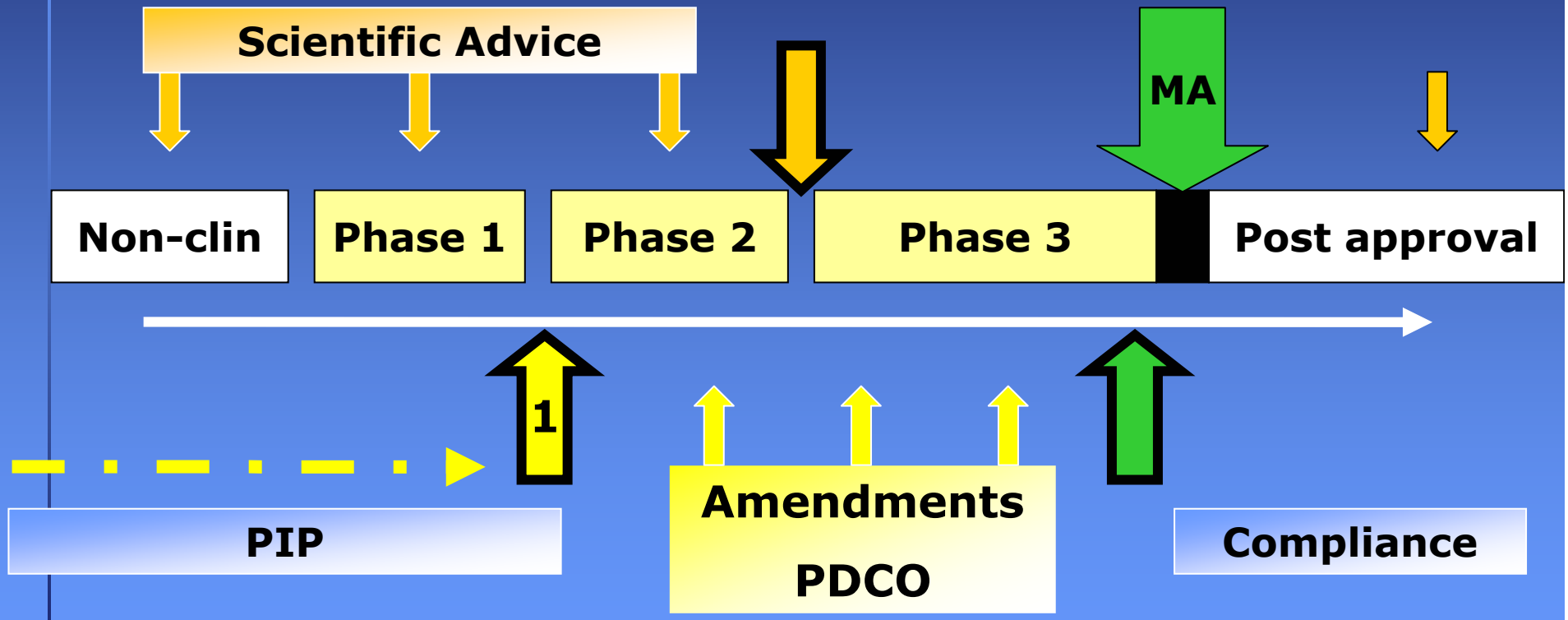
Timing Consultation of PDCO



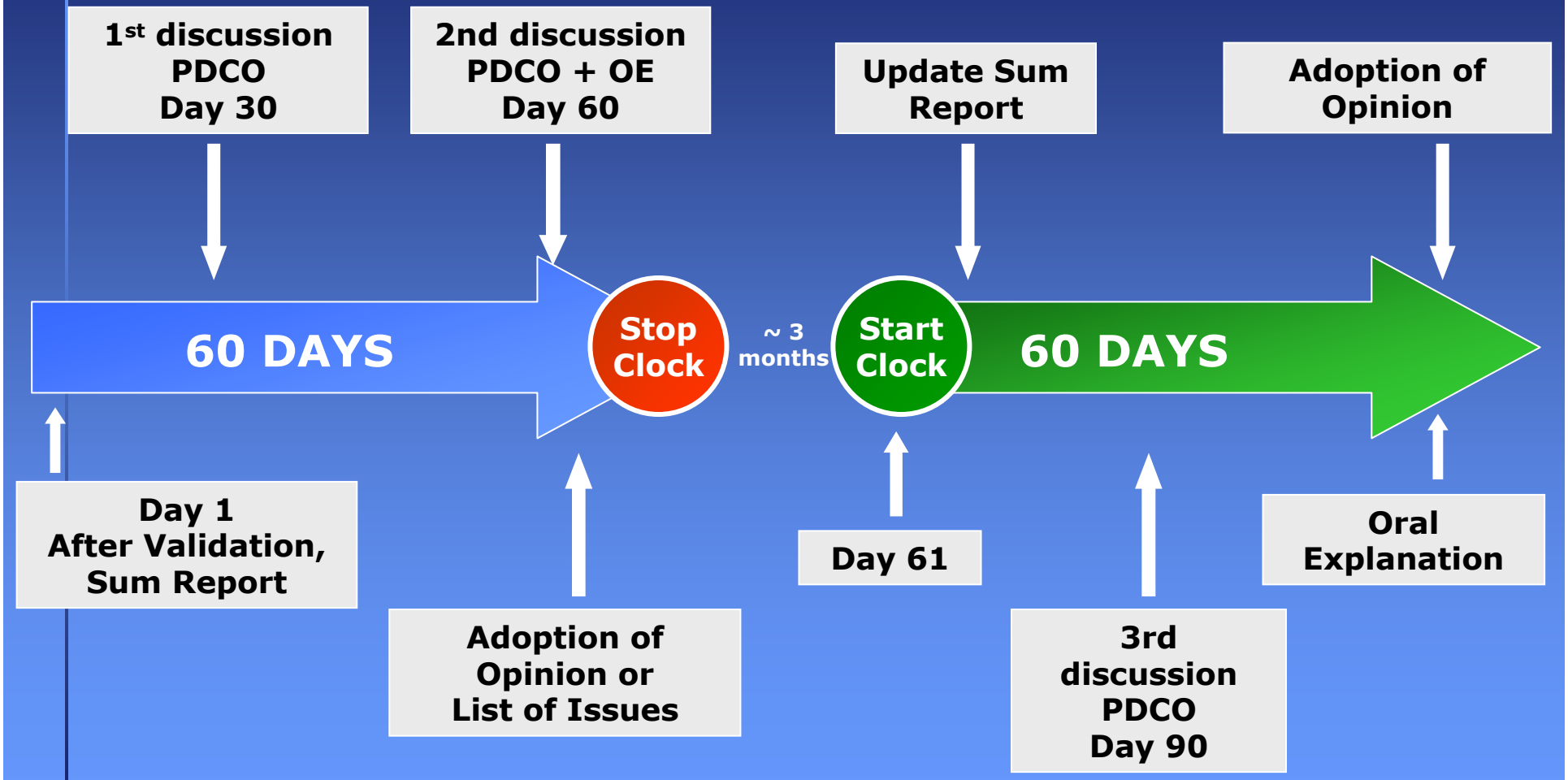
PIP Procedure

Pre-submission meeting Intent to file	- 3 months
Validation & preparation of Summary Report by the EMEA	30 days
Opinion PDCO on PIP	60 days
Optional extension	60 days
Opinion to applicant	10 days
Request for re-examination	30 days
FINAL decision EMEA	10 days
TOTAL	200 days

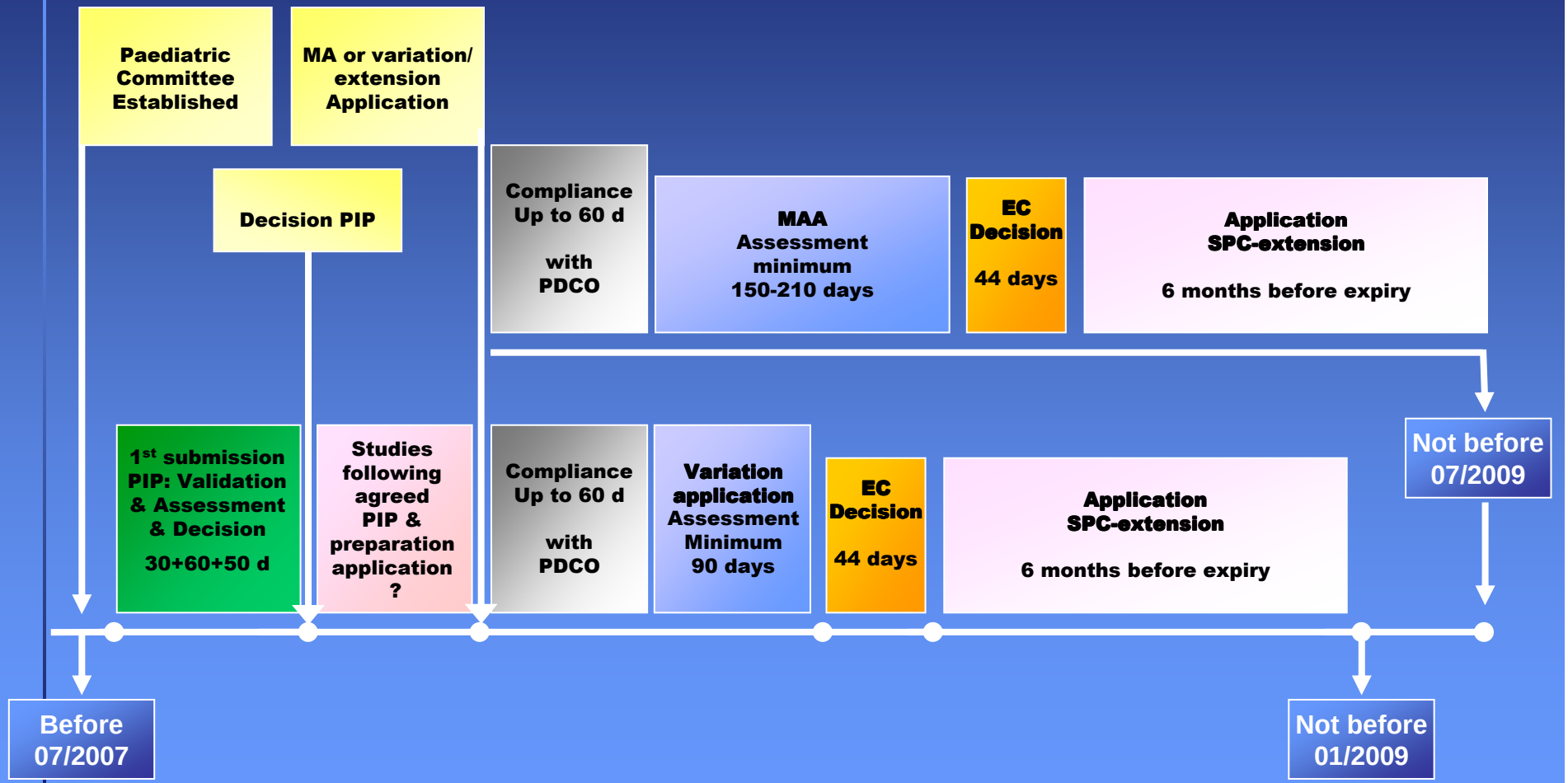
Rapporteur Appointment

Experts?

Overview PIP Procedure



Example for Discussion



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Compliance Check

'The compliance check includes whether all measures agreed in the PIP decision have been conducted in accordance with it, *including the agreed timelines*.'

Non-compliance will lead

- **Non-validation of applications falling under Art. 7, 8**
- **For validated applications, non-inclusion in the MA of the compliance statement, thus ineligibility for the rewards and incentives**

Compliance Check (C.C)

- Only a fully completed PIP can be checked for compliance
- Amendments are no long possible at the time of the C.C
- Stopping a PIP (for safety reasons…) should lead to an amendment or waiver in front of the PDCO before any C.C
- C.C is not linked to any scientific judgement/ assessment of data (Q, S, E)

Compliance Check

- **Step 1 (At Validation)**
  - By competent authority (reference MS)
  - By PDCO at EMEA (60 day procedure)
  - Before or during Validation MAA
- **Step 2 (During Assessment)**
  - Checking facts
- **Statement on Compliance**
  - For granting of rewards and incentives

Guidance, training and learning from experience (feed back from Competent Authorities)

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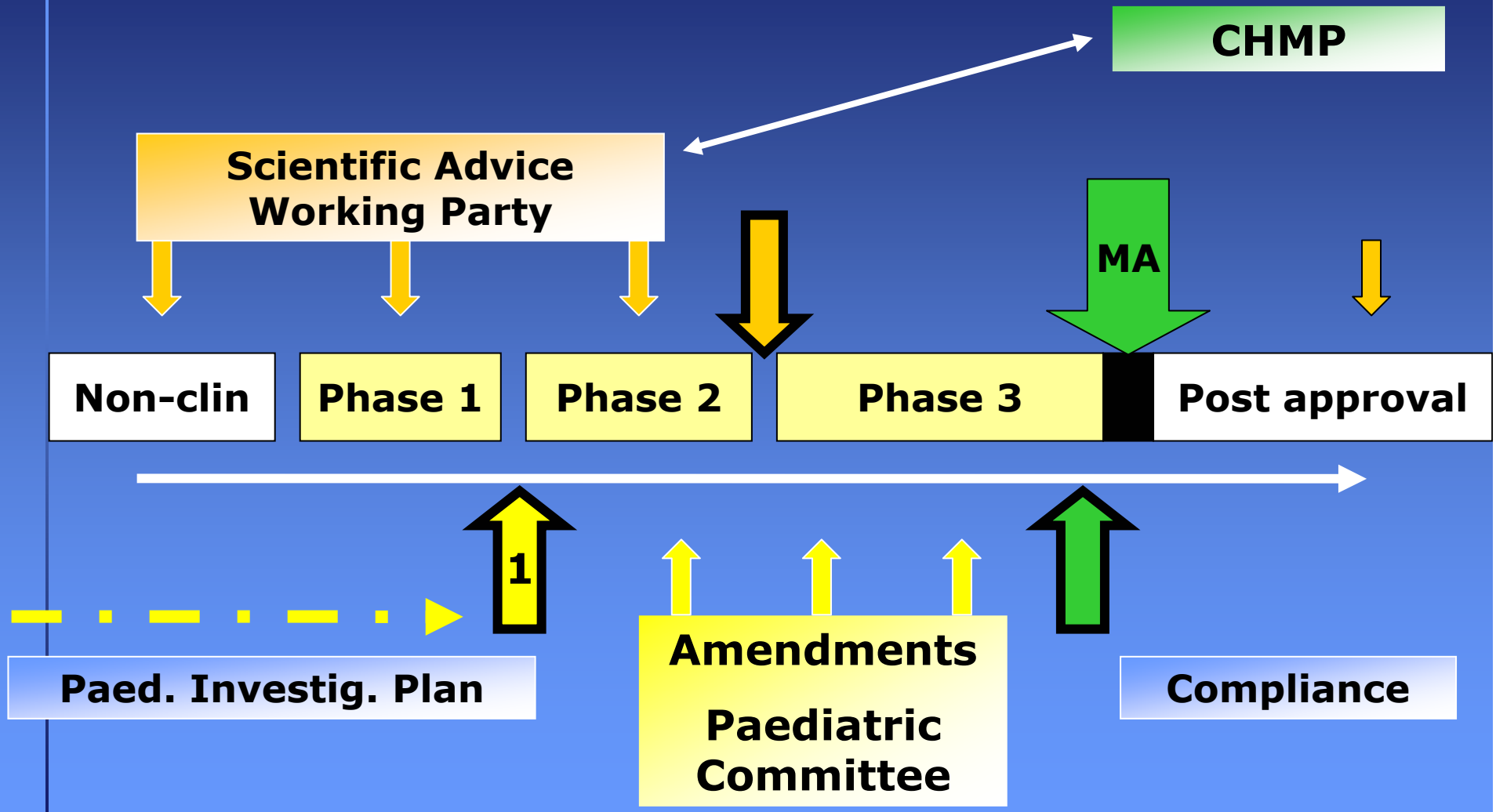
Scientific Advice vs. PDCO

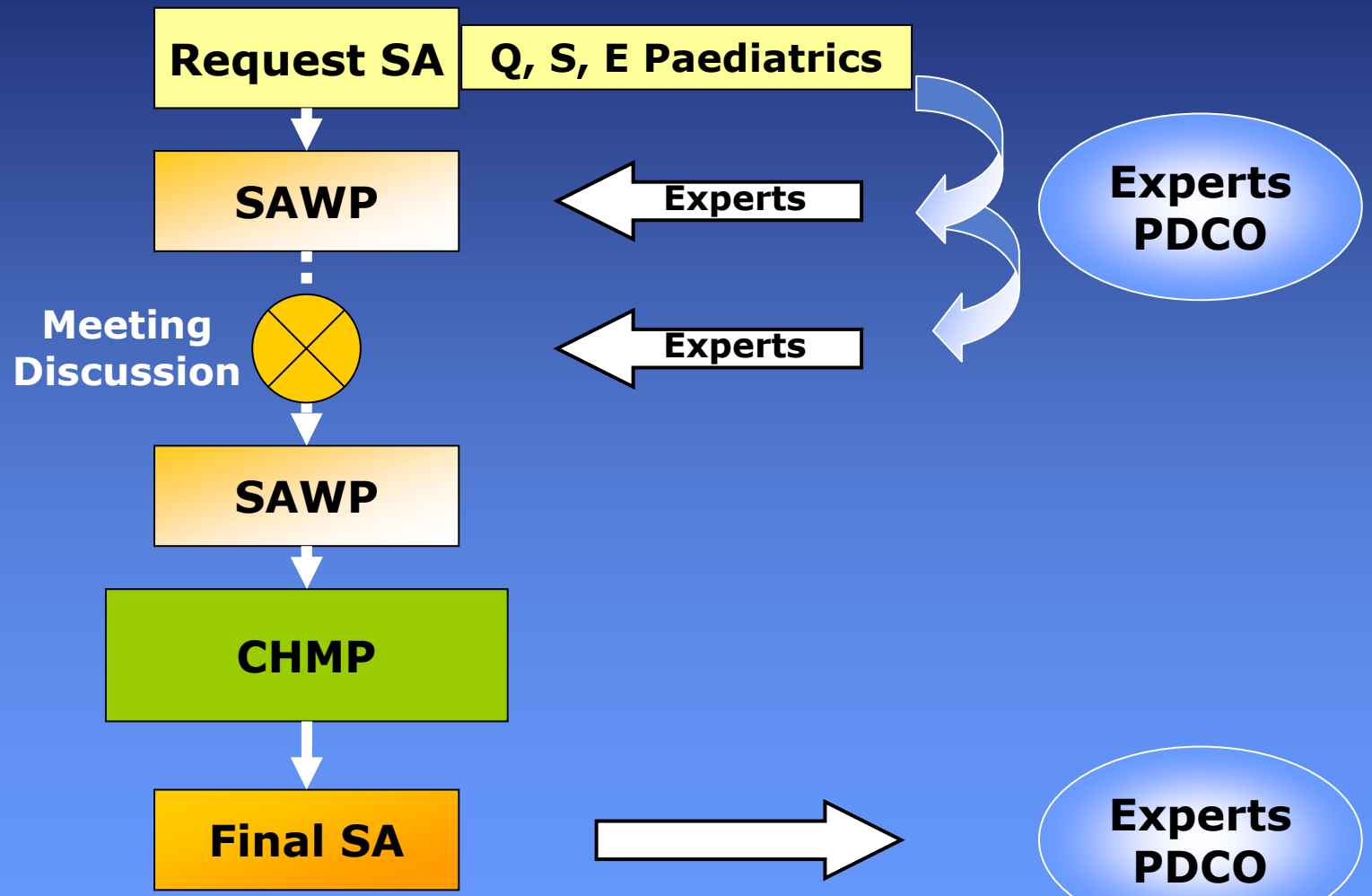


SAWP and PDCO

- Scientific Advice: non binding ⟷ PIP decision is binding on company
- Adults and children development ⟷ Paediatric development only

- Fee attracting procedure (adults, non orphan) ⟷ No fee
- Reduced fee for SME
- Free for orphan (Protocol Assistance) and paediatric indication

PDCO & Scientific Advice (SA)



Publication of PDCO Opinions and EMEA Decisions

- Legal requirement to publish opinions and decisions after deletion of commercially confidential information
- Under discussion
- No publication of detailed PIP
- Waivers
- Timelines of initiation and completion

Summary

- Regulation 1901/2006
- Guidance EU-Commission PIP
- EMEA action Plan implementation
- PDCO
- Development of Research/Clinical Investigations
- Perspectives of Paediatric Indications after July 2008

Conclusions

- A 7-year process but real achievements
- Regulatory framework for Europe
- A major change in the way medicines are developed
- Better medicines for the children of Europe

Thank You

Abbreviations

- EMEA: European Medicines Agency
- EU: European Union
- ICH: International Conference on Harmonization
- Council: Council of Ministers (Council of European Union)
- PIP: Paediatric Investigation Plan
- CHMP: Committee on Medicinal Products for Human Use
- PUMA: Paediatric Use Marketing Authorisation
- PK: pharmaco-kinetics
- EUDRACT: European Database of Clinical Trials
- FP7: 7th Framework Programme

European Medicines Agency

www.emea.europa.eu

DG Enterprise website

pharmacos.eudra.org

- Paediatric regulation proposal and explanatory texts
- Latest version (link)
- Guideline on Ethics