U.S. Food and Drug Administration

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FDA and EMEA: Pediatric Regulatory Processes

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Overview

- Pediatric Knowledge Gap
- Solution to pediatric knowledge gap
- Goal of Pediatric Legislation
- Pediatric Legislation: U.S. and European Union
- FDA Written Request (WR) and EMEA Pediatric Investigational Plan (PIP)
- FDA and EMEA Collaborations
- Lessons Learned
- Vision

Need for Pediatric Legislation

- **The Pediatric Knowledge Gap:**

Historically, drugs have been used in children WITHOUT the same level of evidence as has been obtained in adults.

Solution to Pediatric Knowledge Gap

- Implementation of Pediatric Regulations/Legislation in the U.S. since 1997 has driven pediatric product development.
- Implementation of Pediatric Legislation also in the European Union (EU) since 2007 is, combined with the U.S. legislation, driving global pediatric product development.

Goal of Pediatric Legislation

- As stated in ICH E-11
  - Pediatric patients should be given medicines that have been properly evaluated for their use in the intended population.
  - Product development programs should include pediatric studies when pediatric use is anticipated.
  - Development of product information in pediatric patients should be timely and, often requires the development of pediatric formulations.
  - The rights of pediatric participants should be protected and they should be shielded from undue risk.
  - Shared responsibility among companies, regulatory authorities, health professionals and society as a whole.

U.S. Pediatric Legislation

- 2 separate legislations
  - Incentive:
    - 1997 FDA Modernization Act (FDAMA)
    - 2002 Best Pharmaceuticals for Children Act (BPCA)
  - Requirement:
    - 1998 Pediatric Rule
    - 2003 Pediatric Research Equity Act (PREA)
  - BPCA and PREA reauthorized in 2007 as Food and Drug Administration Amendments Act (FDAAA), which sunsets on October 1, 2012.

Application of U.S. Pediatric Legislation to Oncology

- BPCA
  - Incentive process; studies are voluntary
  - trigger to issue a Written Request: public health need (e.g. life-threatening disease: cancer)
  - applies to drugs only (e.g. drug but not biologic oncology drugs)
  - applies to orphans (e.g. pediatric cancers)

Application of U.S. Pediatric Legislation to Oncology

- PREA
  - Mandatory process so studies required
  - Applies to drugs and biologics (e.g. drug and biologic oncology products).
  - Does not apply to products granted orphan designation.

Application of U.S. Pediatric Legislation to Oncology

- **PREA**
  - **trigger: new indication, new active ingredient, new dosing form, new dosing regimen or new route of administration. Studies required only on the drug and indication under review. Since many adult cancers do not occur in children, studies are waived under PREA. However, supportive care (e.g. prevention of nausea and vomiting or pain) more likely to be similar and thus, studies required under PREA.**

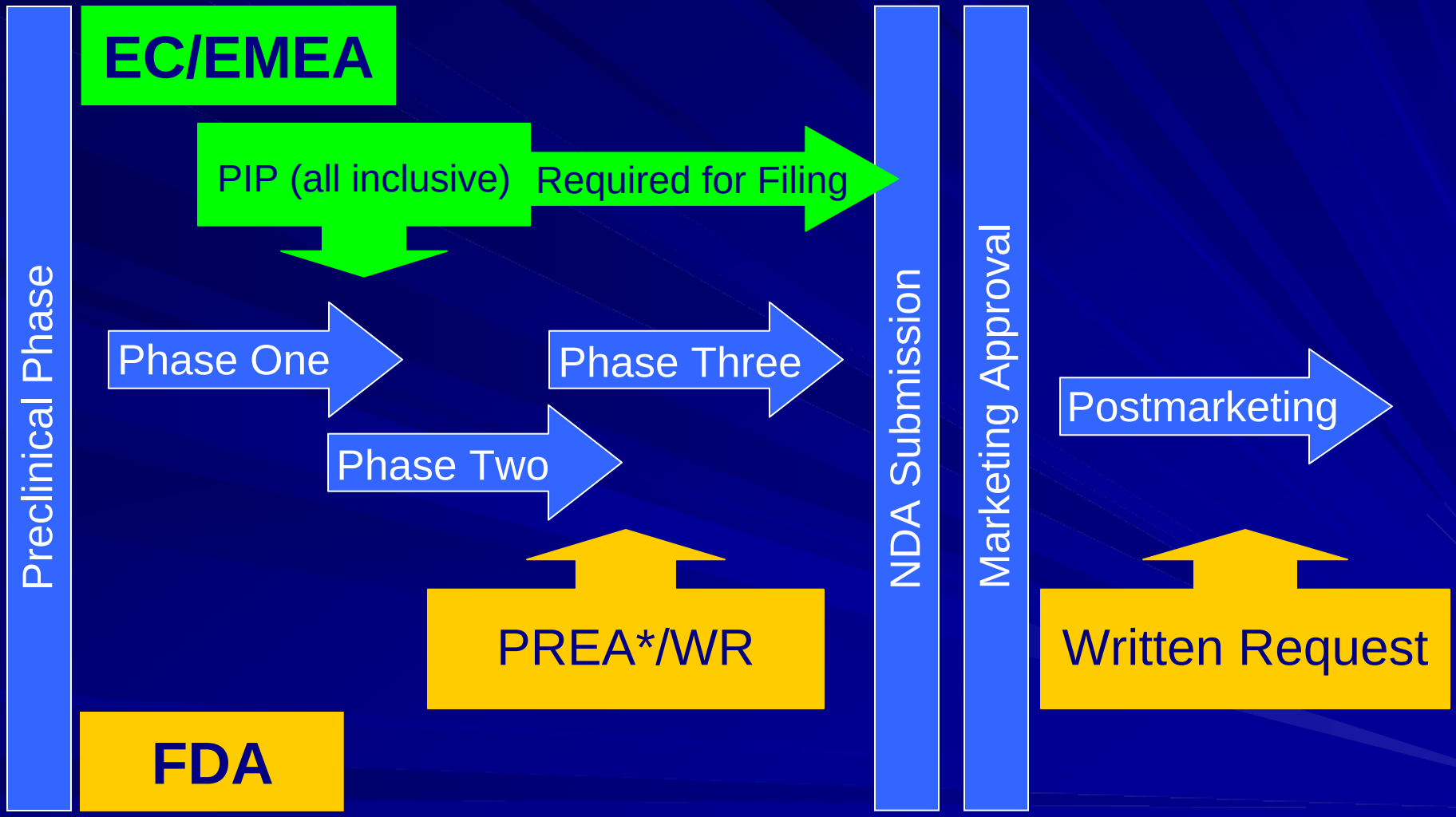
BPCA and PREA: Similarities

- Pediatric Review Committee (PeRC) reviews all activities under BPCA and PREA. PeRC is consultative to FDA review divisions (i.e. PeRC makes recommendations).
- Development of age-appropriate formulation required.
- Pediatric studies must be labeled (both positive and negative studies).
- Public presentation of adverse events for the first year after approved labeling changes and beyond the first year, as appropriate.

European Pediatric Legislation

- Unlike in the U.S., in the EU, the incentive and requirement are unified under one legislation.
- Unlike in the U.S., a marketing authorization application (equivalent to NDA in U.S.) must contain a pediatric plan, waiver or deferral or filing will be denied.
- In the EU, pediatric product development is discussed earlier in the regulatory process compared to U.S.

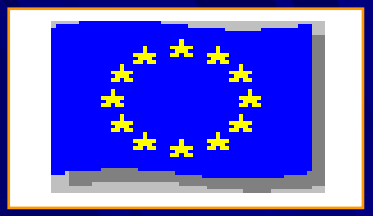
New Drug Development Process



European Pediatric Legislation

- In the EU, the Pediatric Committee (PDCO) is the counterpart to the PeRC in the U.S. However, unlike the PeRC, the PDCO makes binding decisions.

Paediatric Committee



1 elected Chair

- 5 members from Approval Committee (CHMP)
- 25 representatives from other Member States
- 3 Patients/families' representatives*
- 3 Health Professionals representatives*

*still to be appointed

European Pediatric Legislation

- The FDA “feasibility” criteria does not exist in EU legislation. Thus, a study may be required in the EU but waived in the U.S. under PREA. FDA may request such a study under BPCA, using the voluntary financial incentive.
- Unlike the U.S,. the EU does not have a public process whereby pediatric focused post-marketing safety reviews are presented to an Advisory Committee.

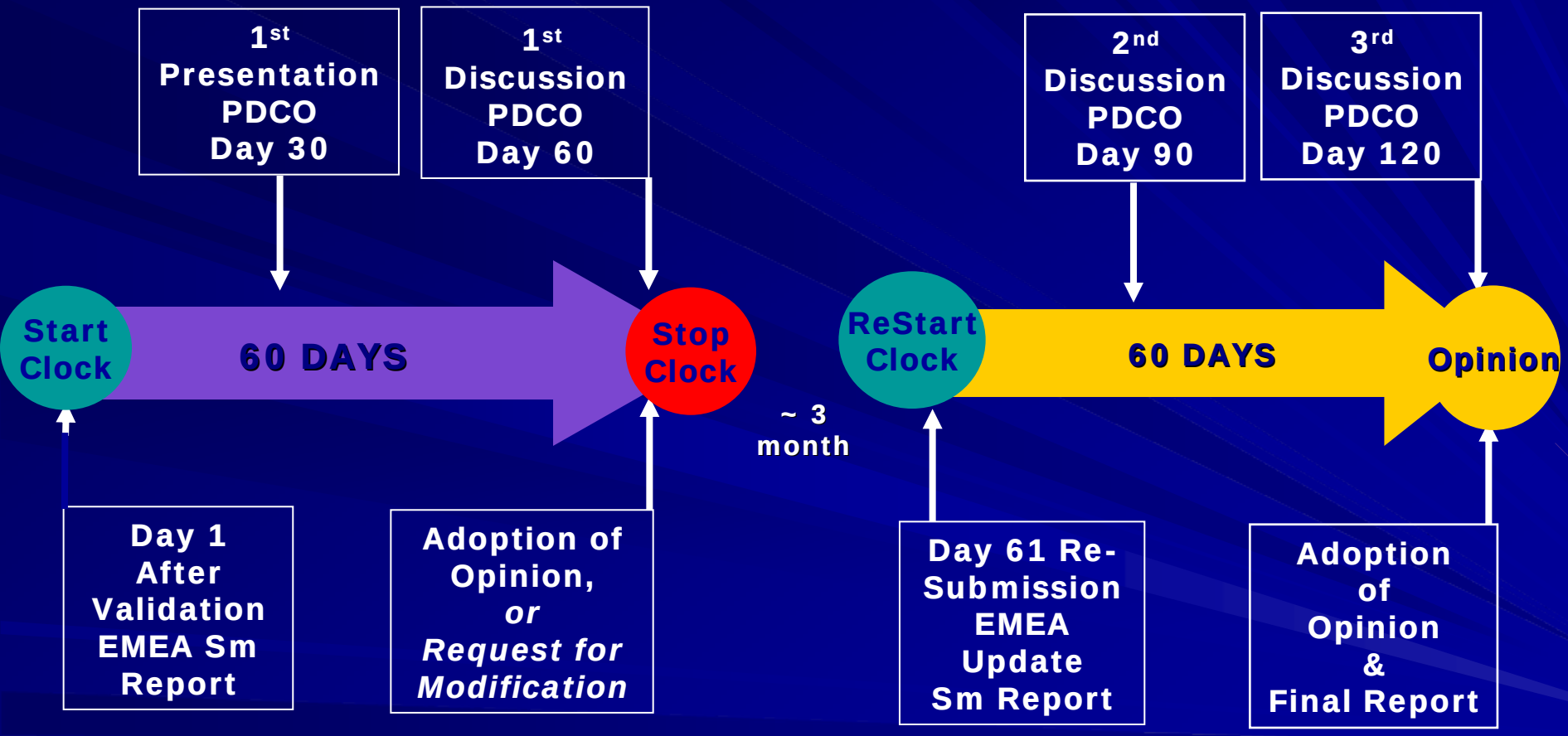
FDA Written Request vs. EMEA Pediatric Investigational Plan

- **Written Request**
  - Voluntary process
  - Issued by FDA (note: PPSR proposed by sponsor)
  - Outline of pediatric studies and timelines
  - May include nonclinical studies
  - Age-appropriate formulation statement
- **PIP**
  - Mandatory process
  - Proposed by sponsor
  - Detailed pediatric studies and timelines
  - Addresses nonclinical requirements
  - Complete product quality (chemistry), including age-appropriate formulation

FDA Written Request vs. EMEA Pediatric Investigational Plan

- **Written Request**
  - Does not include waiver or deferral
  - Drugs only
  - Includes orphans
  - Timing: end of Phase 2 or Phase 4
  - Reward: 6 months patent extension for on-patent drugs
- **PIP**
  - Includes waiver and deferral requests
  - Drugs & biologicals
  - Includes orphans
  - Timing: begins end of Phase 1
  - Reward: 6 months patent extension for on-patent drugs

Overview of the PIP Procedure



Pediatric Collaboration: FDA & EMEA Principles of Interactions

- **Objectives of the exchanges**
  - **Avoid exposing children to unnecessary trials.**
  - **Enhance the science and decrease the risk to children during pediatric product development**
  - **This communication does not mean that pediatric development programs will have exactly the same pediatric protocols or ask the same questions or arrive at the same regulatory decisions.**

FDA and EMEA: Process of Information Exchange

- Monthly t-con to discuss product-specific pediatric development and general scientific/regulatory/safety issues related to product classes. Pharmaceuticals and Medical Devices (PMDA), Japan, has recently joined as observers.

- Documents are exchanged through a secure link, Eudralink.

FDA and EMEA: Type of Information Exchanged

- Pediatric Investigational Plans (PIPs)
- Pediatric Committee (PDCO) Summary Reports
- Written Requests
- Waivers (full and partial) and deferrals
- Type of study: choice of comparator and efficacy endpoint

FDA and EMEA: Type of Information Exchanged

- Status of ongoing pediatric studies
- Results of pediatric studies
- Safety concerns, including clinical hold
- Plans for long-term safety monitoring
- Topics related to product classes (e.g. safety concerns and general study approaches for a specific indication.

FDA and EMEA: Triggers for Discussion

- Ethical or data integrity issues
- Safety concerns
- Different pediatric indications for development
- Pediatric study feasibility issues
- Pediatric studies completed (to avoid duplication)
- Outcome of pediatric studies, including negative studies.
- Marketing approval differences

FDA and EMEA: Scope of Information Exchanged

- August ’07 through November ’09:
  - Product specific
    - Total: FDA provided information for 422 products
    - 181 products were discussed
    - 97 of 181 product discussions included participation by FDA review divisions
  - General topics discussed (not product specific): n= 16

Pediatric Studies

What Have We Learned?

Small populations require the world as a village for clinical trials

Pediatric Studies: Lessons Learned

- Conduct of PK studies are important prior to conduct of clinical efficacy trials to determine an appropriate dose(s) to be given in the clinical trials.
- More work needs to be done, especially in newborns, the most vulnerable and underserved population.
- Ethical considerations are always paramount in pediatric trials.

Pediatric Studies: Lessons Learned

- Age-appropriate formulations are needed to permit accurate and safe dosing.
- Age-appropriate and validated endpoints are needed to permit assessment of efficacy.
- Long-term follow-up studies are needed to assess effects of chronic therapy, including effects on growth.

VISION

- That the goals of ICH E-11 be fully attained. Namely, that children receive therapeutics that have been evaluated in an appropriate and timely and ethical manner. To do this, we must work together.

THANK YOU!