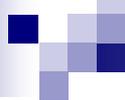




Overview of Pediatric Regulations

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Principles of pediatric drug development that guide regulations

- 
- Pediatric patients should be given medicines that have been properly evaluated for their use
 - Product development should include pediatric studies when pediatric use is anticipated

ICH = International Conference on Harmonization

Objectives

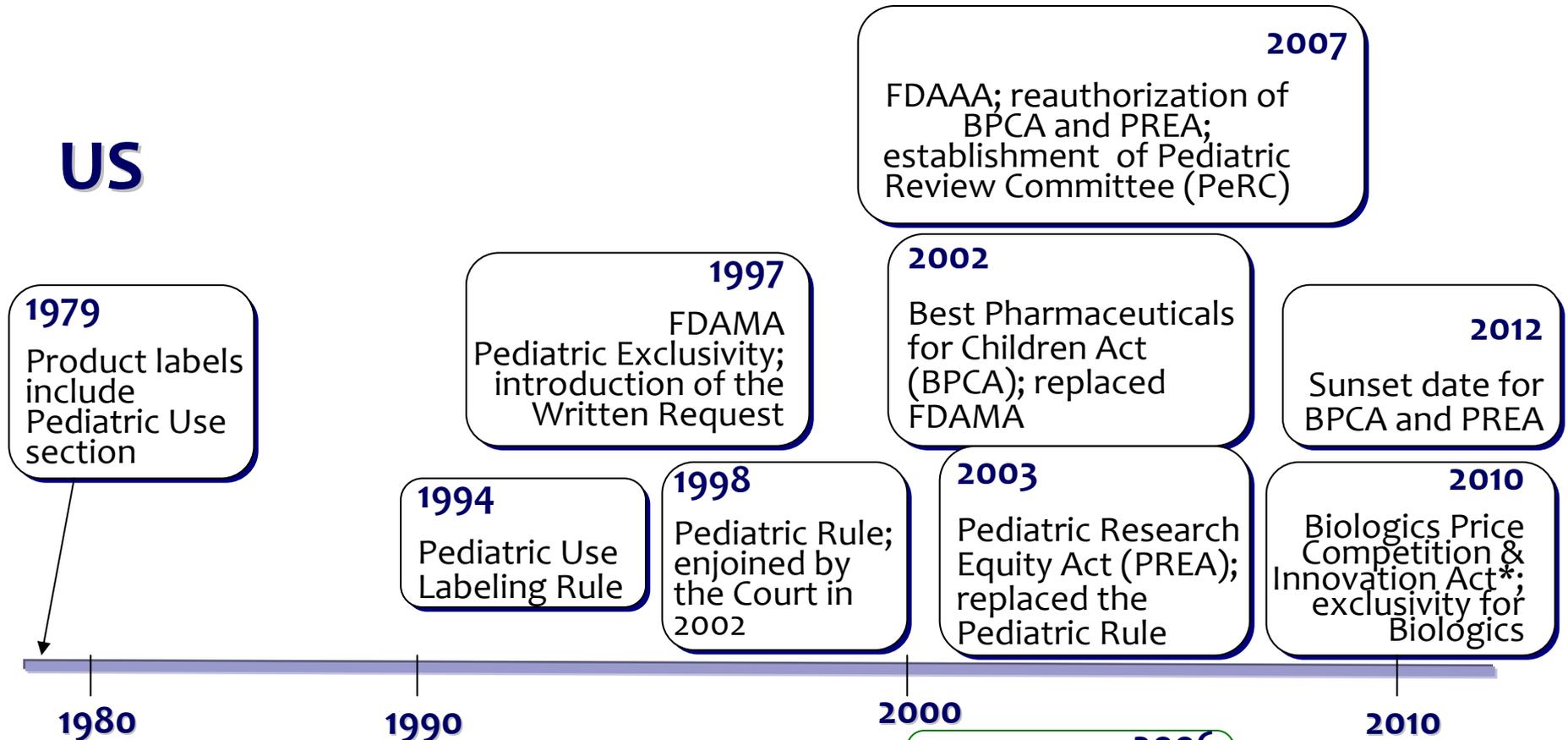
- Brief Overview of Pediatric History at FDA
- Review of major elements of the US laws
- Impact for Oncology Products

Acronyms

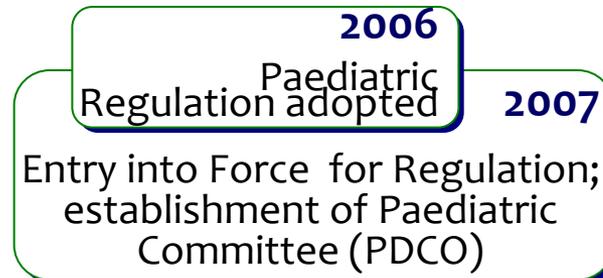
- BPCA – Best Pharmaceuticals for Children Act
- FDAAA – Food and Drug Administration Amendments Act
- PAC – Pediatric Advisory Committee
- PeRC – Pediatric Review Committee
- PREA – Pediatric Research Equity Act
- PPSR – Proposed Pediatric Study Request
- WR – Written Request

Pediatric Regulatory History

US



EU



*Part of the Patient Protection & Affordable Care Act

US Pediatric Laws

PREA and BPCA: Working together



PREA

Studies mandatory

Required studies for adult indication
under review

Not required for orphan indications

Applies to drugs and biologics



BPCA

Studies voluntary

Studies for entire active moiety

WR may be issued for orphan indications

Applies to drugs and biologics*



* Biologics Price Competition & Innovation Act in the
Patient Protection & Affordable Care Act 2010

Required Studies: Application of PREA



- Pediatric studies and a pediatric assessment must be submitted for NDA/BLA or supplements with
 - New active ingredient
 - New indication
 - New dosage form
 - New dosing regimen or
 - New route of administration
- Applies only to indication(s) included in the submission
 - Drugs with Orphan Designation not studied under PREA
- Submission of a pediatric plan must accompany any deferral request in an NDA/BLA submission
 - Includes clinical, non-clinical and formulation plans
- PREA requirements are part of NDA/BLA approval

PREA: Waiver and Deferral



■ Waiver (full or partial)

- Study is not feasible or appropriate or safe for the age group
- Must be supported by data
 - Use of the product in a pediatric population
 - Occurrence of the condition in the pediatric population
 - Evidence that the product would be unsafe or ineffective

■ Deferral

- Studies will be conducted later – usually post approval as a post marketing requirement
- The age group(s) must be specified
- A pediatric plan must be submitted along with the deferral request

BPCA: Written Request (WR)



- A description of pediatric studies issued by a Review Division
 - Can be in response to submission of PPSR
 - Can be for indications and conditions other than the adult indication
- Successful completion results in an award of 6 months exclusivity attached to the patent
- Considerations
 - What is the public health benefit?
 - Are the study designs feasible; sufficient to support dosing, safety and efficacy?
 - Have all populations and conditions been addressed?
 - Is there a PREA requirement?
 - Are there other products already approved for the condition?

Pediatric Review Committee (PeRC)

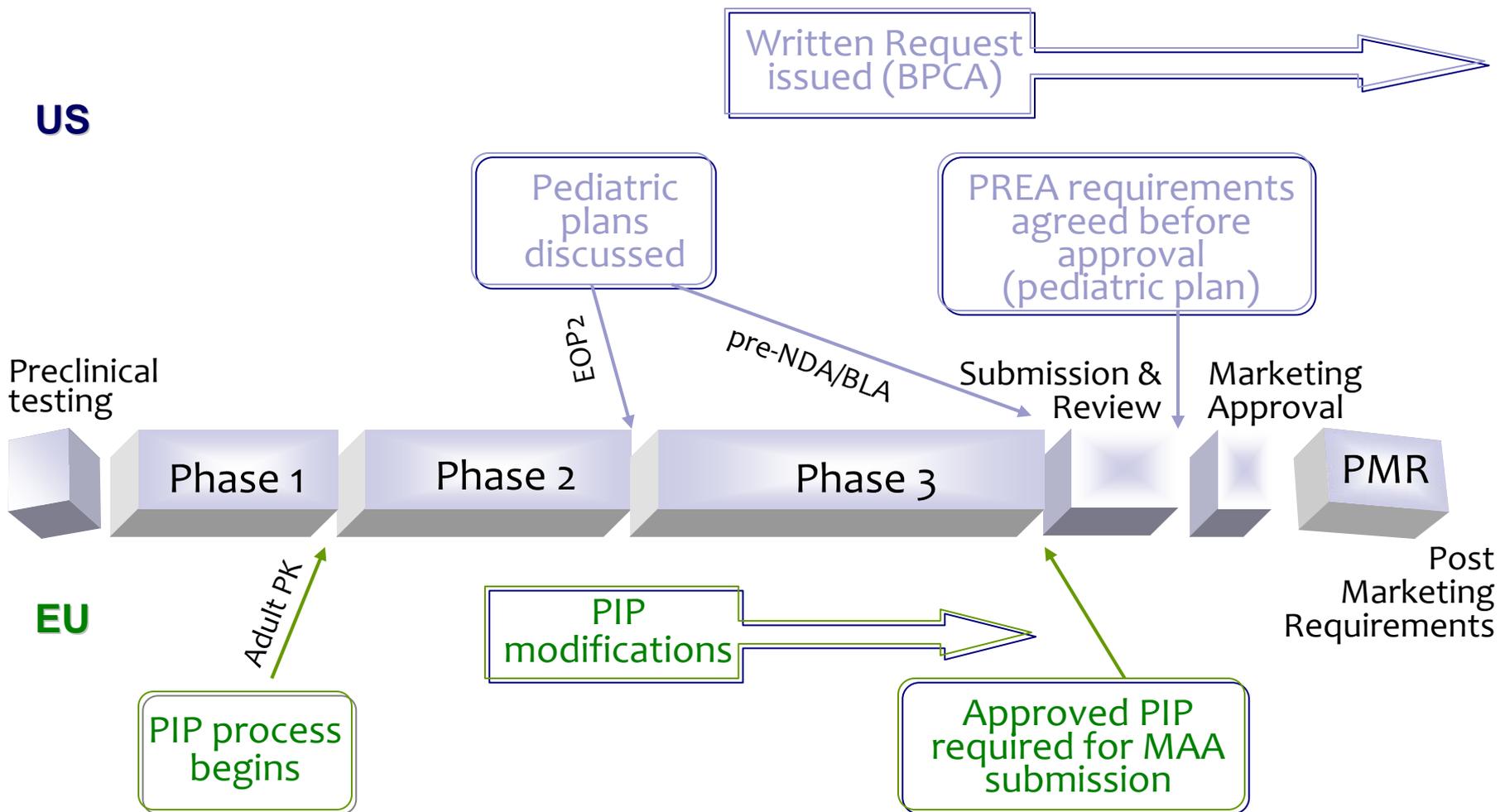
- Internal Review Committee
- Membership drawn from experts across FDA including CDER, PMHS, CBER, OPT
- Expertise includes
 - Pediatrics
 - Chemistry
 - Statistics
 - Legal
 - Clinical Pharmacology
 - Safety
 - Toxicology
 - Ethics
- Reviews
 - PREA - waiver and deferral requests
 - PREA - pediatric plans and pediatric assessments
 - BPCA - pediatric written requests

Paediatrics in Europe – Paediatric Investigation Plan (PIP)



- Regulation encompasses the same elements and considerations as PREA and BPCA
- A pediatric plan that considers all age groups, and conditions for which the product may have utility
 - Includes waiver, deferral agreements as well as description of the studies needed; clinical, non-clinical and formulations
- Opportunity for a 6 month extension of the SPC
- Must have an approved PIP at time of filing of Marketing Authorization Application (MAA)

Pediatric Planning in the Drug Development Process - Timing



What about Drugs for Pediatric Cancers?

- Same regulatory expectations
- Some added considerations
 - Small numbers of patients demand thoughtful approaches and prospect of direct benefit
 - Alternate therapeutic approaches needed to treat cancer in children \implies innovative trial designs
 - Protocols written in conjunction with CTEP and national cooperative research groups
- Majority of products will be studied under BPCA
 - Conditions under study in adults do not have a pediatric correlate
- Few indications are studied under PREA
 - Same as adult; Leukemia/Lymphoma
 - Supportive care; to treat associated symptoms

What about Drugs for Pediatric Cancers?

- Goal of an Oncology Written Request is to develop drugs that provide a meaningful advance in the treatment of children with cancer
- Ideally these drugs would have curative potential
- But at least have the potential to
 - Prolong life and
 - Improve the quality of life
 - Reduce toxicity
 - Improve efficacy

Content of a Written Request

- Description of the indications to be studied
- Studies to be performed
 - Objectives
 - 1° endpoints
 - 2° endpoints
 - Statistical plans
- Nonclinical studies and formulations development – if needed
- Drug specific safety concerns
- Timing and format for report submission
- Labeling
- Template is available
 - [WR Template FDA.gov](http://www.fda.gov)

A Written Request for an Oncology Product

- Selection of candidate therapies
 - Mechanism of Action for the drug suggests potential for activity
 - Scientific rationale exists for the drug to be evaluated in pediatric cancers
 - Activity in preclinical models of pediatric cancers
 - Efficacy has been shown in a related adult cancer
 - Evidence that the therapy will reduce toxicity with similar efficacy to existing therapy
 - There is potential to improve quality of life for the pediatric patient
- External review and advice from the Pediatric subcommittee of the ODAC

A Pediatric Plan for an Oncology Product

Phase 1 studies

- Rationale for the starting dose
- Targeted population with patients
- Pharmacokinetics
- Definition of the maximally tolerated dose, biologically effective dose, dose limiting toxicity
- Stopping rules for toxicity
- Statistical plan

*Studies may be designed to include multiple cancer types

Phase 2 studies*

- Rationale for the starting dose
- Defined population with adequate numbers of patients in each cancer type being investigated
- Criteria to determine the activity of the product
- Stopping rules based on safety or lack of activity
- Statistical plan
- If needed, pharmacogenetic/ pharmacogenomic studies
- Plans for validation of *in vitro* companion diagnostic devices in the appropriate age groups if needed for safe use of the drug

A Pediatric Plan for an Oncology Product

- Work done under a written request for oncology products rarely results in a labeled pediatric indication
- Phase 3 studies are infrequent within a Written Request but can be required as appropriate
 - Recognize the small numbers of patients and the time needed to complete studies
 - Phase 3 studies are a routine requirement for non-oncology products.
- It is expected and encouraged that any needed phase 3 trials would be completed as quickly as possible for consideration of a pediatric indication to allow for comprehensive labeling

Summary

- Small, vulnerable populations require thoughtful, innovative and coordinated clinical trial designs
 - Global engagement with Health Authorities
- The global regulations impact pediatric drug development
- BPCA and its incentive has been successful
 - Provides a mechanism for data to be submitted to the FDA for independent review
 - Expands knowledge for improved pediatric care
 - Informs the product label