



Developing Plans for Pediatric Studies: An OPT Perspective

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Objectives

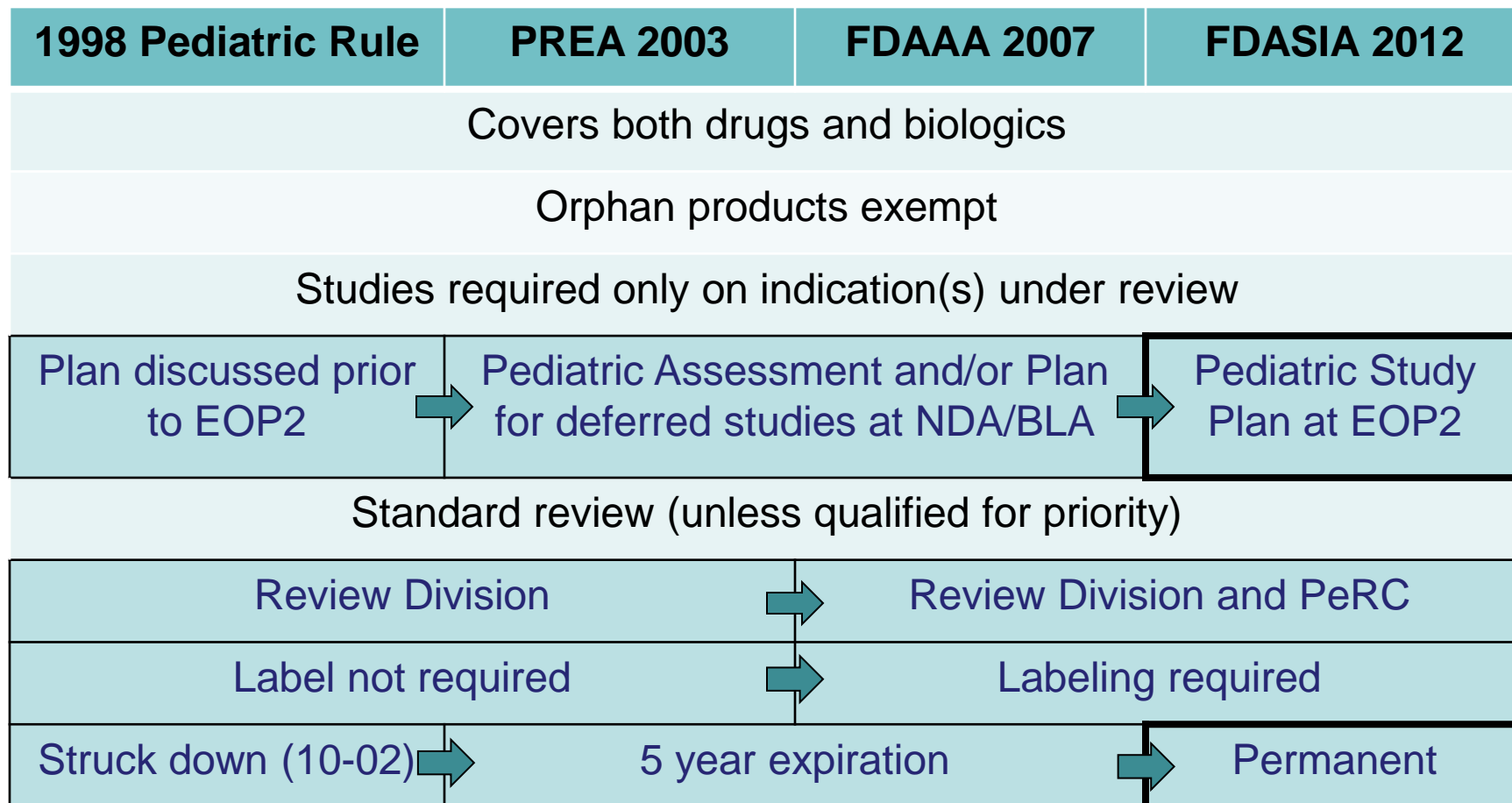
- Exploring the new requirements for submission of a pediatric study plan at the end-of-phase 2 of adult testing
- Discussing the content and issues that are contained in a pediatric study plan
- Assessing the integration with pediatric written requests
- Comprehending the impact of ethical and practical issues in the timing of pediatric studies
- Reviewing FDA and EMA approaches to global coordination of pediatric investigations

FDA Safety and Innovation Act

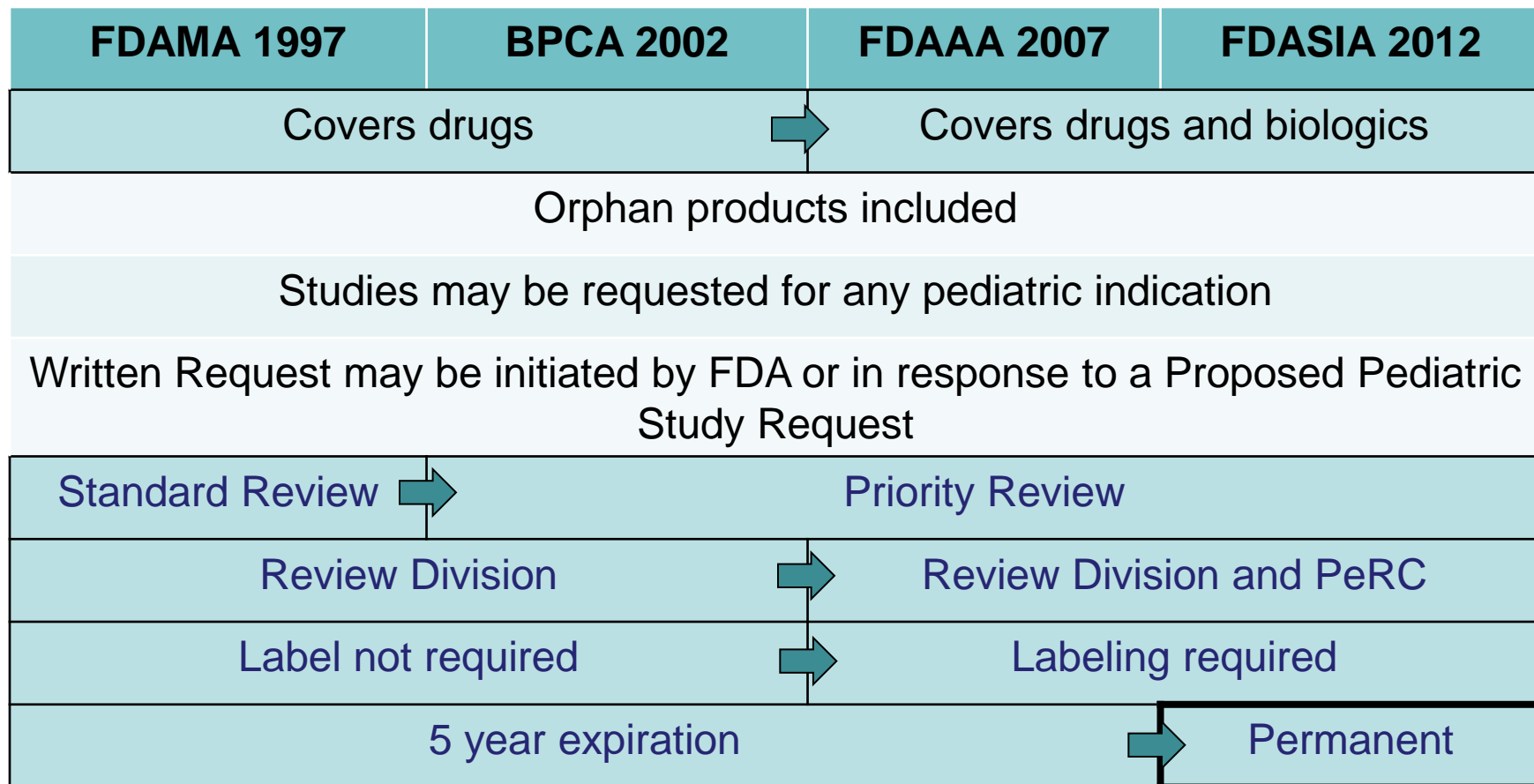
Enacted July 9, 2012

- *Best Pharmaceuticals for Children Act (BPCA)* and *Pediatric Research Equity Act (PREA)* become a permanent part of the Food, Drug, and Cosmetic Act.
- NIH BPCA program reauthorized to Oct. 1, 2017.
- Pediatric humanitarian device exemption (HDE) profit incentive and Pediatric Device Consortia program also reauthorized to Oct. 1, 2017.

Evolution of Required Studies



Evolution of Requested Studies



Two FDASIA Milestones

- Pediatric Study Plans
 - A sponsor who will be submitting an NDA/BLA that is subject to PREA[†] on or after January 5, 2013 must submit a Pediatric Study Plan (PSP) at the End of Phase 2.
 - † includes a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration
 - The Pediatric Review Committee (PeRC) must review pediatric study plans and any significant amendments to such plans.
- Proposed Rule on Pediatric Study Plans
 - FDA must publish a proposed rule and issue guidance to implement the provisions for submission and review of pediatric study plans (legislative date: July 9, 2013).

Coordination of Pediatric Plans under BPCA and PREA

- Historically, incentives to perform pediatric studies were not sufficient to achieve adequate studies to support pediatric labeling for all products
- BPCA and PREA work together to accomplish goal of obtaining adequate pediatric efficacy and safety data for labeling
- FDASIA has permanently reauthorized both laws
- Entering a new phase of pediatric drug development
 - Coordination of pediatric studies under both programs

General Approach

- Evaluate all possible indications based on the mechanism of action of product
 - Literature review, data from other development programs, proof of concept studies, etc.
- Consultation with pediatric experts to assess each indication
- Determine what data would be needed to initiate studies in pediatrics
 - Is there a potential for developmental toxicities that may require juvenile animal studies?
 - Are there additional adult human data?
 - Will a different formulation for use in pediatrics be needed?

General Approach

- Consider the type of information to be collected in pediatric clinical trials
 - If efficacy can be extrapolated, pK and safety may be sufficient
 - Existing safety data may potentially be used to support safety
 - Estimation of the potential sample size of a pediatric trial must be made to determine the type of trial design that may be used (e.g., small sample size may be overcome with large treatment effects or longer study period)

Synthesis of Pediatric Development Program

- Development of program should include:
 - All indications considered
 - Justification for inclusion or exclusion of specific indications
 - What additional data are needed (always support with facts)
 - Feasibility of studies
 - General approach to clinical studies (e.g., use of extrapolation)

Submission of Written Pediatric Product Development Plans

- Studies to be performed as part of development program
 - Should form the basis of the PSP
 - May contain elements that would be generally included in a Written Request
 - May included plans to defer studies under PREA
- What studies would be included a Written Request (WR)
 - Should form the basis of a PPSR
 - Note that PREA and BPCA are not mutually exclusive
 - PREA studies will generally be included in the WR

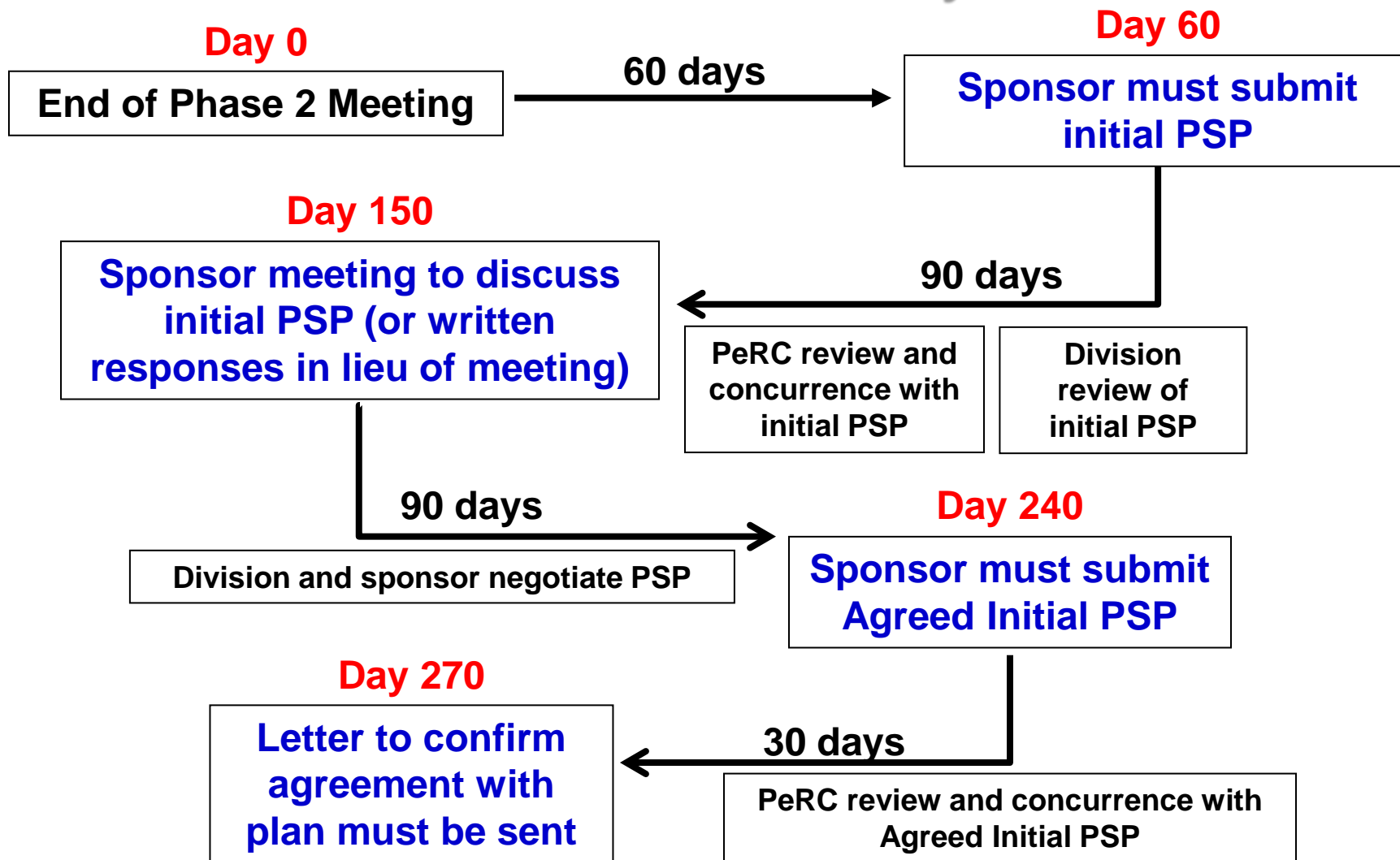
Specific Timing of PSP Submission

- If End of Phase 2 meeting occurred on or after November 6, 2012, the PSP must be submitted within 60 days
- If End of Phase 2 meeting occurred before November 6, 2012 (or no End of Phase 2 meeting will occur)...
 - If NDA/BLA will be submitted prior to January 5, 2014, FDAAA rules apply; pediatric plan must be submitted with the NDA/BLA
 - If NDA/BLA will be submitted on/after January 5, 2014, PSP should be submitted as early as possible and at a time agreed upon by FDA and sponsor.
- FDA strongly encourages PSP to be submitted prior to the initiation of any Phase 3 studies
- PSP must be submitted no later than 210 days prior to submission of NDA/BLA

Timeline for Review of PSP

- Sponsor must submit “initial PSP” within 60 days of EOP2 meeting (or prior to initiating any phase 3 trial)
- Review Division and PeRC must review this initial PSP within 90 days of submission
- Review division must meet with Sponsor by day 90 to discuss the initial PSP (or provide written comments)
- Sponsor must incorporate FDA recommendations and submit “Agreed Initial PSP” within 90 days from meeting
- PeRC must review this “Agreed Initial PSP” within 30 days of submission of Agreed Initial PSP
- FDA Letter to confirm agreement with “Agreed Initial PSP” must be sent to sponsor within this same 30 day window

Timeline for Pediatric Study Plan Review



Pediatric Study Plan (PSP)

- Intent is to encourage sponsors to identify pediatric studies as early as possible in product development
 - And when appropriate, to conduct pediatric studies prior to the submission of NDA or BLA
- Requirement under PREA as amended by FDASIA
 - FDA encourages (but cannot compel) inclusion of all pediatric plans including those plans as may be studied under BPCA (i.e., under Written Request)
- In some situations, it may be premature to include detailed pediatric study designs due to the need for additional data (e.g., endpoints, efficacy, safety)

PeRC Role in PSP Review

- Mandated by law to review of all PSPs, pediatric plans, assessments, deferral and waiver requests, and Written Requests
- PeRC is an INTERNAL advisory committee
 - No direct communications between PeRC and sponsors
 - Sponsors must communicate with review division
- Scheduling of review items (e.g., WR, PSP) are made through PMHS administrative staff
 - Increased length of meetings initiated in January, 2013 to accommodate for increased workload
- Recommendations made by the PeRC are provided to the review division

What is a Pediatric Study Plan?

- An outline of the pediatric study or studies that the sponsor plans to conduct
- Including, to the extent practicable
 - study objectives and design, age groups, relevant endpoints, and statistical approach
 - any planned request for a deferral, partial waiver, or waiver, if applicable
 - any supporting documentation
 - any other information FDA requires

Recommended Sections of PSP

- A template that sponsors should complete with all information available at the time of the initial PSP submission can be found at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM338453.pdf>.

Overview of the Disease in the Pediatric Population (1 to 5 pages)

- Pathophysiology of disease, methods of diagnosis, currently available treatments and/or prevention strategies in the pediatric population, including neonates.
- Incidence and prevalence of the disease in the overall population and the incidence and prevalence in the pediatric population.

Overview of the Drug or Biological Product (1 to 5 pages)

- Proposed mechanism of action of the drug (to the extent understood)
- Description of potential therapeutic benefits or fulfillment of therapeutic needs in pediatric population, including neonates
- Broad consideration of any possible therapeutic uses of the drug in children beyond the disease or indication being sought in adults
 - may serve as basis for Written Request under BPCA.

Overview of Planned Extrapolation to Specific Pediatric Populations (1 to 5 pages)

- Plans to extrapolate efficacy from adult to pediatric patients or from one pediatric age group to another
 - Consider all age ranges of pediatric patients, including neonates
- Provide clear justification and available supporting data
 - Similarities (and differences) between adults and children (or between one pediatric population and another) in disease pathogenesis, criteria for disease definition, clinical classification, and measures of disease progression, as well as pathophysiologic, histopathologic, and pathobiological characteristics of the disease.
 - Supportive data from all available sources (e.g., sponsor data, published literature, expert panels, and workshops).

Pediatric Study Planning & Extrapolation Algorithm

Is it reasonable to assume that children, when compared to adults, have a similar: (1) disease progression and (2) response to intervention?

No to either

Yes to both

Is it reasonable to assume similar exposure-response in pediatrics and adults?

No

Yes

Is the drug (or active metabolite) concentration measurable^{c,d} and predictive of clinical response?

No

Yes

Is there a PD measurement that can be used to predict efficacy in children?

No

Yes

"Full extrapolation"

Conduct:
(1) Adequate PK study to select dose(s) to achieve similar exposure as adults.^e
(2) Safety trials^a at the identified dose(s).

"No extrapolation"

Conduct:
(1) Adequate dose-ranging studies in children to establish dosing.^e
(2) Safety^a and efficacy^b trials at the identified dose(s) in children.

"Partial extrapolation"

"Partial extrapolation"

Conduct:
(1) Adequate dose-ranging study in children to select dose(s) that achieve the target PD effect.^e
(2) Safety trials^a at the identified dose(s).

Footnotes:

- a. For locally active drugs, includes plasma PK at the identified dose(s) as part of safety assessment.
- b. For partial extrapolation, one efficacy trial may be sufficient.
- c. For drugs that are systemically active, the relevant measure is systemic concentration.
- d. For drugs that are locally active (e.g., intra-luminal or mucosal site of action), the relevant measure is systemic concentration only if it can be reasonably assumed that systemic concentrations are a reflection of the concentrations at the relevant biospace (e.g., skin, intestinal mucosa, nasal passages, lung).
- e. When appropriate, use of modeling and simulation for dose selection (supplemented by pediatric clinical data when necessary) and/or trial simulation is recommended.
- f. For a discussion of no, partial and full extrapolation, see Dunne J, Rodriguez WJ, Murphy MD, et al. "Extrapolation of adult data and other data in pediatric drug-development programs." *Pediatrics*. 2011 Nov;128(5):e1242-9.

Product-Specific Waivers

- When application approved, FDA may waive requirement for studies in some or all pediatric age groups if:
 - necessary studies are impossible or highly impracticable;
 - there is evidence strongly suggesting that the drug would be ineffective or unsafe in all pediatric age groups; or
 - drug does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and is not likely to be used in a substantial number of pediatric patients.
- A partial waiver may also be granted if the sponsor can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed.

Request for Product-Specific Waiver(s) (1 to 3 pages)

- Plans to request either full or partial waiver
- Clear justification with supporting data for all age groups for which waiver will be sought
 - Include data from all relevant sources, including sponsor data, published literature, expert panels and workshops, and consensus documents
 - Full or partial waivers of other drugs in the same class that have been previously granted can be considered supportive information
- Requested waivers will not be formally granted or denied until the drug is approved

Summary of Planned Nonclinical and Clinical Studies (table)

- Nonclinical studies (if existing nonclinical data are not sufficient to support the proposed clinical trials)
- Clinical pediatric studies (categorized by age) that will be included in the initial PSP.
 - Include whether a deferral request is planned (i.e., the data are not planned to be submitted until after the application is approved)
- Any age groups for which the sponsor will request waivers should be included in the table



SAMPLE TABLE: Table of Nonclinical and Clinical Studies for Drug X

PLANNED NONCLINICAL STUDIES*			
Species	Type of Study	Comments	Deferral Request Planned for the Study (Y/N)**
Rat (or appropriate animal species)	Toxicology study in juvenile animals	To support clinical studies in children ages x – xx	N
PLANNED PEDIATRIC CLINICAL STUDIES			
Pediatric PK Studies⁺			
Age Group	Type of Study	Comments	Deferral Request Planned for the Study (Y/N)
1-<17 years	Phase 2 PK/PD study ⁺	To determine appropriate dose based on an established PD endpoint	N
Clinical Effectiveness and Safety Studies			
Age Group	Type of Study	Comments	Deferral Request Planned for the Study (Y/N)
0-1 year	Waiver requested	Studies are highly impracticable	
1-6 years	Efficacy study (R, DB, PC) ⁺	Endpoints to be determined	Y
6-12 years	Efficacy study (R, DB, PC)	Endpoints to be determined	Y
12-<17 years	Efficacy study (R, DB, PC)	Study to be submitted with initial NDA	N

* May not be applicable for all drugs.

** See section 11 of the Initial Pediatric Study Plan Template.

⁺ PK = pharmacokinetics; PD = pharmacodynamics; R = randomized; DB = double-blind; PC = placebo-controlled

The table is provided as an example only. The specific studies planned for a specific drug (e.g., the type of studies and the age groups studied) may differ from those studies listed in the sample table.

Pediatric Formulation Development

(1 to 3 pages)

- If current formulation not suitable, provide specific plans for the development of an age-appropriate formulation for all pediatric age groups that will be studied
- Include information regarding all planned excipients, to the extent practicable
- Include details about the size of all planned capsules or tablets to be used in pediatric studies

Nonclinical Studies (1 to 5 pages)

- Summary of data from relevant nonclinical studies that support use of product in all pediatric age groups to be studied
- Information supporting maximum dose and duration of treatment to be used in pediatric studies
- If additional nonclinical studies are **not** planned, the rationale for this decision should be included.
- Brief description of studies to be performed, including:
 - Species to be studied; Age of animals at start of dosing; Duration of dosing; Target organ systems of concern with key developmental endpoints to be evaluated.

Clinical Data to Support Studies in Pediatric Patients (1 to 5 pages)

- Brief summary of any clinical data that support the design and/or initiation of pediatric studies
- Available data in adult or pediatric patients who have received treatment with the drug (or related drugs) for the proposed indication, for other conditions, or in earlier studies.

Planned Pediatric Clinical Studies

- Pediatric Pharmacokinetic Studies (1 to 10 pages)
 - Outline of each pediatric PK/PD study(ies) planned
 - Type of study/study design, and objectives of study
 - Age group and population to be studied
 - Pediatric formulation(s) to be used
 - Dose ranges to be used in the PK studies
 - Endpoints/justification (PK parameters; PD biomarkers)
 - Existing/planned modeling/simulation of doses to be used
 - Any planned pharmacogenomic analyses

Planned Pediatric Clinical Studies

- Clinical Effectiveness/Safety Studies (1 - 10 pages)
- Include the following to the extent practicable:
 - Type of study/study design, and objectives of study
 - Age group and population to be studied
 - Inclusion and exclusion criteria
 - Endpoints (primary and key secondary) to be used
 - Timing of endpoint assessments
 - Safety assessments (with timing and length of follow-up)
 - Statistical approach (e.g., sample size justifications, noninferiority margins, if applicable)

Timeline of the Pediatric Development Plan (1 to 2 pages)

- Provide general timeline for completion of specific PSP components (as outlined in the table)
- Estimate dates based on current projections for the drug development program.
 - If dates provided in initial PSP change as drug development proceeds, sponsor must submit a request to amend the initial PSP
 - Must include justification for requested change in dates
- Dates should include estimated protocol submission, estimated study initiation, and estimated final study submission (listed as, “No later than _____”)

Timing of Pediatric Studies

- Default objective: concurrent licensure
 - Deferral of pediatric studies because the product is ready for approval in adults should be avoided whenever possible.
- Pediatric clinical trials should begin when sufficient non-clinical and adult human data (if applicable) are available to conclude either that:
 - The risk of administering an investigational product is no more than a minor increase over minimal risk, and thus could proceed under 21 CFR 50.53 (assuming other conditions are met); or,
 - Administering an investigational product offers a sufficient prospect of direct benefit to justify the risk, and the relation of anticipated benefit to risk is comparable to available alternatives, and thus could proceed under 21 CFR 50.52.

Plan to Request Deferral of Pediatric Studies

(1 to 2 pages)

- Plans to request deferral of pediatric studies in some or all pediatric age groups until after approval of future application (or supplement)
- Include adequate justification for requesting deferral
- FDA may grant a deferral of required pediatric studies if:
 - product ready for approval in adults before pediatric studies completed;
 - pediatric studies should be delayed until additional safety or effectiveness data have been collected; or
 - there is another appropriate reason for deferral.
- Deferred assessments will include data from the following:
 - Studies that will be completed, but are not included in application
 - Studies that will be ongoing or not have started at time of the application
- Requested deferrals are not granted or denied until product approved

Agreements for Pediatric Studies With Other Regulatory Authorities (1 to 5 pages)

- If available, include summary of agreed-upon pediatric investigation plan with the European Medicines Agency (EMA).
- If negotiations with EMA are in progress, a summary of the draft plan should be included.
- A summary of any agreements with other regulatory authorities also should be included.

Global Pediatric Development

- Pediatric clinical trials are often global, involving multiple sites in different regions and countries.
- These clinical trials often are being done to satisfy FDA and EMA requirements.
- We have a moral obligation to ensure that children are not exposed unnecessarily to the risks of investigational products by eliminating duplicative and/or uninformative clinical trials.
- Towards this end, FDA and EMA share information and discuss pediatric product development plans on a monthly basis in an effort to understand and reduce differences.

Summary

- The submission of an initial PSP should encourage sponsors to identify pediatric studies as early as possible in product development
- PeRC must review all initial PSP and amended PSPs as well as pediatric plans, assessments, waivers, deferrals, and Written Requests
- Coordination of pediatric studies to be performed as part of a clinical development program for a product will ideally incorporate studies that may be performed to satisfy both BPCA and PREA



Thank you.

