Pediatric Drug Development: Where Have We Been and Where Are We Going?

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Where Have We Been?

- Building a regulatory story (FDA and EMA)
- Defining the patient population
  - Age, weight, sex, ethnicity, etc.
- Deciding if we need formulation development
  - Palatability
  - Increased cost of study
Where Have We Been?

- Developing the internal pediatric expertise to handle the mandate for pediatric study
  - Pharma, academia developing new skill sets and personnel
  - BMS, Pfizer, J&J, and Shire
- Creating the internal regulatory expertise for pediatrics within the agencies (EMA and FDA)
  - FDA considering neonatologist under FDASIA
- FDA and EMA having monthly teleconferences to discuss pediatric programs
Where are We Going?

- Increase in pediatric requirements from FDA and EMA
- Age categories for study will move to the neonatal patient population
- Orphan drug designation will drive the birth of new pharmaceutical companies within companies
Where are We Going?

• New pharmaceutical company expertise will emerge
  – Orphan disease groups
  – Pediatric pharmacometrics
• Dedicated pediatric research organizations will emerge to handle the volume of pediatric trials
• Site networks will be formed executing a new paradigm in recruitment globally
Regulatory Path Forward

- PIP process begins (adult PK)
- Approved PIP required for MAA submission
- PSP end of ph2
- Agreed PREA requirements
- Written request issued (BPCA)
- PSP modifications
- PIP modifications
- Preclinical testing
- Phase 1
- Phase 2
- Phase 3
- Submission & Review
- Marketing Approval
- PMR
- EU
- US
Pediatric Research Sites

Academic Experts “Specialty Clinics”

Trained Research “Medical Practice Centers”

Condition-of-use “General Clinics”

Phase I/Phase II

Phase II/Phase III

Phase IIIB, IV
Sustainable Network Vision

Centrally managed network of 30 international sites
10 US, 10 EU, and 10 LA

Consortia of pharma companies collaborate

Auxiliary site staff dedicated to identifying and recruiting patients into consortia trials

Reduction of site administrative burden

Cost effective model for pharma decreases start up and enrollment timelines

XXX company will work with sites to understand their unique challenges to enrollment and to develop mitigation plans. These plans will include resources to be financially supported by the consortia, paid and managed through XXX Company, and dedicated to consortia trial enrollment at the site.
Continuum of learn and apply cycles for traditional drug development program in adults, with specific triggers points (shaded arrows) for developing dosing rationale in pediatric patients.

FDA set a target to design 50% of all pediatric trials using simulations by 2015 and 100% by 2020.
• EMA (European Medicines Agency) is not an FDA for Europe!
• Member States (MS) have pooled their sovereignty for authorization of medicines for children
• EMA coordinates the existing scientific resources of Member States
• An interface with all partners
Objectives of the EU Regulation

• **Improve the health of children globally:**
  – Increase high quality, ethical research into medicines for children
  – Increase availability of authorized medicines for children
  – Increase information (data) on medicines

• **Achieve the above:**
  – Without unnecessary studies in children
  – Without delaying authorization for adults
The Latest USA Regulation
• Makes **permanent** the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA).

• Clarifies the Secretary’s authority to award exclusivity for studies conducted pursuant to a written request, including a conforming change for biological products.

• Requires the Secretary to issue guidance providing for Pediatric Review Committee (PeRC) review of any significant modifications made to written requests or pediatric study plans.

• Requires the Secretary, within three years of enactment, to make public the medical, statistical, and clinical pharmacology reviews of written requests made between 2002 and 2007 that resulted in a labeling change.

• Allows for extensions of pediatric study deadlines in appropriate circumstances. Current tracking requirements would be expanded to collect data about deferral extensions and the timeline to completion of assessments. If a required pediatric study was not completed or deferred, the Secretary would issue a letter and require a response within 45 days, both of which would be made publicly available.
• Ties the submission of an initial pediatric study plan (PSP) to the sponsor’s end of the **Phase II meeting with FDA**, unless the Secretary and the applicant agree to an alternative date. The requirements and process for pediatric study plan submissions would be further clarified through regulations.

• Reauthorizes the Pediatric Advisory Committee, reauthorize the Pediatric Subcommittee of the Oncologic Drug Advisory Committee (ODAC) in a manner consistent with the authorization of ODAC, reauthorize the Humanitarian Device Exemption Extension through 2017, and reauthorize the Program for Pediatric Study of Drugs.

• Requires a report every five years evaluating the effectiveness of BPCA and PREA.

• Requires the FDA’s Office of Pediatric Therapeutics to have a **neonatologist** on staff.
What is Required to Meet the New Legislation?
Guidance for Industry
Pediatric Study Plans:
Content of and Process for Submitting
Initial Pediatric Study Plans and
Amended Pediatric Study Plans

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document contact (CDER) Rosemary Addy at 301-796-1640 or (CBER) the Office of Communication, Outreach, and Development at 301-827-1800 or 800-835-4709.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2013
Procedural
• Who must submit an initial PSP
• When an initial PSP must be submitted
• What should be included in an initial PSP
• What should be included in a requested amendment to an agreed-upon initial PSP
• A template that should be used for an initial PSP submission
TIMING OF A PSP SUBMISSION

• A sponsor must submit the initial PSP no later than **60 calendar days** after the date of the **end-of-phase 2** meeting.

• In the absence of an end-of-phase 2 meeting, the initial PSP may be submitted as early as practicable but before the initiation of any phase 3 studies.
  – If a phase 3 study will not be conducted, the sponsor should submit the initial PSP no later than **210 calendar days** before a marketing application or supplement is submitted.

• In cases when there is no active IND for the drug, but the sponsor expects upon submission of the IND that the initial studies would include a phase 3 study, the initial PSP should be submitted as a pre-IND submission. In this situation, the FDA encourages sponsors to schedule a pre-IND meeting before submission of the initial PSP.
Regulatory Path Forward

- **US**
  - Preclinical testing
  - Phase 1
  - Phase 2
  - Phase 3
  - Submission & Review
  - Marketing Approval
  - PMR

- **EU**

**PIP process begins (adult PK)**

**Approved PIP required for MAA submission**

- **Written request issued (BPCA)**
- **PSP end of ph2**
- **Agreed PREA requirements**
- **PSP modifications**
1. Overview of the Disease Condition in the Pediatric Population

• Brief summary of the pathophysiology of the disease, methods of diagnosis, and 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 should be discussed.
3. Overview of Planned Extrapolation to Specific Pediatric Populations

- **Plans for extrapolation of efficacy** data from adults to pediatrics (or from adolescents).
  - Appropriate if the course of the disease and the effects of the drug are sufficiently similar in adult and pediatric patients. Extrapolation of efficacy from one pediatric age group to another pediatric age group.
  - Application of exposure-response relationships in adults to pediatrics and ability to extrapolate.
  - Include information on similarities (and differences) between adults and children in disease pathogenesis, criteria for disease definition, clinical classification, and measures of disease progression, as well as pathophysiologic, histopathologic, and pathobiological characteristics.

- All age ranges of pediatric patients should be considered, including neonates. A justification for the extrapolation, including any available supporting data for all age groups for which efficacy will be extrapolated should be provided.

- **Supportive data from all available sources** (e.g., sponsor data, published literature, expert panels, and workshops) should be provided. Extrapolation of efficacy for other drugs in the same class, if previously accepted by the FDA, also can be considered supportive information.
4. Request for Drug-Specific Waiver(s)

- **Plans and justification** to request a waiver (either full or partial) of the requirement to provide data from pediatric studies.

- Supportive data should include data from **all relevant sources**, including sponsor data, published literature, expert panels and workshops, and consensus documents. Full or partial waivers previously granted for other drugs in the same class can be considered supportive information.

- It should be noted that requested waivers in the PSP will not be formally granted or denied until the application is approved.

- If studies will be waived because there is evidence that the drug would be ineffective or unsafe in any pediatric age group, this information must be included in the product labeling. Generally, this information would be included in the Pediatric Use subsection of labeling.
5. **Summary of Planned Nonclinical and Clinical Studies**

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

<table>
<thead>
<tr>
<th>Species</th>
<th>Type of Study</th>
<th>Comments</th>
<th>Deferral Request Planned for the Study (Y/N)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat (or appropriate animal species)</td>
<td>Toxicology study in juvenile animals</td>
<td>To support initiation of clinical studies in children ages x – xx</td>
<td>N</td>
</tr>
</tbody>
</table>

**PLANNED PEDIATRIC CLINICAL STUDIES**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Type of Study</th>
<th>Comments</th>
<th>Deferral Request Planned for the Study (Y/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-&lt;17 years</td>
<td>Phase 2 PK/PD study*</td>
<td>To determine appropriate dose based on an established PD endpoint</td>
<td>N</td>
</tr>
</tbody>
</table>

**Clinical Effectiveness and Safety Studies**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Type of Study</th>
<th>Comments</th>
<th>Deferral Request Planned for the Study (Y/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 year</td>
<td>Waiver requested</td>
<td>Studies are highly impracticable</td>
<td></td>
</tr>
<tr>
<td>1-6 years</td>
<td>Efficacy study (R, DB, PC)*</td>
<td>Endpoints to be determined</td>
<td>Y</td>
</tr>
<tr>
<td>6-12 years</td>
<td>Efficacy study (R, DB, PC)</td>
<td>Endpoints to be determined</td>
<td>Y</td>
</tr>
<tr>
<td>12-&lt;17 years</td>
<td>Efficacy study (R, DB, PC)</td>
<td>Study to be submitted with initial NDA</td>
<td>N</td>
</tr>
</tbody>
</table>

* 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
6. Pediatric Formulation Development

• Provide details of any pediatric-specific formulation development plans, if appropriate, including whether the formulation that is being developed can be used for all pediatric populations.

• Age-appropriate formulation for all pediatric age groups that will be studied. Sponsors also should provide details about the size of all planned capsules or tablets, to the extent practicable, to be used in pediatric studies.
7. Nonclinical Studies

- A brief summary of the data from relevant nonclinical studies that support the use of the drug in all pediatric age groups.

- The sponsor should include information that supports the 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. If the existing nonclinical data are not sufficient to support the proposed clinical trials, sponsors should provide a brief description for each of the studies they will conduct, including, at a minimum:
  - The species to be studied
  - The age of animals at start of dosing
  - Duration of dosing
  - Target organ systems of concern with key developmental endpoints to be evaluated
8. Clinical Data to Support Design and/or Initiation of Studies in Pediatric Patients

- This section should provide a brief summary of any clinical data that support the design and/or initiation of pediatric studies.

- This section also can include 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.
9. Planned Pediatric Clinical Studies

9.1 Pediatric PK/PD Studies

• This section should provide an outline of each of the pediatric pharmacokinetic/pharmacodynamic (PK/PD) study (or studies) planned, if applicable. The studies should be discussed in the order they are presented in the table in section 5. For each study, to the extent practicable, the sponsor should address the following:
  • Type of study/study design
  • Objectives of study
  • Age group and population in which the study will be conducted
  • Pediatric formulation(s) used in this study
  • Dose ranges to be used in the PK studies
  • Endpoints and justification (PK parameters; PD biomarkers)
  • Existing or planned modeling and simulation to support dose selection and/or study design for the pediatric studies
  • Any planned pharmacogenomic analyses
  • Sample size justification
9.2 Clinical Effectiveness and Safety Studies

- This section should provide an outline of each pediatric study planned, discussed in the order they are presented in the table in section 5. For each study, to the extent practicable, the sponsor should address the following:
  - Type of study/study design
  - Objectives of the study
  - Age group and population in which the study will be conducted
  - Inclusion and exclusion criteria for the study
  - Endpoints (primary and key secondary) to be used
  - Timing of endpoint assessments
  - Safety assessments (including timing and length of follow-up)
  - Statistical approach (e.g., statement of null and alternative hypotheses, sample size/power justification)
10. Timeline of the Pediatric Development Plan

- Each study listed in the table in section 5 should include a general timeline for completion of the study in this section. The sponsor should estimate these dates based on current projections for the drug development program.

- If the dates provided in the initial PSP change as drug development proceeds, a request to amend the initial PSP should be provided. Furthermore, the request should include justification for the change in the dates provided below for amendment of the initial PSP.

1. Formulation development, if applicable
2. Nonclinical studies, if applicable
3. Clinical Studies
   - PK studies, if applicable:
     - Estimated protocol submission date: No later than ___ (month/year)
     - Estimated study initiation date: No later than ___ (month/year)
     - Estimated final report submission date: No later than ___ (month/year)
   - Efficacy/safety studies
     - Estimated protocol submission date: No later than ___ (month/year)
     - Estimated study initiation date: No later than ___ (month/year)
     - Estimated final report submission date: No later than ___ (month/year)

4. Target date of application submission
11. Plan to Request Deferral of Pediatric Studies

- The initial PSP should include any plans to request deferral of pediatric assessments in some or all pediatric groups until after approval of a future application (or supplement) in other age groups.

- If new information, such as data from ongoing or planned studies, indicates that a criterion for a waiver (or partial waiver) is met, planned requests for deferral of pediatric assessments in the initial PSP can be changed to planned requests for waiver (or partial waiver).

- These changes should be submitted as an amendment to an agreed-upon initial or amended PSP.

- The FDA may grant a deferral of required pediatric studies if it finds that: (1) the drug or biological product is ready for approval for use in adults before pediatric studies are complete; (2) pediatric studies should be delayed until additional safety or effectiveness data have been collected; or (3) there is another appropriate reason for deferral. The planned request for a deferral should be listed in the order of the proposed studies in the table in section 5, and should include adequate justification and any currently available evidence justifying the request for a deferral (1 to 2 pages). It should be noted that requested deferrals in the initial PSP will not be formally granted or denied until the drug is approved.
12. Agreements for Other Pediatric Studies

• A summary of the agreed-upon pediatric investigation plan with other regulatory authorities (e.g., European Medicines Agency) should be provided.

• If negotiations with a regulatory authority 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.

• A summary of any clinical investigation conducted under an IND for an indication other than the indication that is the subject of the initial PSP also should be included.
The Future:  
“The Way Forward”

- Globalization of pediatric research is a reality ✓
- Volume of pediatric trials will escalate globally ✓
- PREA (mandate and exclusivity) will sunset in October 1, 2012, possibly reauthorized ✓
- EU passed legislation mandating pediatric clinical trials (2006), no reauthorization necessary ✓
- EU passed exclusivity tied to study performance (6 months patent extension) ✓
- EU mandate required for MAA ✓
“If we don’t stand up for children, then we don’t stand for much.”

Marian Wright Edelman