International Pediatric Initiatives

Jean Temeck, M.D., FAAP
Supervisor, International Team
Office of Pediatric Therapeutics
Office of the Commissioner, FDA

International Collaboration For Harmonization of Pediatric Product Development

• Why is it Important and Necessary?
  – Limited pediatric population with certain diseases available for study. Small populations require the world for clinical trials.
Pediatric Product Development

- Pediatric product development is being driven on a global scale by pediatric legislation in the U.S. and EU
Pediatric Legislation: U.S. and EU

• Pediatric legislation
  – In the U.S. since 1997 and in the EU since 2007

• Comparison between the U.S. and EU
  – 2 processes vs. one
    • U.S. has 2 separate processes for the incentive (BPCA) and requirement (PREA) that are only partially unified
    • EU’s pediatric process is unified under their legislation
  – Condition (broad use of the product) vs. indication (specific)
    • EMA’s PIP includes condition and indication
    • FDA’s PPSR under BPCA: ALL indications for which there is an anticipated public health benefit for the active moiety
    • FDA’s PSP under PREA: tied to or applicable to the specific adult indication
  – Review of adult and pediatric development programs
    • EMA’s Office of Paediatric Medicines: pediatric only (although a summary of the adult program is included in the PIP)
    • FDA’s review divisions: adult AND pediatric programs
Pediatric Legislation: U.S. and EU

• Comparison between the U.S. and EU
  – Timing for initial submission of pediatric plan
    • EMA’s PIP: End of Phase 1
    • FDA’s PSP: within 60 days of the End of Phase 2 meeting
  – Timeline for review of PIP vs. PSP
    • EMA’ PIP: 120 days (note: clock stop period of 3 months or longer between Day 60 and Day 90 PDCO discussion of the PIP; therefore, not really 120 days)
    • FDA’ PSP: 210 days (7 months) with review by PeRc at 90 days after initial submission and, again, upon agreement of PSP between sponsor and review division.
Overview of the PIP Procedure

1st Presentation PDCO Day 30
1st Discussion PDCO Day 60

Stop Clock

60 DAYS

Start Clock

Day 1 After Validation EMEA Sm Report
Adoption of Opinion, or Request for Modification

2nd Discussion PDCO Day 90
3rd Discussion PDCO Day 120

ReStart Clock

60 DAYS

Day 61 Re-Submission EMEA Update Sm Report
Adoption of Opinion & Final Report

Opinion

~ 3 month

Expertise & Efficiency

OE= oral explanation
Pediatric Legislation: U.S. and EU

• **Comparison between the U.S. and EU**
  – **Regulatory decision on pediatric plan**
    • EU: PDCO (Paediatric Committee)
    • U.S. FDA review divisions (PeRC renders advice, NOT regulatory decisions)
  – **Modification of an agreed pediatric plan**
    • EU: only the sponsor, NOT EMA
    • US: regulator (i.e. FDA review division)
  – **Submission of adult marketing application**
    • EU: agreed PIP necessary to submit adult marketing application
    • U.S.: agreed pediatric plan NOT a requirement to submit adult NDA
  – **Regulatory decision on marketing application (adult or pediatric)**
    • EU: EMA’s CHMP (Committee for Medicinal Products for Human Use), which is a separate entity from the Office of Paediatric Medicines who receives and reviews the PIP.
    • U.S.: FDA review divisions receive, review and render regulatory decisions on the adult and pediatric marketing applications.
Pediatric Legislation: U.S. and EU

• Clinical Trial Data Transparency
  – EU
    • Policy currently is draft (i.e. not yet finalized). Two phases:
      – First phase: Publication of clinical reports (e.g. clinical overview, clinical summary, clinical study reports, protocol and protocol amendments, sample case report form and documentation of statistical methods)
      – Second phase: Making available individual patient data
        » This phase is still in negotiation
  – U.S.
    • Under FDAAA, a description of the study and a summary of the results are publicly posted.
  – Conclusion
    • Proposed greater transparency and data sharing policy in EU.
<table>
<thead>
<tr>
<th>Legislative Comparison: post FDASIA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>U.S. BPCA</strong></td>
</tr>
<tr>
<td><strong>Development</strong></td>
</tr>
<tr>
<td><strong>Instrument</strong></td>
</tr>
<tr>
<td><strong>Waiver</strong></td>
</tr>
<tr>
<td><strong>Submission Timing</strong></td>
</tr>
<tr>
<td><strong>Reward</strong></td>
</tr>
<tr>
<td><strong>Drugs &amp; Biologics</strong></td>
</tr>
<tr>
<td><strong>Orphan</strong></td>
</tr>
<tr>
<td><strong>Decision Authority</strong></td>
</tr>
</tbody>
</table>
International Pediatric Collaboration
The Pediatric Cluster

• History
  – FDA and EMA: since August 2007. Since then, Japan’s PMDA, Health Canada and Australia’s TGA have joined.

• Objectives
  – Provide a forum for informal exchange of scientific and ethical information on pediatric development programs to avoid exposing children to unnecessary trials (i.e. avoid trial duplication, trials that do not answer a valid scientific question or that are not conducted in an ethical manner).
  – Aim for global pediatric development, i.e. harmonization of FDA and EMA pediatric trials. Understand rationale when scientific approaches differ.
The Pediatric Cluster

• **Process of Information Exchange**
  – Monthly exchange coordinated by OPT’s International Team
  – Nomination of issues for discussion usually from EMA, sometimes from U.S. and only occasionally from others. PeRC may suggest topics. FDA review division should contact Suzanne Malli in OPT to request a topic be placed on the agenda.
  – EMA sends the Summary Reports, which contain the PIP and the PDCO discussion(s) if they have occurred.
  – OPT prepares comparisons of studies in PIP and PSP and/or PPSR.
  – Experts at EMA and FDA identified for discussion. From the FDA side, participation by the review divisions is critical as the scientific expertise resides with them.
  – FDA’s OPT prepares the agenda and a written summary of the background information for distribution prior to the discussion.

• **Scope of information exchanged (August 2007 - May 2014)**
  – 348 products discussed and 92 general topics.
The Pediatric Cluster

- **Triggers for Discussion**
  - Ethical or data integrity issues
  - Trial design issues
  - Choice of endpoint
  - 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
Pediatric Cluster Case Study: Type 2 Diabetes

• Issues discussed
  – Patient population
  – Study design, including duration of the controlled efficacy period
  – Choice of primary endpoint and timing for its measurement
  – Age group for study
  – Total study duration
  – Timing for initiation of pediatric studies
Pediatric Cluster Case Study: Type 2 Diabetes

• FDA and EMA agree
  – May include both treatment-naïve and add-on to metformin patient populations and stratify by background therapy
  – Include ages 10 to 17/18 years
  – Need to determine PK and need for randomized, controlled trial(s) for efficacy and safety
  – HbA1c is the primary endpoint
  – Total study duration of 1 year
  – Timing: during or after adult Phase 3
Pediatric Cluster Case Study: Type 2 Diabetes

- FDA and EMA disagree
  - Duration of controlled efficacy period and hence, timing of the primary efficacy assessment
    - EMA: at least 12 weeks (but exceptions possible, e.g. for long half-life products)
    - FDA: 24 weeks with strict glycemic rescue criteria
  - Conclusion
    - Different approach to modulating risk for endpoint assessment.
Pediatric Cluster Case Study: Type 2 Diabetes

• According to sponsors, it has been very difficult to recruit pediatric patients in type 2 diabetes trials despite global recruitment efforts. Reasons are multifactorial and include many new competing products for a limited pediatric patient pool and lack of an adequately developed pediatric clinical research infrastructure.

• In an editorial accepted by Diabetes Care: “Joining Forces: A Call for Greater Collaboration To Study New Medicines in Children and Adolescents with Type 2 Diabetes”, FDA and EMA propose:
  – Consideration of a multi-agent trial using a shared control arm
  – Partial extrapolation of efficacy
  – Develop a type 2 diabetes pediatric research infrastructure whose aim is to develop a large network of investigators and centers with pediatric type 2 diabetes clinical research expertise across the EU and the U.S.
Pediatric Cluster: Common Commentary

- Pilot program that is part of the Pediatric Cluster
- Tool to inform sponsors of products discussed at the Pediatric Cluster.
- FDA or EMA propose discussion of
  - Product with a pediatric plan submitted to both Agencies and that is currently under review, preferably early on in the regulatory process.
  - General approach to study a specific disease
- Both Agencies agree to the proposal
- Issue(s) are identified for discussion (e.g. study design)
- Discussion(s) of issue(s) at Pediatric Cluster.
- Discussion points, identifying similarities and/or differences in FDA’s and EMA’s approach, are summarized and approved by FDA and EMA.
- Approved common commentary document sent to sponsor. Comments sent are NOT binding on either Agency (i.e. they do NOT constitute regulatory advice).
Common Commentary vs. Parallel Scientific Advice

**Common Commentary**
- Proposed by: regulators
- To: Pediatric Cluster
- Process: informal and can be done quickly
- Participants: regulators only
- End product: informal comments sent to sponsor; NOT official scientific advice
- Regulatory impact: none

**Parallel Scientific Advice**
- Proposed by: sponsor
- To: CDER
- Process: formal and takes several months
- Participants: regulators and sponsors
- End product: regulatory advice
- Regulatory impact: binding
Pediatric Cluster: Common Commentary

• Between October 2012- May 2014: N=12
  – 11 products (note: teriflunomide common commentary was incorporated in the general common commentary for multiple sclerosis or MS)
    • 6 oncology products
    • 3 GI products
    • 1 cardiology product
    • 1 neurology product
  – 2 general approach to study products to treat a specific disease
    • 1 for MS
    • 1 for Gaucher disease
## Pediatric Cluster: Common Commentary

<table>
<thead>
<tr>
<th>Area</th>
<th>Product</th>
<th>Indication</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 oncology</td>
<td>LDE225</td>
<td>medulloblastoma</td>
<td>Novartis</td>
</tr>
<tr>
<td>2 &quot;</td>
<td>volasertib</td>
<td>AML</td>
<td>BI</td>
</tr>
<tr>
<td>3 &quot;</td>
<td>nivolumab</td>
<td>melanoma/other solid tumors</td>
<td>BMS</td>
</tr>
<tr>
<td>4 &quot;</td>
<td>blinatumomab</td>
<td>ALL</td>
<td>Amgen</td>
</tr>
<tr>
<td>5 &quot;</td>
<td>TH-302</td>
<td>RMS/NRMS</td>
<td>Threshold</td>
</tr>
<tr>
<td>6 &quot;</td>
<td>Inotuzumab</td>
<td>ALL</td>
<td>Pfizer</td>
</tr>
<tr>
<td></td>
<td>(PIP ONLY)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 Gl</td>
<td>adalimumab</td>
<td>ulcerative colitis</td>
<td>Abbvie</td>
</tr>
<tr>
<td>8 &quot;</td>
<td>golimumab</td>
<td>ulcerative colitis</td>
<td>J&amp;J</td>
</tr>
<tr>
<td>9 &quot;</td>
<td>tofacitinib</td>
<td>ulcerative colitis</td>
<td>Pfizer</td>
</tr>
<tr>
<td>10 CV</td>
<td>riociguat</td>
<td>PPHN (PIP only); PAH (both)</td>
<td>Bayer</td>
</tr>
<tr>
<td>11 neurology</td>
<td>teriflunomide and other products for MS</td>
<td>multiple sclerosis</td>
<td>multiple sponsors</td>
</tr>
<tr>
<td>12 inborn errors</td>
<td>multiple products to treat Gaucher disease</td>
<td>Gaucher disease</td>
<td>multiple sponsors</td>
</tr>
</tbody>
</table>
Case Study: Common Commentary for Tofacitinib for Moderate to Severe Ulcerative Colitis (UC)

• Tofacitinib common commentary document is representative of the issues discussed for other products under development for pediatric UC.

• Issues discussed at the Pediatric Cluster and at the IBD UC Working Group (WG). This WG was formed for further in-depth discussion of the issues initiated at the Pediatric Cluster. Members of the IBG UC Working Group included representatives from FDA (OPT, DGIEP, SEALD), EMA, Japan’s PMDA and Health Canada.

• The issues discussed included
  – Extrapolation
  – Dose-finding
  – Study design
  – Endpoints
Common Commentary Example: Pediatric Ulcerative Colitis

- FDA and EMA agree
  - Partial extrapolation from informative adult studies is a necessary element to construct a pediatric drug development program.
  - Conduct an initial pediatric dose-finding study before starting the pediatric efficacy study.
  - Efficacy study: not necessary to fully power for efficacy in the setting of partial extrapolation. For moderate- to severe UC, use of placebo during the induction phase represents greater than minimal risk. It is acceptable to use placebo during the maintenance phase provided the duration of exposure to placebo is minimized and escape criteria are specified. Alternatively, an active control can be used as the comparator.
  - Endpoint: Mucosal healing is the ultimate endpoint. The Mayo Score should be used as the primary endpoint. Due to lack of validation, PUCAI can be a secondary endpoint.
Common Commentary Example: Pediatric Ulcerative Colitis

• Conclusion
  – These discussions have resulted in 2 manuscripts, which have been accepted for publication this year by JPGN (already available on line)
    • “Steps Toward Harmonization for Clinical Development of Medicines in Pediatric Ulcerative Colitis- a Global Scientific Discussion Part 1: Efficacy Endpoints and Disease Outcome Assessments” Haihao Sun et al.
    • “Steps Towards Harmonization for Clinical Development of Medicines in Pediatric Ulcerative Colitis- Global Scientific Discussion Part 2: Data Extrapolation, Trial Design, and Pharmacokinetics” Haihao Sun et al.
Common Commentary Example: General Approach to Study Pediatric Gaucher Disease

• Given the rarity of Gaucher disease (the incidence in Europe is below their definition of “orphan” and meets the regulatory definition of “orphan” in the U.S.) and the emergence of many candidate products for treatment, it is critical that FDA and EMA develop a collaborative approach to study this disease.

• EMA drafted a working collaborative document, which was discussed at a joint EMA/FDA workshop in September 2012 and over 10 Pediatric Cluster teleconferences between December 2011 and April 2014. It has been finalized and was posted on May 14, 2014.

• Issues discussed were
  – Multi-arm, multi-company trials
  – Extrapolation
  – Endpoints
  – Trial duration
  – Nonclinical aspects
Common Commentary Example: General Approach to Study Pediatric Gaucher Disease

• FDA and EMA agree
  – double-blind, controlled, randomized, multi-arm, multi-company non-inferiority trial
  – extrapolation of efficacy from adults to children for visceral and hematologic endpoints within Type 1
  – change in normalized hemoglobin for treatment-naïve
  – 2-year study duration for primary endpoint
  – trial extension at least 3 years but at least 5 years is recommended
  – need for juvenile animal toxicity studies will be decided on a case-by-case basis

• Conclusion
  – Public posting: “Gaucher disease- a Strategic Collaborative Approach from EMA and FDA”
FDA, EMA, PMDA, HC and TGA
Additional Pediatric Collaborations

• **EMA’s Nonclinical Working Group**
  – includes FDA representation

• **EMA’s Formulations Working Group**
  – includes FDA representation

• **FDA and EMA pediatric expert meetings and workshops**
  – e.g. type 2 diabetes, pediatric osteoporosis, ADEPT 1: Pediatric Bone Health

• **Disease specific Working Groups (WGs)**
  – e.g. Inflammatory Bowel Disease WGs for ulcerative colitis and Crohn’s disease
CONCLUSIONS

• The PIP process and its timing are having an increasing impact on pediatric product development worldwide.

• An agreed PIP is necessary to submit an adult marketing application to EMA’s CHMP. This is not the case in the U.S.

• Greater clinical trial data transparency has been proposed in the EU, including making individual patient data available. However, this process is still in draft.
CONCLUSIONS

- Through the monthly Pediatric Cluster, issues pertaining to product development have been discussed for almost 350 products and 92 general topics.
- The monthly Pediatric Cluster provides a forum where scientists can informally listen to each other’s perspective and it has served well to resolve many issues.
- Common Commentary is a new informal process that provides sponsors with feedback on products discussed at the Pediatric Cluster.
- Multiple discussions may be needed at the Pediatric Cluster to work through the issues and workshops or working groups may be formed if extended discussion is required.
CONCLUSIONS

• As the cases illustrate, complete or partial resolution of many issues is reached through the discussions. These have resulted in joint scientific publications and joint EMA-FDA Strategic proposals.

• However, differences will remain due to differences in legislative approaches, cultural differences and differences in scientific practices.

• Nevertheless, having a forum for scientists to talk frankly and openly about these issues, helps bridge those differences and often results in modifications.
Conclusions

• Global collaboration and information sharing: critical to assure enrollment of children in scientifically and ethically sound trials that answer a needed question.
• We must work together
Resources

• Contact Suzanne Malli in OPT to:
  – Include a product or general topic on the Pediatric Cluster agenda
  – Obtain information on a PIP under review

• Access EMA’s website to obtain agreed PIP. The link is:
  www.ema.europa.eu
THANK YOU!