Multiregional Regulatory Considerations in Pediatric Drug Development

Lynne Yao, M.D.
Director Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
U.S. FDA

Disclosure Statement

- I have no financial relationships to disclose relating to this presentation

- The views expressed in this talk represent my opinions and do not necessarily represent the views of FDA

Pediatric Drug Development
General Principles

- Pediatric patients should have access to products that have been appropriately evaluated
- Product development programs should include pediatric studies when pediatric use is anticipated

From FDA guidance to industry titled *E11 - Clinical Investigation of Medicinal Products in the Pediatric Population,* December 2000

European Union Pediatric Drug Development Legislation

- Pediatric Regulation entered into force in 2007
  - (EC No 1901/2006)
  - Pediatric development obligatory in EU for new products, new indications, new routes of administration or new pharmaceutical forms protected by a Supplementary Protection Certificate (SPC) or a patent that qualifies
  - Fulfillment of requirements qualifies the product for incentive under this regulation

U.S. Pediatric Drug Development Legislation

- Best Pharmaceuticals for Children Act (BPCA)
  - Section 505A of the Federal Food, Drug , and Cosmetic Act
  - Provides a financial incentive to companies to voluntarily conduct pediatric studies
- Pediatric Research Equity Act (PREA)
  - Section 505B of the Federal Food, Drug , and Cosmetic Act
  - Requires companies to assess safety and effectiveness of certain products in pediatric patients
  - Applies to any product application for new indication, new active ingredient, new dosage form, new dosing regimen, or new route of administration

Canadian Pediatric Drug Legislation

- Health Canada has incentive provision for pediatric studies
  - Six month extension of data protection under Food and Drug Regulations
  - No specific requirements to conduct pediatric studies under current Food and Drug Regulations
  - No PIP/PSP equivalent in Canada
- Considering its stewardship role in both protecting Canadians and facilitating the provision of products vital to their health and well-being, Health Canada recognizes the importance of developing safe and effective medicines specifically for children
- Health Canada supports international harmonization efforts aimed at improving drug development for children and facilitating the conduct of studies that will permit appropriate labelling and use of medicinal products in the pediatric population
- Applying clinically and scientifically sound methodologies to the conduct of studies is expected to provide the evidence necessary to ensure that this important patient group has access to the full benefits of therapies available to adults

Important Differences

- Legal Framework
  - EU: Incentive and Requirements are unified under the Pediatric Regulation
  - US: The incentive and requirements are under separate laws
  - HC: Incentive provisions only
- The scope of requirements
  - EU: Requirements are derived from adult indication, within same condition
  - US: Requirements based on adult indication only
- Orphan Products
  - EU: Orphan products are ***not*** exempt from requirements
  - US: Orphan products are exempt from requirements
- Biosimilar Products
  - EU: Biosimilar products are exempt from requirements
  - US. Biosimilar products are ***not*** exempt from requirements
- Products excluded
  - EU: Homeopathic, generic, hybrid, well-established use, traditional herbal
  - US: Generic and dietary supplements (including herbal products regulated as dietary supplements)

Global Pediatric Collaboration

- Multiregional pediatric drug development programs face specific challenges
  - differences in pediatric regulatory requirements, operational practicalities, standards of care, and cultural expectations
- Ongoing alignment of the scientific approach is critical
  - Pediatric Cluster teleconferences
  - Joint Working Groups, Workshops and Joint Publications
  - Global Pediatric Trials Networks and Consortiums
  - International Conference on Harmonization

Pediatric Cluster Calls

- FDA, EMA and HC regularly share information related to the development of pediatric drug products
- At least monthly informal discussions between regulators
  - Includes FDA, EMA, HC, Japan's Pharmaceuticals and Medical Devices Agency (PMDA) and Australia's Therapeutic Goods Administration (TGA).
- Since 2007, 444 products and 148 general topics (e.g. safety concerns pertaining to a product class) have been discussed in 114 teleconferences.
- Frequently discussed product issues include scope of pediatric product development, safety, trial design and endpoints.
- Convergence on approaches have been achieved for 73% of the issues discussed in the past 3 years.

Joint Pediatric Working Groups, Workshops and Publications

- Working Groups
  - Inflammatory Bowel Disease WG for ulcerative colitis: Jan-Dec 2012
  - Inflammatory Bowel Disease WG for Crohn's Disease: Jan 2014-June 2015
  - Pediatric Rare Disease WG: Ongoing
- Workshops
  - Gaucher Disease Workshop: September 17-18, 2012
  - Draft joint proposal to facilitate the clinical investigation of new medicines for the treatment of Gaucher disease in children published May , 2014
  - PAH Workshop today and tomorrow
- Publications
  - Numerous publications on pediatric medicines development (e.g., ulcerative colitis, type 2 diabetes mellitus, Gaucher disease, and general topics)

Pediatric Research Initiatives and Networks

- United States
  - International Neonatal Consortium (INC)
  - Pediatric Trials Consortium (PTC)—now an independent non-profit (Institute for Advanced Clinical Trials for Children)
  - Several other research networks (Pediatric Trials Network, rheumatology, nephrology, etc.)
- Canada
  - Maternal Infant Child Youth Research network (MICYRN)
  - Several other research networks (e.g., infectious diseases, emergency medicine, surgery)
- European Research Network initiatives
  - European Network of Pediatric Research at EMA (Enpr-EMA)
  - GriP (Global Research in Paediatrics)
  - Consortium for Innovative Therapies for Children with Cancer (ITCC)
  - Paediatric European Network for Treatment of AIDS (PENTA)
  - UK Clinical Research Network (UK CRN)

International Council for Harmonisation

- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
  - Regulatory authorities and pharmaceutical industry gather “to make recommendations towards achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration and the maintenance of such registrations”
- Current ICH E11 guideline being revised based on scientific, clinical, and regulatory advancements
  - Updates on several topics including extrapolation, modeling and simulation, ethics, formulations
  - Final endorsement and publication expected before the end of 2017
- New concept paper on Pediatric Extrapolation approved by ICH assembly
  - Expert Working Group formation expected before the end of 2017

Summary

- The best therapy for a child is an approved therapy
- Multiregional pediatric drug development programs face differences in pediatric regulatory requirements
- Developing a common scientific approach will help to align differences in regulatory requirements
- Our common goal is to provide timely and efficient access to approved therapies for children

Acknowledgements

- Cecile Ollivier and EMA for organizing and hosting the workshop
- Contributions to content of this presentation
  - Jean Temeck, M.D., Office of Pediatric Therapeutics, FDA
  - Ariel Arias, M.D., Senior Advisor, Centre for Biologics Evaluation, HC

U.S. FOOD & DRUG ADMINISTRATION

Thank you for your attention

Lynne Yao, M.D.
lynne.yao@fda.hhs.gov
Division of Pediatrics and Maternal Health
WO22 Room 6406
10903 New Hampshire Ave.
Silver Spring, MD 20993

Backup Slides

Comparison between PSP and PIP template

Contains Nonbinding Recommendations

Draft — Not for Implementation

APPENDIX 2:
INITIAL PEDIATRIC STUDY PLAN TEMPLATE[37]

1. OVERVIEW OF THE DISEASE IN THE PEDIATRIC POPULATION (1-5 pages)
2. OVERVIEW OF THE DRUG OR BIOLOGICAL PRODUCT (1-5 pages)
3. OVERVIEW OF PLANNED EXTRAPOLATION TO SPECIFIC PEDIATRIC POPULATIONS (1-5 pages) *
4. REQUEST FOR DRUG-SPECIFIC WAIVER(S) (1-3 pages)
5. SUMMARY OF PLANNED NONCLINICAL AND CLINICAL STUDIES
6. PEDIATRIC FORMULATION DEVELOPMENT (1-3 pages)
7. NONCLINICAL STUDIES (1-5 pages)
8. CLINICAL DATA TO SUPPORT DESIGN AND/OR INITIATION OF STUDIES IN PEDIATRIC PATIENTS (1-5 pages)
9. PLANNED PEDIATRIC CLINICAL STUDIES
   - 9.1 Pediatric Pharmacokinetic Studies (1-10 pages)
   - 9.2 Clinical Effectiveness and Safety Studies (1-10 pages)
10. TIMELINE OF THE PEDIATRIC DEVELOPMENT PLAN (1-2 pages)
11. PLAN TO REQUEST DEFERRAL OF PEDIATRIC STUDIES (1-2 pages)
12. AGREEMENTS FOR OTHER PEDIATRIC STUDIES (1-5 pages)

(EMA PIP)

[37] This template is also available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM338453.pdf.

Table of contents