General Landscape of Drug Development of Analgesics for Acute Pain in Birth to less than 2 years

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FDA

Acknowledgments

- Division of Anesthesiology, Addiction Medicine, and Pain Medicine
  - Lisa Wiltrout, MD
  - Rigo Roca, MD
- Division of Pediatrics and Maternal Health
  - Mona Khurana, MD
  - Lynne Yao, MD
  - John Alexander, MD
  - Heather Buck
  - Kerri-Ann Jennings
- University of Maryland CERSI
  - Dina El Metwally, MD (Division of Neonatology)
  - Ann Annonsen, Jim Poli
- All speakers and panelists

Disclaimer

- 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

- **Acute pain** is defined as pain that is self-limited and generally requires treatment for **no more than up to a few weeks** (e.g., postoperative or acute musculoskeletal pain).

- Chronic pain is defined as either pain persisting for longer than 1 month beyond resolution of the underlying insult, or pain persisting beyond 3 months.

U.S. evidentiary standard for approval

- For approval, pediatric product development is held to same evidentiary standard as adult product development
- A product approved for children must:
  - Demonstrate **substantial evidence of effectiveness/clinical benefit** (21CFR 314.50)

Substantial evidence of effectiveness

"Evidence consisting of adequate and well -controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved"

– Section 505(d), Food, Drug & Cosmetic Act

Clinical benefits to support drug approval

Clinical outcomes

- Direct measure of how a patient feels, functions, or survives
- Improvement or delay in progression of clinically meaningful aspects of the disease

Surrogate endpoints

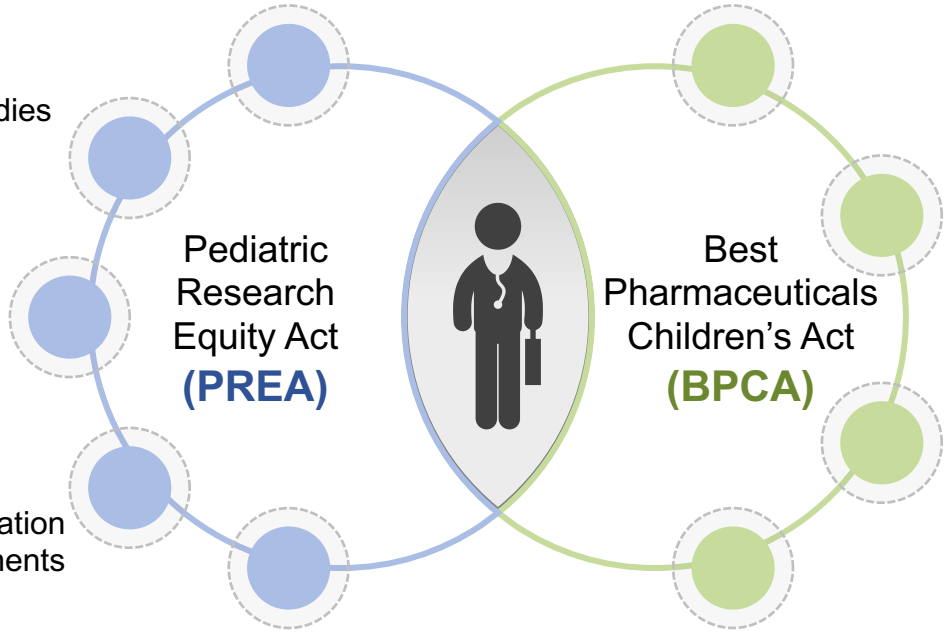
- A substitute for how a patient feels, functions, or survives
- **Established surrogates** (e.g. blood pressure, low density lipoprotein (LDL) in adults, forced expiratory volume in 1 sec (FEV_1) in asthma)
- Surrogates reasonably likely to predict clinical benefit
  - Accelerated approval
  - Requires additional studies post-marketing to confirm clinical benefit
  - For serious conditions and unmet medical need

Pediatric extrapolation

"If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, [FDA] may conclude that **pediatric effectiveness** can be extrapolated from adequate and well - controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies." (21 CFR §355c)

Drug development in pediatric acute pain: regulatory framework

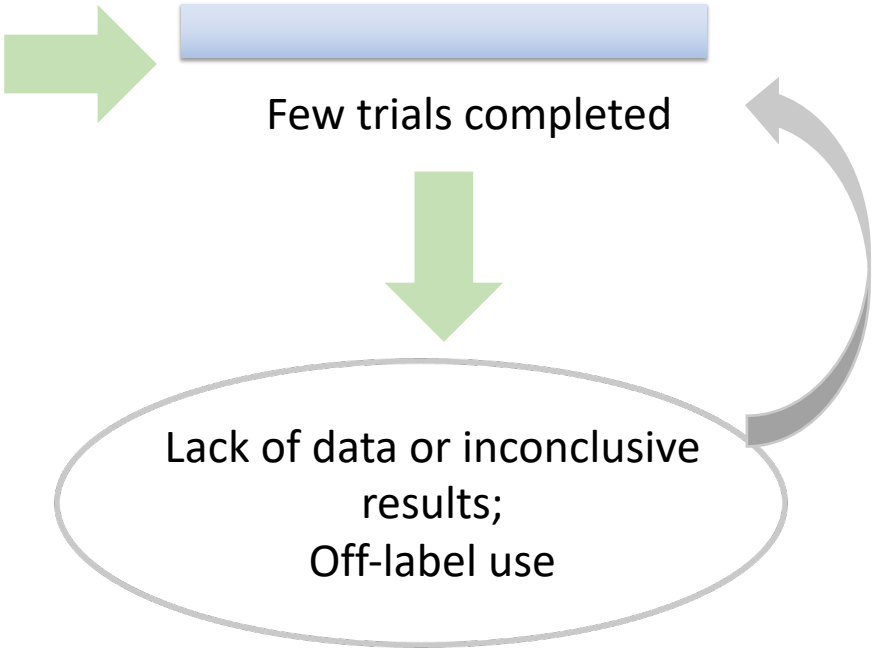
The context is a drug/biological product developed for **adult acute pain, studied in adult patients** and then investigated for its potential use in children



- Sponsors are encouraged to begin discussions about their **pediatric clinical development plan early in development**:
  - Applicants submitting NDAs (or supplements) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration of a drug are required **to submit pediatric study plans no later than 60 days after an end-of-phase 2 meeting,** unless another time has been separately agreed upon…

Multiple challenges associated with acute pain trials in pediatric patients

- Standard parallel placebo-controlled trials used in adults have ethical and practical concerns
  - "Lack of equipoise"
- Accurate pain assessment for infants and children who are unable to self-report measures is challenging
- Reluctance of study sites and institutional review boards
  - Trial feasibility and recruitment challenges



Evolution of Pediatric Study Requirements: Acute Pain

- Pre 2010: randomized, controlled trials in all age groups:
  - Sponsors reluctant to conduct randomized, double-blind trials to assess efficacy
  - Ethical and practical difficulties with placebo-controlled trials

Current Approach to Acute Pain

- Dec 2009, FDA scientific workshop of thought leaders in pediatric pain

- For drugs with **well-established mechanism of action** (Opioids, Nonsteroidal Anti-inflammatory Drugs, Acetaminophen, and Local Anesthetics):
  - 2 years and older: Efficacy can be fully extrapolated; PK/safety data needed
  - **Birth to < 2yrs**: Efficacy/safety/PK data using "add-on" design with opioid-sparing as primary endpoint rather than pain scores
- For drugs with less established mechanism of action:
  - PK/efficacy/safety in all age groups

*Berde, CB, et.al., Pediatrics 2012 Feb;129(2):354-64.

Persistent challenges in acute pain

- Unmet need in acute pain in pediatric patients, especially in patients less than 2 years
- While studies have been required under PREA since 2003 in this age group:
  - Few analgesic studies have been completed
  - Completed trials are difficult to interpret
  - Only one analgesic (ibuprofen) approved below 2 years
  - Most use continues to be off-label

Today's workshop: Acute Pain in Patients Less than 2 years

Focus for workshop presentations/discussions

For drugs with well established MOAs (Opioids, NSAIDs, Acetaminophen, and Local Anesthetics):

Session 1

- Discuss available evidence to support extrapolation of efficacy in patients birth to less than 2 years including drug class specific considerations

Session 2:

- Discuss trial design considerations for the assessment of efficacy and safety

Day 1

10:00 – 10:15	**Welcome/Introductory remarks: Setting the scene (DPMH)** Lily Mulugeta, PharmD (Division of Pediatrics and Maternal Health, FDA)
10:15 – 10:35	**Introductory remarks** Peter Stein, MD (Office of New Drugs, FDA) Rigo Rocca, MD (Division of Anesthesiology, Addiction Medicine, and Pain Medicine, FDA)
10:35– 10:50	**General landscape of extrapolation of efficacy in pediatric drug development and Ethical considerations in Pediatric Drug Trials** Beth Durmowicz, MD (Office of Pediatric Therapeutics, FDA)

Session 1: Extrapolation of Efficacy (goals: To define an age limit for using PK-based extrapolation (i.e. exposure-matching))

Moderators: Lily Mulugeta (FDA) and Lisa Wiltrout (FDA)

10:50 – 11:10	**Development of nociception and pain--**Suellen Walker, PhD (UCL GOS Institute of Child Health)
11:10 – 11:30	**Pain epidemiology in neonates and infant patients**--Ricardo Carbajal, MD (Hospital Armand Troussea)
11:30 – 11:45	**Developmental pharmacology of analgesics--**Chris Mcpherson, PharmD (Washington University School of Medicine, St Louis)
11:45– 12:05	**Extrapolation of adult efficacy data to pediatric patients** John van den Anker, MD (Children's Hospital, Washington DC)
12:05—1:20	**Panel Discussion (Moderators: Lily Mulugeta and Charles Berde)** **Q&A: All speakers** **Panelists:** John Alexander (FDA), Yun Xun (FDA), Lisa Wiltrout (FDA), Tamorah Lewis; Suellen Walker, Gary Walco, Ellen Fields, Kanecia Zimmerman, John Van Den Anker
1:20—1:30	**Closing Remarks – Charles Berde**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