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

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FDA
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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
“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

- **Pediatric Research Equity Act (PREA)**
  - **Required** studies
  - Applies to products developed for diseases/conditions that occur in both the adult and pediatric populations
  - Products with orphan designation are exempt from requirements
  - Information on pediatric studies must be labeled

- **Best Pharmaceuticals Children’s Act (BPCA)**
  - **Voluntary** studies; Additional 6 months of marketing exclusivity
  - Studies may be requested for indications unrelated to approved indications and for products with orphan designation
  - Information on pediatric studies must be included in labeling
• 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

Few trials completed

Lack of data or inconclusive results;
Off-label use
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

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 Wiltzrout (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 Trousseau)

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 Wiltzrout (FDA), Tamorah Lewis; Suellen Walker, Gary Walco, Ellen Fields, Kanecia Zimmerman, John Van Den Anker

1:20 – 1:30  Closing Remarks – Charles Berde