Analgesic Development for Pediatric Patients

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Why Do We Need Pediatric Trials?

- Children should have access to medicines that have been properly evaluated for use in the intended population
- Thoughtful drug development and inclusion of children in trials is critical to pediatric health

Pediatric Research: A Moral Imperative

"The performance of research studies to evaluate drugs in children is critical for determining the safety and efficacy of medications in children. …Without proper drug studies in children, children may not benefit from and may even be harmed by drugs that are available to adults. Also, certain disorders affect children primarily, necessitating drug testing on appropriately aged subjects. It is morally imperative, therefore, to formally study drugs in children so that they can enjoy appropriate access to existing and new therapeutic agents."

- Robert E. Shaddy, MD, Scott C. Denne, MD and The Committee on Drugs and Committee on Pediatric Research. PEDIATRICS Vol. 125 No. 4 April 2010, pp. 850-860

Pediatric Patients

- Defined in drug regulation as 0 to < 17 years old
- Age cohorts are not established in regulation and should be based on scientific rationale (e.g., metabolism of a critical enzyme, clinical endpoints, ability to swallow the formulation)
- An example of pediatric cohorts
  - Neonates (birth to 1 month)
  - Infants (1 month to 2 years)
  - Children (2 to 12 years)
  - Adolescents (12 to < 17 years)

Pediatric Drug Legislation

- 1994: Pediatric Labeling Rule
  - Extrapolation introduced
- 1997: FDAMA
  - Exclusivity provision
- 1998: Final Rule:
  - Pediatric studies required (enjoined 2002)
- 2001: Subpart D- Interim Rule
  - Additional safeguards for children in clinical investigations of FDA-regulated products

Pediatric Drug Legislation

- Best Pharmaceuticals for Children Act (BPCA) (2002)
- Pediatric Research Equity Act (PREA) (2003)

Best Pharmaceuticals for Children Act (BPCA)

- Provides for **voluntary** pediatric drug assessments via a Written Request (WR), including clinical and non-clinical studies
- Authorizes FDA to request studies for the drug moiety, for approved and/or unapproved pediatric indications including orphan indications
- Reflects a public health need for pediatric studies
- Provides a process for studying off-patent drugs
- Establishes an internal committee (PeRC) to review all WRs prior to their issuance

BPCA

- Sponsors often submit a proposed pediatric study request (PPSR)
- FDA also can issue a WR without a PPSR
- Six months of marketing exclusivity granted if the terms of the WR have been met (does not require positive pediatric studies)
- FDA reviews studies and the WRs are posted on the web
- Pediatric safety data are presented publicly to an advisory committee one year after studies are conducted

Pediatric Research Equity Act (PREA)

- Triggered by an application for a new indication, new dosage form, new dosing regimen, new route of administration or new active ingredient
- Authorizes FDA to **require** a pediatric assessment of certain drug/biologic products at the time the application is submitted.
- Provides criteria for FDA to waive or defer pediatric studies and requires a plan for deferred studies
- Establishes the Pediatric Review Committee (PeRC) to review pediatric plans & assessments and waiver & deferral requests

Pediatric Drug Legislation

- 2007: FDAA Reauthorizes BPCA & PREA for 5 years
  - Pediatric Review Committee (PeRC) formed
  - Studies submitted will result in labeling, including negative and positive results of pediatric studies
- FDA Safety and Innovation Act (FDASIA) - Enacted July 9, 2012
  - BPCA and PREA become a **permanent** part of the Food, Drug, and Cosmetic Act
  - NIH BPCA program reauthorized to Oct. 2017
  - Additional provisions for devices through Oct. 2017

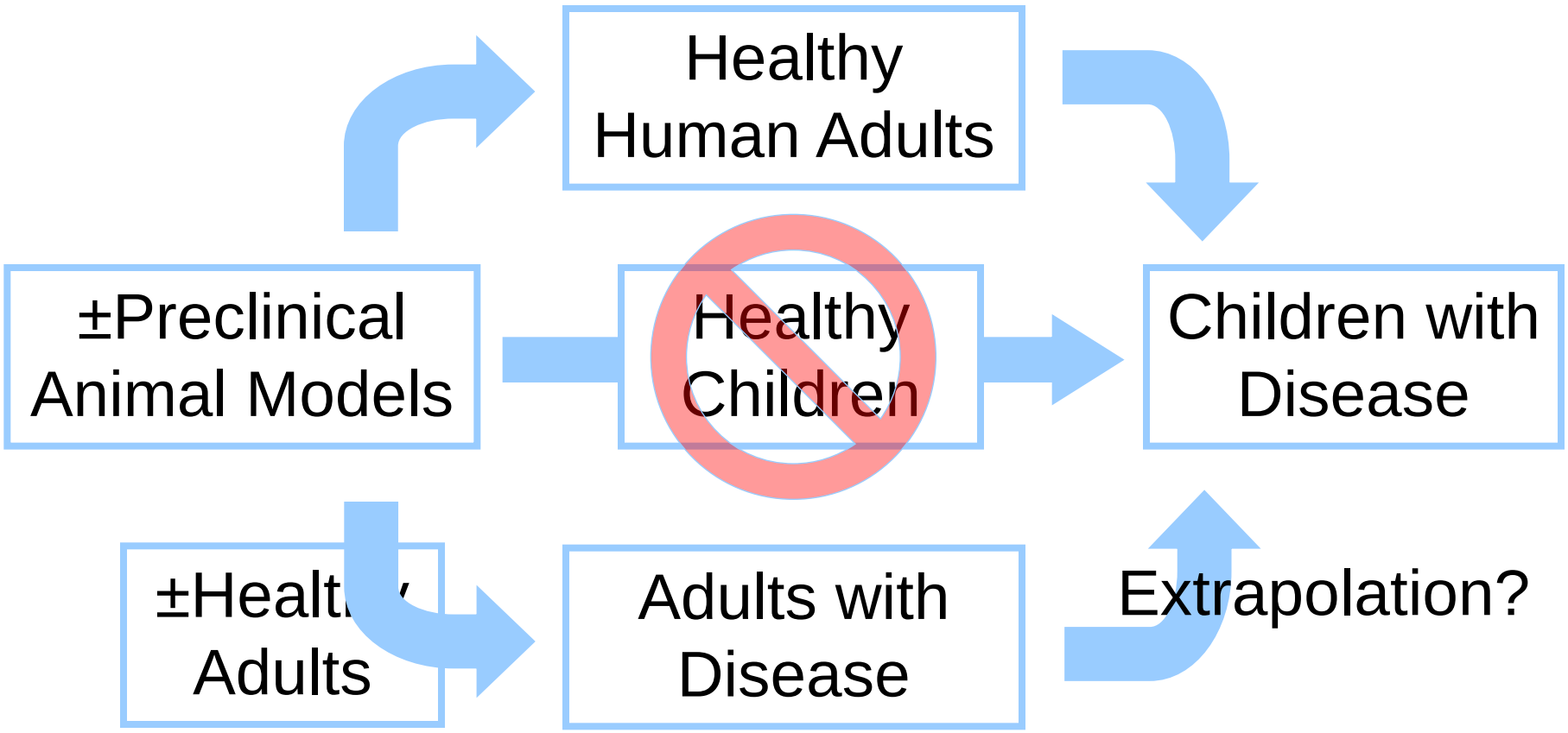
Pediatric Drug Development:

FDA Guidance to Industry - *E11 Clinical Investigation of Medicinal Products in the Pediatric Population,* December 2000

General Principles

- Give pediatric patients products that have been appropriately evaluated for them
- Drug development programs should include pediatric studies when anticipate pediatric use

Pediatric Drug Development



Current Situation

- Unmet needs in pediatric pain management
- While pediatric studies have been required by law since 2003 (PREA)
  - Few analgesic studies have been completed
  - Few analgesics are labeled for pediatric use
  - Most use in pediatric patients is off-label

Analgesics with Pediatric Indications/Labeling

Acetaminophen, Aspirin, NSAIDs

- Acetaminophen (APAP) (≥2 y)
- Aspirin (ASA)
- Ibuprofen (≥ 6 m)

Juvenile Inflammatory Arthritis

- Celecoxib
- Diflunisal
- Etodolac XL
- Indomethcin
- Ketorolac
- Mefenamic acid
- Meloxicam
- Naproxen
- Oxaprozin
- Tolmetin

Opioids

- Buprenorphine injection
- Fentanyl citrate injection
- Fentanyl transdermal (≥2y)
- Meperidine
- *OxyContin (11≤17y)*

Combination Products

- Codeine/Acetaminophen (≥ 3y)
- Hydrocodone/Acetaminophen (≥2y)
- Oxycodone/Ibuprofen
- Pentazocine/ Acetaminophen
- Pentazocine/Naloxone
- Acetaminophen/Butalbital +/- Caffeine
- Carisoprodol/Aspirin/Codeine
- Codeine/Aspirin/Butalbital/Caffeine
- Dihydrocodeine/Aspirin/Caffeine

Analgesics without Pediatric Labeling

NSAIDs

- Diclofenac
- Diclofenac potassium
- Diclofenac sodium/misoprostal
- Fenprofen
- Flurbiprofen
- Ketoprofen
- Nabumetone
- Piroxicam
- Sulindac

OTHER

- Carbamazepine
- Duloxetine
- Gabapentin
- Pregabalin

OPIOIDS

- Fentanyl Oral Transmucosal
- Hydrocodone ER
- Hydromorphone IV/IR/ER
- Methadone
- Morphine sulfate IV/IR/ER
- Morphine/Naltrexone ER
- Oxycodone IR/ER
- Oxycodone/Naloxone ER
- Oxymorphone IV/IR/ER
- Tramadol IR/ER
- Tapentadol IR/ER
- Butorphanol
- Levorphanol
- Nalbuphine
- Pentazocine

Opioid/Nonopioid Combination Products

- Hydrocodone/ Ibuprofen
- Oxycodone/ Acetaminophen
- Oxycodone/ Aspirin
- Tramadol/ Acetaminophen

Study Requirements: Pediatric Pain

Pre 2010: Pharmacokinetic, efficacy and safety studies all analgesics, all age groups

Little Progress

- Sponsors reluctant to conduct randomized, double-blind trials to assess efficacy
- Standard parallel placebo-controlled trial used in adults had ethical and practical difficulties in pediatrics

Enrollment Challenges

- Parental reluctance
  - Fear of harm to children, especially extensive blood sampling
- Ethical concerns
  - Use of placebo
  - Risk of pediatric patients experiencing more than minor pain when there are effective treatments
- Relatively small patient populations especially for youngest patients and chronic pain
- Additional concerns regarding studying neonates
    - Painful procedures including blood sampling
    - Emotional impact on parents of sick newborn

Extrapolation

- Concept of extrapolation introduced in the 1994 Pediatric Labeling Rule (59 Fed. Reg. 64240)
- Definition of extrapolation of pediatric efficacy, 21CFR §355c:

  "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."

Why is Extrapolation Important?

- Often, there is a limited number of pediatric patients available for enrollment in clinical trials
- Children are vulnerable and require additional safeguards
  - developing systems
  - inability to communicate feelings or symptoms
  - Inability to consent
- Important to decrease the number of patients required for a pediatric trial and to maximize the information obtained
- Pediatric trials should be efficiently and effectively designed

FDA Workshop

- December, 2009 FDA convened scientific workshop of thought leaders in pediatric pain, pediatric clinical studies, pediatric ethics and pediatric drug development
- Participants discussed available science to support extrapolation for analgesic drug classes
- When efficacy trials required, approaches to study design considered
- 2012 Publication: “Pediatric Analgesic Clinical Trial Designs, Measures, and Extrapolation: Report of an FDA Scientific Workshop”, Berde, CB, et. al.*

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

Current Approach to Study Requirements

- Opioids, Nonsterioidal Anti-inflammatory Drugs, Acetaminophen, and Local Anesthetics
  - Pharmacokinetics and safety all age groups
  - Extrapolate efficacy down to age 2 years
  - Efficacy studies only in patients less than age 2
- All other drug classes
  - Pharmacokinetics, efficacy, and safety all age groups
- Chronic pain (define) or ER
  - Waive studies in patients less than 7 years

Study Design – Efficacy

- When efficacy cannot be extrapolated, encourage the use of “add-on” design with opioid-sparing as primary endpoint rather than pain scores
- Particularly useful
  - in neonates and infants where there are limitations in pain assessments made by surrogates (parents, investigators)
  - Evaluation of post op pain by using nurse or patient controlled analgesia rescue as primary endpoint for oral analgesic
- Not useful for stand-alone analgesics

Industry continues to struggle with design and conduct of pediatric pain trials

Ongoing Challenges - Enrollment

- Sponsors have trouble enrolling pediatric patients into trials
  - Too few patients
  - Parental concerns
- Reluctance of study sites and institutional review boards
- Can take years to complete enrollment - what is “reasonable period of time”?

Ongoing Challenges - Measurement

- Accurate pain assessment especially in children too young to self-report is challenging
- Pediatric age range so wide that more than one scale is necessary to capture verbal and nonverbal children in the same study
- Particularly challenging in the youngest patients

Measurement

- Efforts to address some of the measurement and clinical trial issues:
  - Newborn Drug Development Initiative*, Feb 2003
  - Pediatric IMMPACT+, March 2005
- Discuss outcome domains and measures for pediatric acute and chronic pain clinical trials
- Large number of tools available for assessing pain, few are validated
- Multidimensional indices of behavioral and physiologic responses are used in neonates and infants

* Kanwaljeet J.S. Anand, et.al., Summary Proceedings From the Neonatal Pain-Control Group, Pediatrics 2006;117(Sup 1):S9-S22.

+Patrick J. McGrath, et.al., Core Outcome Domains and Measures for Pediatric Acute and Chronic/Recurrent Pain Clinical Trials: PedIMMPACT Recommendations, J of Pain 2008; 9 (9):771-783

Pediatric Instruments to Assess Pain*

- 1 year and above
  - Face, Legs, Arms, Cry, Consolability
  - Children's Hospital of Eastern Ontario Pain Scale
  - Parents' Postoperative Pain Measure
  - On ventilator: COMFORT scale
  - Toddler-Preschooler Postop Pain Scale
- 3-4 years
  - Poker Chip Tool
- 4-12 years
  - Faces Pain Scale-Revised
- 8 years +
  - Visual Analog Scale (VAS), Numerical Rating Scale (NRS)

*McGrath, et al, J of Pain, Vol 9(9) 2008, 771-783

Infant Pain Scales*

A1: INFANT PAIN SCALES

Scale	Age	Type of Pain	Psychometric Properties	Use in Analgesic Trials
		Preterm Infants		
Premature Infant Pain Profile (PIPP)	Preterm to term infants (28–40 wk GA)	Acute (procedural) Acute (prolonged)	Interrater reliability Internal consistency Construct validity	RCT; sucrose trials for heel lance[42]
Neonatal Pain Agitation and Sedation Scale (N-PASS)	Preterm to term infants (23–40 wk GA)	Acute (procedural) Acute (prolonged)	Interrater reliability Internal consistency Construct validity	RCT; sucrose trials for retinopathy of prematurity screening[43]
Neonatal Infant Pain Scale (NIPS)	Preterm and full term neonates	Acute (procedural)	Interrater reliability Internal consistency Construct validity	RCT; sucrose for heel lance[44]
Douleur Aiguë du Nouveau-né (DAN)	Preterm to term (24–41 wk GA)	Acute (procedural)	Interrater reliability Internal consistency Construct validity	RCT; opioids,[45] RCT; Breastfeeding,[46] Glucose[47]
		Full Term Infants <2 mo		
Neonatal Facial Coding System (NFCS)	Preterm to term and infants (27 wk GA – 2 mo PCA)	Acute (procedural pain)	Interrater reliability Construct validity	RCT; opioid trials,[48] topical analgesics,[49,50] sucrose,[51] SSRI exposure[52]
		Full Term Infants <12 mo		
Faces, Legs, Activity, Crying, Consolability Scale (FLACC)	Full term infants >2 mo	Acute prolonged (postoperative)	Interrater reliability Internal consistency Construct validity	
COMFORT Scale	Infants 0–12 mo (+ children up to 17 y)	Acute (prolonged), Chronic, or level of sedation	Interrater reliability Internal consistency Construct validity	Opioids[53–56]
Modified Behavioral Pain Scale (MBPS)	Infants 2–6 mo	Acute (procedural – immunization)	Interrater reliability Internal consistency Construct validity	Topical anesthetics[57–59]

GA, gestational age; RCT, randomized controlled trial; SSRI, selective serotonin reuptake inhibitor.

Berde, CB, et.al., Pediatrics 2012 Feb;129(2):354-64. doi: 10.1542/peds.2010-3591.

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Overall Successes for Pediatric Patients

- 1997-2016: Over 600 products have been studied in pediatrics and have new pediatric information in the label
- Of these over 500 involved new pediatric studies
- First product study results submitted and labeled as a result of the “Docket” process involving FDA/NIH/investigators. Dozen more products are soon to be submitted.

Substantial Work Still Needed with Analgesics

- Most analgesics still lack pediatric indications or pediatric-specific information in the package insert
- Use PREA to require studies when possible, BPCA to encourage additional work
- Information Needed
  - Pharmacokinetic profile by age
  - Safe dosing and administration instructions
  - Efficacy in patients under 2 years NSAIDs, opioids, all ages for novel analgesic classes

Substantial Work Still Needed…

Currently many analgesic products with pending PREA requirements:

- NDA 207932 Belbuca (buprenorphine)
- NDA 021306 Butrans (buprenorphine)
- NDA 022348 Caldolor (ibuprofen)
- NDA 022370 Conzip (tramadol)
- NDA 22148 Cymbalta (duloxetine)
- NDA 019034 Dilaudid (hydromorphone)
- NDA 022396 (diclofenac)
- NDA 021217 Exalgo (hydromorphone)
- NDA 206627 Hysingla (hydrocodone)
- NDA 021338 Ionsys (fentanyl)
- NDAs 022207, 022195 Morphine
- NDAs 200533, 203794 Nucynta (tapentadol)
- NDA 022450 Ofirmev (acetaminophen)
- NDAs 021610, 021611 Opana (oxymorphone)
- NDAs 200534, 200535, 201194 Oxycodone)
- NDA 021044 Palladone (hydromorphone)
- NDA 021693 Rybix ODT (tramadol)
- NDA 205777 Targiniq (hydrocodone)
- NDA 204768 Tivorbex (indomethacin)
- NDA 204031 Xartemis (oxycodone/acetaminophen)
- NDA 202880 Zohydro (hydrocodone)
- NDA 204592 Zorvolex (diclofenac)

Recent FDA Activities

February 4, 2016: FDA Opioid action plan

- Re-examine the risk-benefit paradigm/ wider public health effects
- Advisory committee - any new opioid without abuse-deterrent properties
- Assemble and consult with the Pediatric Advisory Committee regarding a framework for pediatric opioid labeling before any new labeling is approved
- Develop changes to immediate-release opioid labeling – announced March 22, 2016
- Advisory committee recommendations for opioid REMS (May 3-4, 2016)
- Expand access to, and encourage the development of, abuse-deterrent formulations of opioid products
- Improve access to naloxone and medication-assisted treatment options for patients with opioid use disorders
- Support better pain management options, including alternative treatments

Recent FDA Activities

March 1, 2016: Meeting of the FDA Science Board

- the role of opioids in pain management
- scientific challenges facing FDA in supporting the development of pain medications, including opioids, that have reduced risks of being abused
- scientific challenges facing FDA in seeking to understand the real-world use of opioids to treat pain, including the impact of opioids with potentially less risk for abuse
- the role that FDA plays as a part of a larger Federal, State and local response to the challenges of providing appropriate pain treatment while reducing opioid abuse
- postmarket surveillance activities related to opioids.

Upcoming Meetings

May 3-4, 2016: Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee

- Discuss the results from assessments of the extended-release and long-acting Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS)
  - Does this REMS with elements to assure safe use does assure safe use
  - Is it not unduly burdensome to patient access to the drugs
  - Does it minimize the burden to the healthcare delivery system.

Joint Advisory Committee Meeting September 15-16, 2016

- Anesthetic and Analgesic Drug Products Advisory Committee
- Drug Safety and Risk Management Advisory Committee
- Pediatric Advisory Committee

- Discuss the appropriate development plans for establishing the safety and efficacy of prescription opioid analgesics for pediatric patients, including obtaining pharmacokinetic data and the use of extrapolation.
  - Docket for public comment on this meeting, FDA-2016-N-0584
  - Open from February 19, 2016 through September 30, 2016