Pediatric Drug Development Regulatory Considerations

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Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee, the Drug Safety and Risk Management Advisory Committee, and the Pediatric Advisory Committee
September 15-16, 2016

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

Pediatric Product Development: The Historical Problem

Acknowledged different drug responses, toxicity, and metabolism in adults versus children

Discouraged the study of drugs in children
- Concerns related to ethical issues
- Fears of harming children
- Perceived increased liability of testing drugs in children

Lacked an incentive for drug companies to conduct pediatric trials

Choices for Pediatric Practitioners

- Not treat children with potentially beneficial medications because they are not approved for use in children
- Treat with medications based on adult studies with limited or anecdotal pediatric experience (off-label use)

Pediatric Drug Development Laws

- 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
  - FDA and the National Institutes of Health partner to obtain information to support labeling of products used in pediatric patients (Section 409I of the Public Health Service Act)
- 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

PREA vs. BPCA

PREA

- Drugs and biologics
- **Required** studies
- Studies may only be required **for approved indication(s)**
- Products with orphan designation are exempt from requirements
- Pediatric studies must be labeled

BPCA

- Drugs and biologics
- **Voluntary** studies
- Studies relate to entire moiety and **may expand indications**
- Studies may be requested for products with orphan designation
- Pediatric studies must be labeled

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** Clinical benefit:
    - The impact of treatment on how patient feels, functions or survives
    - Improvement or delay in progression of clinically meaningful aspects of the disease

21CFR 314.50: Content and format of an application

Substantial Evidence

- Evidence of effectiveness
  - Evidence consisting of adequate and well – controlled investigations on the basis of which it could fairly and responsibly be concluded that the drug will have the effect it purports to have under the conditions of use prescribed, recommended, or suggested in the labeling

21 U.S.C. §355 (d) Grounds for refusing application; approval of application; “substantial evidence” defined

Adequate and Well-Controlled Study

- Study should "distinguish the effect of a drug from other influences, such as spontaneous change…, placebo effect, or biased observation"
- Must incorporate generally accepted scientific principles for clinical trials
- Well-controlled studies of adequate design must show effectiveness, ordinarily a statistically significant effect on a clinically meaningful endpoint, usually replicated, as a basis for approval.

21 CFR 314.26: Adequate and well-controlled studies

Pediatric Research Equity Act (PREA)

- PREA requires pediatric assessments of new drugs and biological products for all new active ingredients, indications, dosage forms, dosing regimens, and routes of administration.
  - To assess the safety and effectiveness of a drug/biologic for the claimed indications in all relevant pediatric subpopulations AND
  - To support dosing and administration for each pediatric subpopulation for which the drug or biological product is safe and effective
  - Pediatric studies must be conducted using age-appropriate formulations
- Authorizes FDA to require pediatric studies of approved drug/biologic indications
- Provides criteria for FDA to waive or defer pediatric studies

PREA

- Waivers may be granted when there is evidence strongly suggesting that
  - Necessary studies are impossible or highly impracticable (e.g., number of patients in that age group is so small)
  - the drug or biological product would be ineffective or unsafe in that age group
  - the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group; and is not likely to be used by a substantial number of pediatric patients in that age group
  - or reasonable attempts to produce a pediatric formulation necessary for that age group have failed
- Deferral of submission of pediatric assessment can be granted if:
  - the drug or biological product is ready for approval for use in adults before pediatric studies are complete;
  - pediatric studies should be delayed until additional safety or effectiveness data have been collected; or
  - there is another appropriate reason for deferral

PREA: Deferrals and Waivers

- OND review divisions and sponsors should discuss PREA requirements early in the drug development process
- Pediatric Study Plans are required to be submitted for all products subject to PREA
  - Outline of the pediatric study or studies the applicant plans to conduct
  - Must include plans to request deferrals, waivers or partial waivers with supporting data
- Final deferral and waiver decisions are made at the time of NDA/BLA approval

Best Pharmaceuticals for Children Act (BPCA)

- Provides for voluntary pediatric drug studies via a Written Request (WR)
- Reflects need for information that may produce health benefits in the pediatric population
- Authorizes FDA to request pediatric studies of approved and/or unapproved indications
- A sponsor may request the FDA issue a WR by submitting a Proposed Pediatric Study Request (PPSR)
- PPSR should contain:
  - Rationale for studies and study design
  - Detailed study design
  - Appropriate formulations for each age group
- Sponsors who submit studies to fulfill a WR may be eligible to receive pediatric exclusivity

BPCA: Pediatric Exclusivity

- If the terms of the WR have been met and studies were conducted using good scientific principles, the company is awarded an additional 6 months of exclusivity
  - Exclusivity attaches to all existing marketing exclusivities and patents for the drug moiety (initial WR)
  - Pediatric exclusivity does not require positive pediatric studies (initial WR)
- Granting of exclusivity is reviewed by the FDA Pediatric Exclusivity Board

Pediatric Review Committee (PeRC)

- Established by statute to carry out the activities described under PREA and BPCA
- Intended to provide internal FDA oversight and guidance related to scientific and regulatory issues related to pediatric product development under BPCA and PREA
- Committee membership
  - Includes members with expertise in pediatrics, clinical pharmacology, statistics, chemistry, legal issues, pediatric ethics, neonatology, and other expertise pertaining to pediatric products under review
  - PeRC meets weekly for 3 hours and reviewed almost 800 pediatric submissions last year
- The PeRC reviews submissions related to PREA and BPCA prior to final divisional approval

Pediatric Advisory Committee

- Established under BPCA and PREA
- Committee membership must include representatives of pediatric health organizations, pediatric researchers, relevant patient and patient-family organizations, and other experts
- Mandated that 18 months after pediatric labeling changes under BPCA or PREA, the FDA is to conduct pediatric postmarketing safety review
- FDA findings are presented to the Pediatric Advisory Committee
  - Between 2007-2013, 14 PAC meetings convened and post-marketing safety reviews were presented for 181 products

Cope, JL, et. al, Pediatrics 2015;136;1125

Success of PREA and BPCA

- Before these laws, 22% of drug labeling had pediatric information
- In 2009, 46% with pediatric information
- Now over 600 pediatric labeling changes
- Congress recognized the importance of BPCA and PREA and permanently reauthorized both in 2012
- Extensive internal review of pediatric product development under BPCA and PREA
  - In 2014, FDA approved pediatric labeling changes in 36 different products, none of which were discussed at by an advisory committee
  - In 2015, FDA approved 53 labeling changes under BPCA and/or PREA and only 2 (fluticasone furoate /vilanterol inhalation powder; and mepolizumab) were discussed during the review of the original application (studies included adults and children down to 12 years of age)
- Pediatric-focused post-marketing safety review performed by FDA based after pediatric labeling changes under BPCA or PREA

Sachs et al. Pediatric Information in Drug Product Labeling, *JAMA*, 2012:1914-5.

Additional Safeguards for Children in Clinical Investigations

(21 CFR 50 subpart D)

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Disclaimer

- The views expressed in this presentation do not necessarily represent the policies of the Food and Drug Administration or the Department of Health and Human Services.
- Robert Nelson has no financial conflicts of interest to disclose.

Ethical Context

- We have evolved from a view that we must protect children from research to a view that we must protect children through research.
- The consequences of protecting children from research is the off-label use of marketed products with insufficient knowledge of dosing, safety and efficacy of drugs in children.
- Thus, protecting children requires data to support the safe and effective use of drugs and biological products in pediatric patients.
- The critical need for pediatric research on drugs, biologics and devices reinforces our responsibility to assure that children are only enrolled in research that is both scientifically necessary and ethically sound.
- Children are widely considered to be vulnerable persons who, as research participants, require additional (or special) protections beyond those afforded to competent adult persons.

Topics

- Ethical framework for pediatric research
- Extrapolation as a practical application of the ethical principle of “scientific necessity”
- “Low risk” and “higher risk” pathways for pediatric product development
- Parental permission and child assent

Basic Ethical Framework in Pediatrics

1. Children should only be enrolled if scientific and/or public health objective(s) cannot be met through enrolling subjects who can consent personally.
2. Absent a prospect of direct therapeutic benefit, the risks to which children are exposed must be “low.”
3. Children should not be placed at a disadvantage by being enrolled in a clinical trial.
4. Vulnerable populations unable to consent (including children) should have a suitable proxy to consent for them.

"Nested" Protections

1: Scientific Necessity

4: Parental Permission

4: Child Assent

2,3: Appropriate Balance of Risk and Benefit

Ethical Principle of Scientific Necessity

- Children should not be enrolled in a clinical trial unless necessary to answer an important scientific and/or public health question about the health and welfare of children
  - Practical application (using extrapolation): determine the type (and timing) of clinical studies required to establish "safe and effective" pediatric use of drugs or devices
- Derives from requirements for equitable selection†
  - Subjects capable of informed consent (i.e., adults) should generally be enrolled prior to children

† Minimize Risks and Equitable Selection [US 21 CFR 56.111(a)(1) and (b)]

General Justification of Research Risk (Both Adult and Pediatric)

- Criterion for IRB approval of research.
  - Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result.
    - 21 CFR 56.111(a)(2); 45 CFR 46.111(a)(2)
- This general criterion is modified by the additional protections for children enrolled in clinical investigations and/or research in that there is a limit to the risk that knowledge can justify.

Additional Safeguards for Children
21 CFR 50 Subpart D
(Appropriate Balance of Risk and Benefit)

- Research involving children either
  - must be restricted to "minimal" risk or a "minor increase over minimal" risk absent a potential for direct benefit to the enrolled child, or
    - 21 CFR 50.51/53;45 CFR 46.404/406
  - must present risks that are justified by anticipated direct benefits to the child; the balance of which is at least as favorable as any available alternatives.
    - 21 CFR 50.52;45 CFR 46.405

Two Key Concepts

- Prospect of Direct Benefit
  - The risks to which a child may be exposed depend on whether the intervention does or does not offer that child a prospect of direct benefit.
  - Thus, defining and assessing the possibility of direct (clinical or therapeutic) benefit is an essential aspect of the ethical acceptability of the (interventions included in a) research protocol.
- Component Analysis
  - A protocol may (and usually does) contain multiple interventions or procedures, some that offer a prospect of direct (clinical) benefit and others that do not.
  - These interventions and procedures must be analyzed and justified separately (i.e., as “components” of the protocol).
  - Thus, a protocol may include components that must be evaluated under 21 CFR 50.52 and others that must be evaluated under 21 CFR 50.53.

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Extrapolation

- Generally understood, extrapolation is an inference from the known to the unknown.
  - to use known facts as the starting point from which to draw inferences or conclusions about something unknown
  - to predict by projecting past experience or known data
- Extrapolation of pediatric efficacy has a specific legal definition.
  - "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)
- A powerful tool to be used carefully.

Use of Extrapolation

- The use of extrapolation was first introduced in the 1994 Pediatric Labeling Rule, but did not have much of an impact until the pediatric incentives (BPCA “exclusivity” in 1997, and PREA “requirement” in 2003) were established.
- “A pediatric use statement may also be based on adequate and well-controlled studies in adults, provided that the agency concludes that the course of the disease and the drug's effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. Where needed, pharmacokinetic data to allow determination of an appropriate pediatric dosage, and additional pediatric safety information must also be submitted.”

59 Fed. Reg. 64241 (1994)

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" [1962]

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

  – "Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness."

- "FDA has been flexible…, broadly interpreting the statutory requirements to the extent possible where the data on a particular drug were convincing."

  – In 1997, "Congress amended section 505(d)… to make it clear that [FDA] may consider 'data from one adequate and well-controlled clinical investigation and confirmatory evidence' to constitute substantial evidence if FDA determines that such data and evidence are sufficient to establish effectiveness."

  – In doing so, "Congress confirmed FDA's interpretation of the statutory requirements for approval."

FDA Guidance - May 1998

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm078749.pdf

Extrapolation from Existing Studies

- "In certain cases, effectiveness of an approved drug product for a new indication, or effectiveness of a new product, may be adequately demonstrated *without* additional adequate and well-controlled clinical efficacy trials. Ordinarily, this will be because *other types of data* provide a way to apply the known effectiveness to a new population or a different dose, regimen or dosage form." (emphasis added)

For Extrapolation of Effectiveness from Adult to Pediatric Population

- "Evidence that could support a conclusion of similar disease course and similar drug effect in adult and pediatric populations includes evidence of common pathophysiology and natural history of the disease in the adult and pediatric populations, evidence of common drug metabolism and similar concentration-response relationships in each population, and experience with the drug, or other drugs in its therapeutic class, in the disease or condition or related diseases or conditions."

FDA Guidance - May 1998
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm078749.pdf

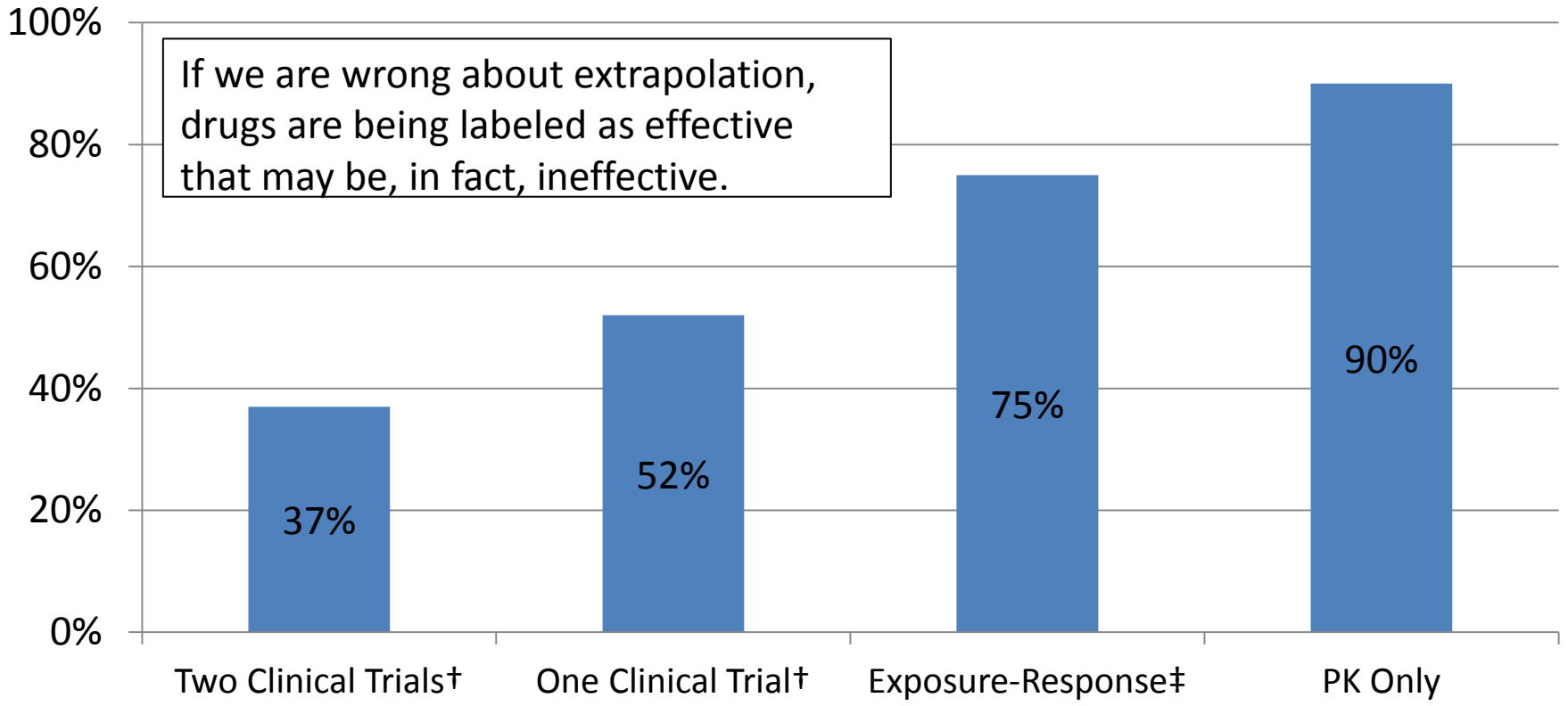
Summary of Approaches to Extrapolation
(Assessment of 166 products between 1998-2008)

Extrapolation	Supportive Evidence Requested From Pediatric Studies	Products n/N (%)	New or Expanded Indication
None **17%**	Two adequate, well-controlled, efficacy and safety trials plus PK data.	19/166 (11)	7/19 (37)
	Oncology products only: sequential approach starting with phase 1/2. Do not proceed if no evidence of response.	10/166 (6)	3/10 (30)
Partial **68%**	Single, adequate, well-controlled, efficacy and safety trial (powered for efficacy) plus PK data.	67/166 (40)	35/67 (52)
	Single, controlled or uncontrolled, efficacy and safety trial (qualitative data) plus PK data.	20/166 (12)	15/20 (75)
	Single exposure-response trial (not powered for efficacy) plus PK and safety data, PK/PD and uncontrolled efficacy plus safety data, or PK/PD plus safety data.	26/166 (16)	19/26 (73)
Complete **14%**	PK and safety data.	10/166 (6)	9/10 (90)

Adapted from Table 1: Dunne J et al. Pediatrics 2011;128;e1242.

New or Expanded Indication

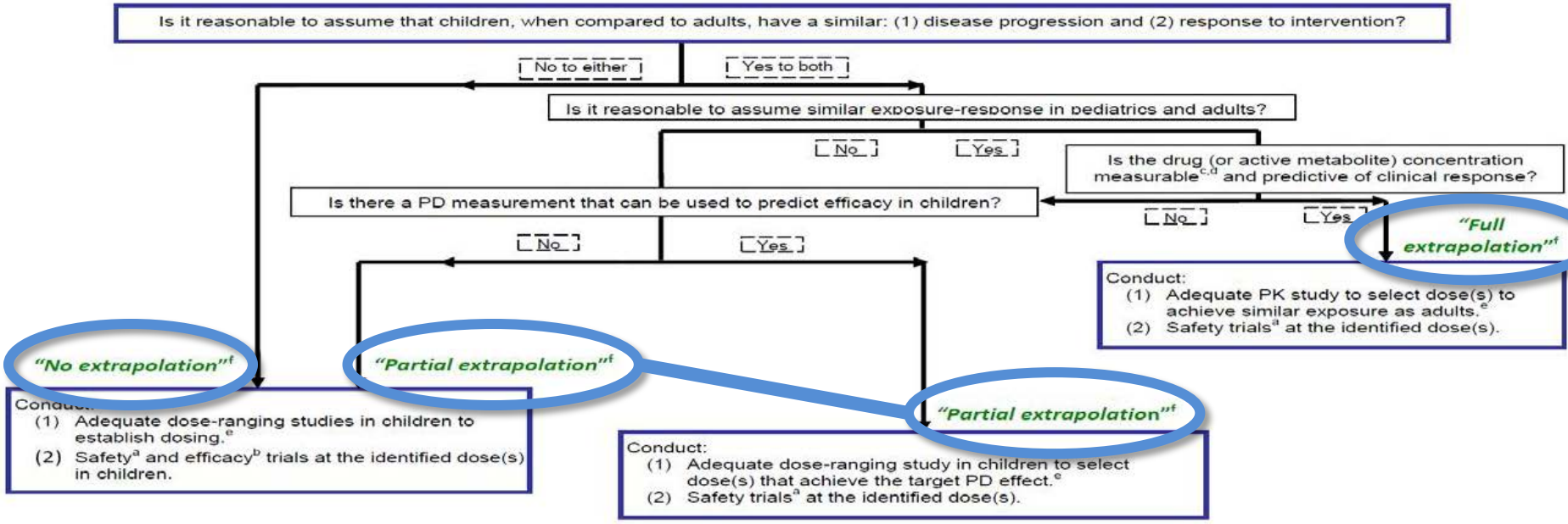
A powerful tool to be used carefully!



† Adequate, well-controlled, efficacy and safety trial(s) (powered for efficacy), plus PK data.

‡ Single, controlled or uncontrolled, efficacy and safety trial (qualitative data) plus PK data; or single exposure-response trial (not powered for efficacy) plus PK and safety data, PK/PD and uncontrolled efficacy plus safety data, or PK/PD plus safety data.

Pediatric Study Planning & Extrapolation Algorithm



Footnotes:

a. For locally active drugs, includes plasma PK at the identified dose(s) as part of safety assessment.
b. For partial extrapolation, one efficacy trial may be sufficient.
c. For drugs that are systemically active, the relevant measure is systemic concentration.
d. For drugs that are locally active (e.g., intra-luminal or mucosal site of action), the relevant measure is systemic concentration only if it can be reasonably assumed that systemic concentrations are a reflection of the concentrations at the relevant biospace (e.g., skin, intestinal mucosa, nasal passages, lung).
e. When appropriate, use of modeling and simulation for dose selection (supplemented by pediatric clinical data when necessary) and/or trial simulation is recommended.
f. For a discussion of no, partial and full extrapolation, see Dunne J, Rodriguez WJ, Murphy MD, et al. "Extrapolation of adult data and other data in pediatric drug-development programs." Pediatrics. 2011 Nov;128(5):e1242-9.

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425885.pdf

No Extrapolation

Is it reasonable to assume that children, when compared to adults, have a similar (1) disease progression and (2) response to intervention?

Also applies to extrapolation between definable pediatric subpopulations

either

Conduct:

(1) Adequate dose-ranging studies in children to establish dosing.[a]

(2) Safety[b] and efficacy trials at the identified dose(s) in children.

Refer to May 1998 FDA Guidance on substantial evidence of efficacy

Footnotes:

a. When appropriate, use of modeling and simulation for dose selection (supplemented by pediatric clinical data when necessary) and/or trial simulation is recommended.

b. For locally active drugs, includes plasma PK at the identified dose(s) as part of the safety assessment.

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425885.pdf

Full Extrapolation

Is it reasonable to assume that children, when compared to adults, have a similar: (1) disease progression and (2) response to intervention?

Yes to Both

Is it reasonable to assume similar exposure-response in pediatrics and adults?

Yes

Is drug (or active metabolite) concentration measureable & predictive of clinical response?

Yes

Conduct:

(1) Adequate PK study to select dose(s) to achieve similar exposure as adults.[a]

(2) Safety[b] trials at the identified dose(s) in children.

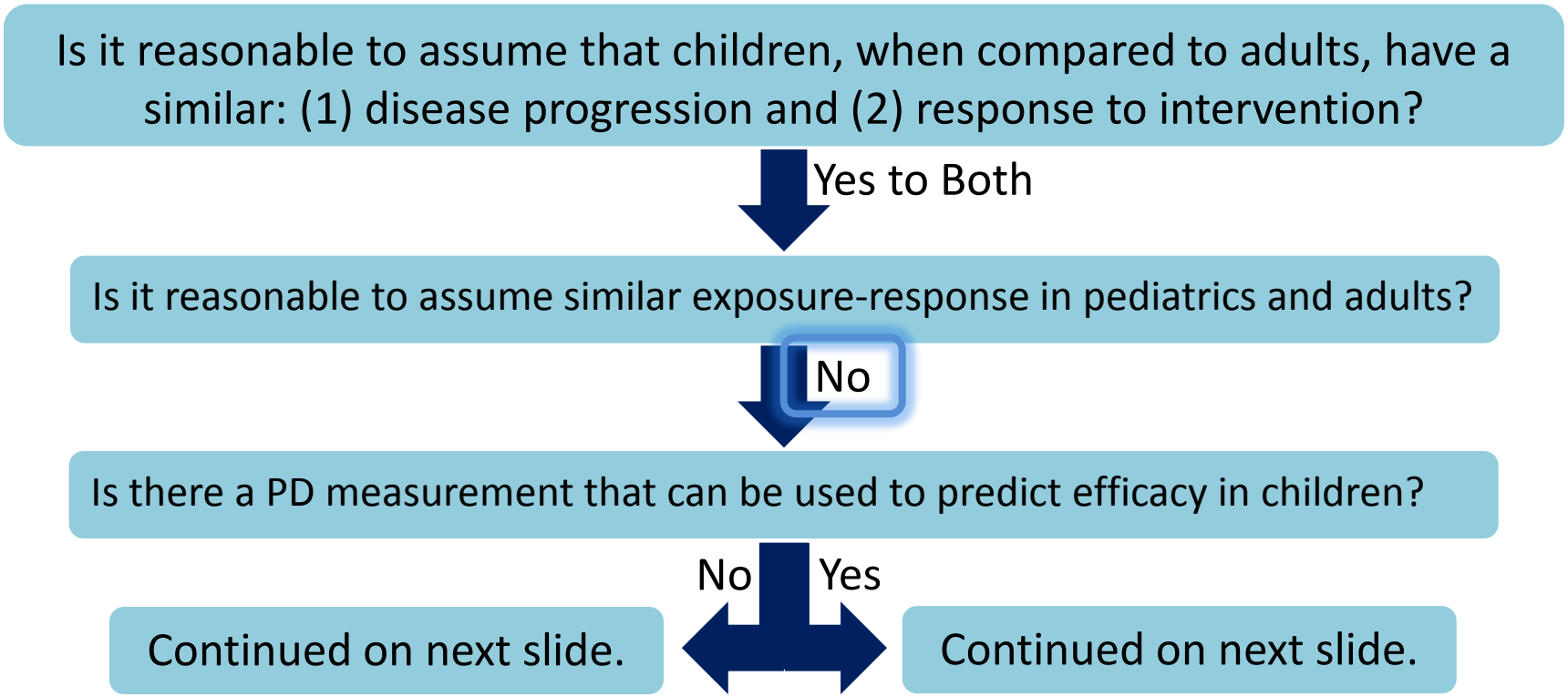
Footnotes:

a. When appropriate, use of modeling and simulation for dose selection (supplemented by pediatric clinical data when necessary) and/or trial simulation is recommended.

b. For locally active drugs, includes plasma PK at the identified dose(s) as part of the safety assessment.

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425885.pdf

Partial Extrapolation



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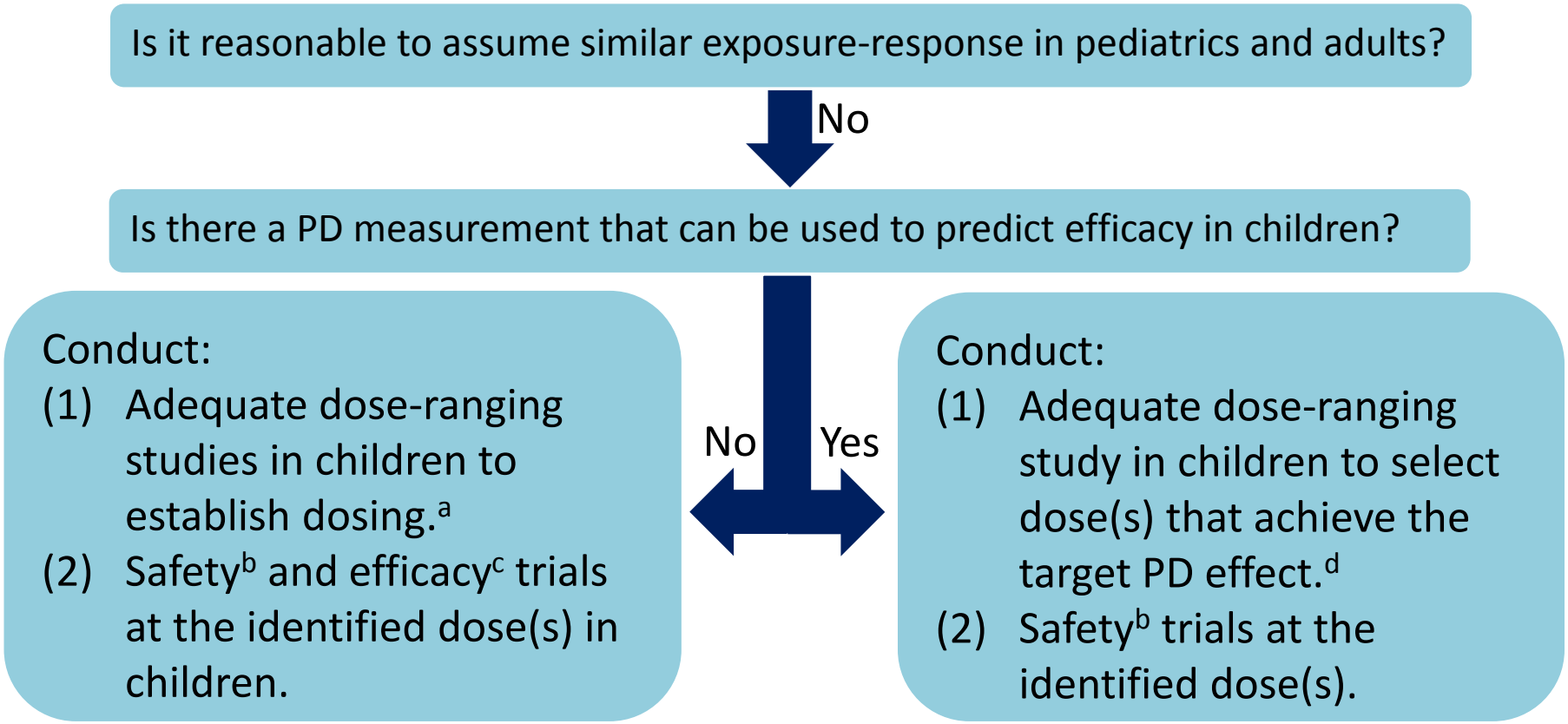
Partial Extrapolation (cont.)



Footnotes:

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b. For locally active drugs, includes plasma PK at the identified dose(s) as part of the safety assessment.
c. For partial extrapolation, one efficacy trial may be sufficient.
d. For drugs that are systemically active, the relevant measure is systemic concentration.

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- “Low risk” and “higher risk” pathways for pediatric product development
- Parental permission and child assent

Linking Science and Ethics

- To start a pediatric clinical trial, the ethical challenge is to establish sufficient evidence using either preclinical animal models or adult human clinical trials† to conclude:
  - "Low Risk" Pathway: Absent sufficient prospect of direct benefit, administration of investigational product to children presents an acceptably "low" risk (minimal, minor increase over minimal), or…
    - 21 CFR 50.51/50.53 (cf. ICH E-6 §4.8.14)
  - "Higher Risk" Pathway: Administration of investigational product to children presents a sufficient prospect of direct benefit to justify "higher" risks.
    - 21 CFR 50.52

† Data also may come from post-marketing pediatric (i.e., "off label") and/or adult data

"Low" Risk in FDA Regulations

- "Minimal risk" is defined as those risks "ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." [21 CFR 50.3(k)]
  - The recommendation is that this definition be indexed to the experience of "healthy children."
  - Generally, administration of an experimental drug/biological product is not considered "minimal" risk.
- Interventions/procedures that do not offer a prospect of direct benefit must be no more than a "minor increase over minimal risk;" and enrollment limited to children with a "disorder or condition" (absent a federal exception). [21 CFR 50.53]
  - There is no definition of a "minor increase over minimal risk." It is generally described as "slightly more" than minimal risk, and not presenting any "substantial risk."

"Disorder or Condition"

- FDA regulations do not define either "disorder" or "condition"
- A Proposed Definition
  - "A specific (or set of specific)… characteristic(s) that an established body of scientific evidence or clinical knowledge has shown to negatively affect children's health and well-being or to increase their risk of developing a health problem in the future."

    Institute of Medicine (US): Recommendation 4.3†
- Key Concept: being "at risk" for disorder or disease.
- Using the word "healthy" can be misleading.
  - A child can be healthy and "at risk" (i.e., have a "condition"); a child with a condition may not have the condition related to the research (and thus be "healthy").

† IOM, Ethical Conduct of Clinical Research Involving Children (2004)

Key Points: "Low Risk" Pathway

- Need to be able to generate an accurate risk estimate for administration of the investigational product given adult testing experience AND this risk estimate needs to indicate that risks are sufficiently "low" to proceed under this pathway.
- If risks are not "low" OR insufficient information is available to generate an accurate risk assessment, product will be considered under the "higher risk" pathway.
- Some single-dose PK studies may be considered "low" risk.
- Longer-term dosing of investigational drugs or biological products generally not considered "low" risk.

"Higher Risk" Pathway

- Any clinical investigation… in which more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject… may involve children as subjects only if:
  a) The risk is justified by the anticipated benefit to the subjects;
  b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches.

21 CFR 50.52 / 45 CFR 46.405

Prospect of Direct Benefit (PDB)

- A “direct benefit” may improve the health or well-being of the individual child and results from the research intervention being studied (and not from other clinical interventions included in protocol).
- What evidence (either from adult humans or animal models) is available about this intervention/product?
  - Do these data make us reasonably comfortable that children might benefit from this intervention/product?
  - Is the dose and duration of treatment with the investigational drug long enough to offer the intended benefit?
  - For diagnostic procedures, would the procedure normally be done as part of routine clinical care? Would the data potentially impact on clinical care?

Prospect of Direct Benefit (PDB)

- The necessary level of evidence to support PDB ("proof of concept") is lower than the level of evidence required to establish efficacy.
  - "Proof of concept" may be based on animal or adult human data, using a "clinical" endpoint or a "surrogate" based, for example, on disease pathophysiology.
- Whether experimental intervention offers PDB separate from whether that PDB of sufficient probability, magnitude and type to justify the anticipated risks of the intervention, given the overall clinical context.
  - Risk/benefit evaluation is a complex quantitative and qualitative judgment that is similar to clinical practice.
  - Contextual justification of risk by PDB can include:
    - Importance of "direct benefit" to subject; possibility of avoiding greater harm from disease; degree of "tolerable" uncertainty; justification set in context of disease severity (e.g., degree of disability, life-threatening) and availability of alternative treatments; should have "as good a chance for benefit as the clinical alternatives"

Justification of Risks

- Are data regarding the drug's potential (clinical) benefit to the patient (subject) sufficiently compelling to justify the potential (known, suspected, and unknown) risks?
- Is the balance of these risks and potential benefits at least as favorable as the (evidence-based) alternative treatments (if any)?
- This assessment is similar to the judgment a clinician might make regarding whether to use a therapy in clinical practice.

Timing of Pediatric Studies

- For “higher risk” interventions, administration of FDA-regulated products in a clinical investigation must present risks that are justified by anticipated direct benefits to the child; the balance of which is at least as favorable as any available alternatives.
  - Additional Safeguards for Children (21 CFR 50.52)
- Thus, we need “proof of concept” data from human adults and/or animal disease models establishing a sufficient prospect of direct benefit to justify exposing children to the known (and unknown) risks of the intervention.
- This requirement does not imply that adult studies must be completed before beginning pediatric studies. Rather, once sufficient adult and/or animal data exist to make this judgment, pediatric development should proceed without further delay.

Topics

- Ethical framework for pediatric research
- Extrapolation as a practical application of the ethical principle of “scientific necessity”
- “Low risk” and “higher risk” pathways for pediatric product development
- Parental permission and child assent

Parental Permission

- Agreement… to participation of child… in clinical investigation. Permission must be obtained in compliance with 21 CFR §50.20-27 (IC regulation)

  – 21 CFR §50.3(r)

  – The parental permission document (and process) follows the same regulations for informed consent (e.g., must include the same required elements).

- Waiver? Only EFIC for emergency research

  – 21 CFR §50.24

  – FDA does not include the same waiver for minimal risk research as contained in HHS regulations 45 CFR 46 (proposed change currently included in pending legislation).

Child Assent

- Affirmative agreement to participate in research
  - Mere failure to object may not be construed as assent

21 CFR 50.3(n)

- Adequate provisions for soliciting a child's assent
  - Determine when a child is capable of providing assent
  - Accounting for age, maturity, and psychological state
- Assent may be waived if…
  - capability so limited that cannot be consulted, or
  - prospect of direct benefit important to child's health or well-being available only in research, or
  - minimal risk research that otherwise is not feasible

21 CFR 50.55

Thank you.

Pediatric Utilization of Opioid Analgesic Products

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Outline

- Sales distribution
- Pediatric outpatient retail utilization
  - Dispensed prescription data
  - Patient-level data
  - Duration of therapy
  - Prescriber specialties
  - Diagnoses data
- Data limitations
- Summary

Opioid Analgesics

Extended-Release/Long-Acting Formulation (ER/LA)	Immediate-Release Formulation (IR)	
• Buprenorphine Transdermal • Fentanyl Transdermal • Hydrocodone • Hydromorphone • Methadone • Morphine • Morphine-Naltrexone • Oxycodone • Oxycodone-Acetaminophen • Oxymorphone • Tapentadol • Tramadol	• Butorphanol • Codeine • Codeine-Acetaminophen • Hydrocodone-Acetaminophen • Hydrocodone-Ibuprofen • Hydromorphone • Levorphanol • Meperidine • Meperidine-Promethazine • Morphine • Opium • Oxycodone • Oxycodone-Acetaminophen • Oxycodone-Ibuprofen	• Oxymorphone • Pentazocine-Acetaminophen • Pentazocine-Naloxone • Propoxyphene • Propoxyphene-Acetaminophen • Tapentadol • Tramadol • Tramadol-Acetaminophen • Transmucosal Immediate-Release Fentanyl (TIRF)

*Only opioid analgesics with oral, transdermal, and nasal formulations are included in the drug use analyses.

Sales Distribution Data

National estimates of bottles/packages of opioid analgesics sold from manufacturers to retail and non-retail channels of distribution in U.S.

	Year 2015		
Product	**Retail**	**Mail-Order/Specialty**	**Non-Retail**
Opioid analgesic products	**72%**	**1%**	**27%**

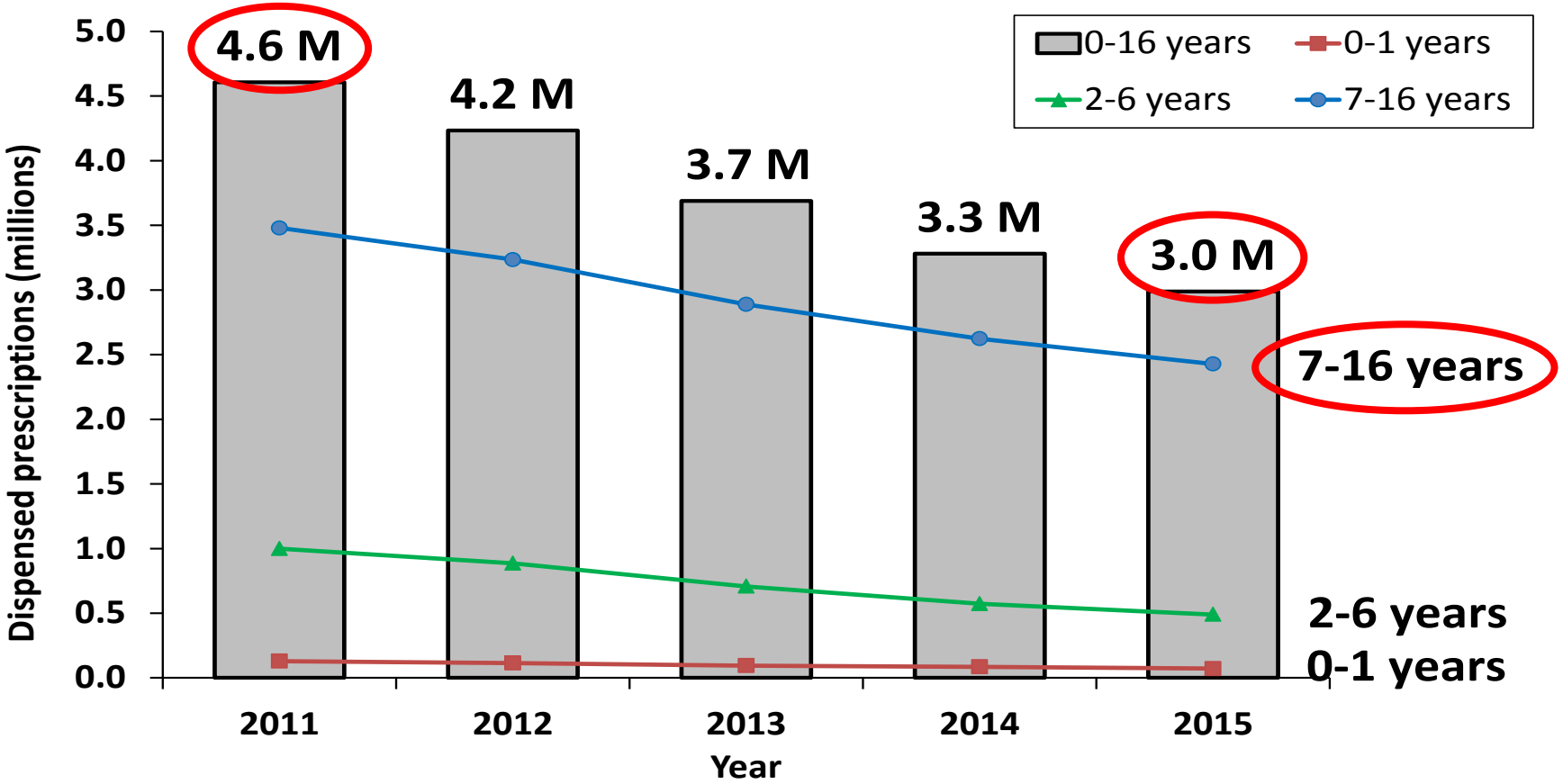
Source: IMS Health, National Sales Perspectives™. Year 2015. Data extracted June 2016.

Dispensed Prescription Data 2011-2015

IMS Health, National Prescription Audit™ Database

Pediatric Utilization: Prescription Data

National estimates of total prescriptions dispensed to pediatric patients (0-16 years*) for opioid analgesics** from U.S. outpatient retail pharmacies



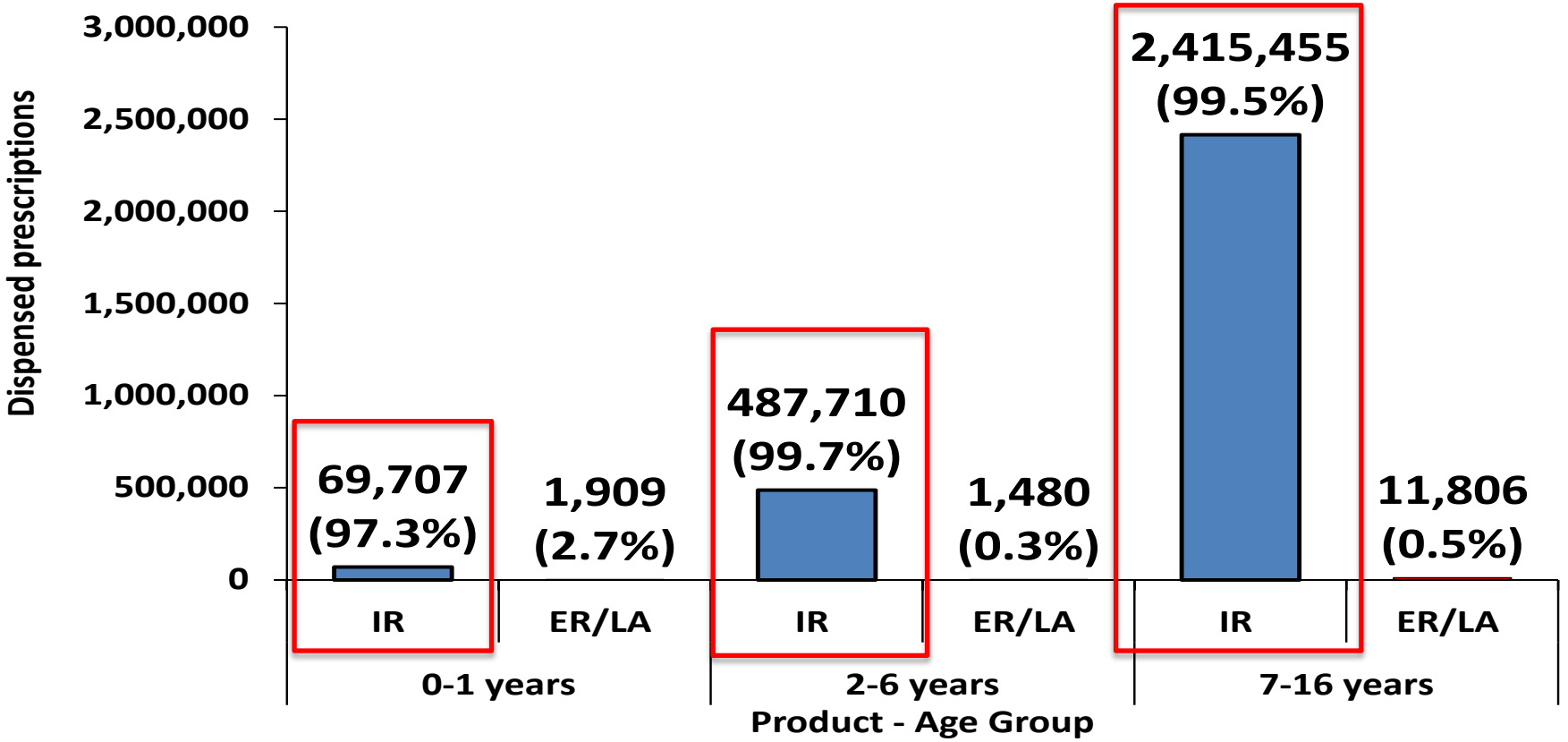
Source: IMS Health, National Prescriptions Audit™. Years 2011-2015. Data extracted June 2016.

**Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years old (16 years and 11 months).*

***Data included opioid analgesics with oral, transdermal, and nasal formulations.*

Prescription Data:
IR and ER/LA Opioid Analgesic Prescriptions

National estimates of prescriptions dispensed to pediatric patients*, stratified by IR and ER/LA opioid analgesics**, from U.S. outpatient retail pharmacies in 2015



Source: IMS Health, National Prescriptions Audit™. Year 2015. Data extracted June 2016.

**Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years old (16 years and 11 months).*

***Data included opioid analgesics with oral, transdermal, and nasal formulations.*

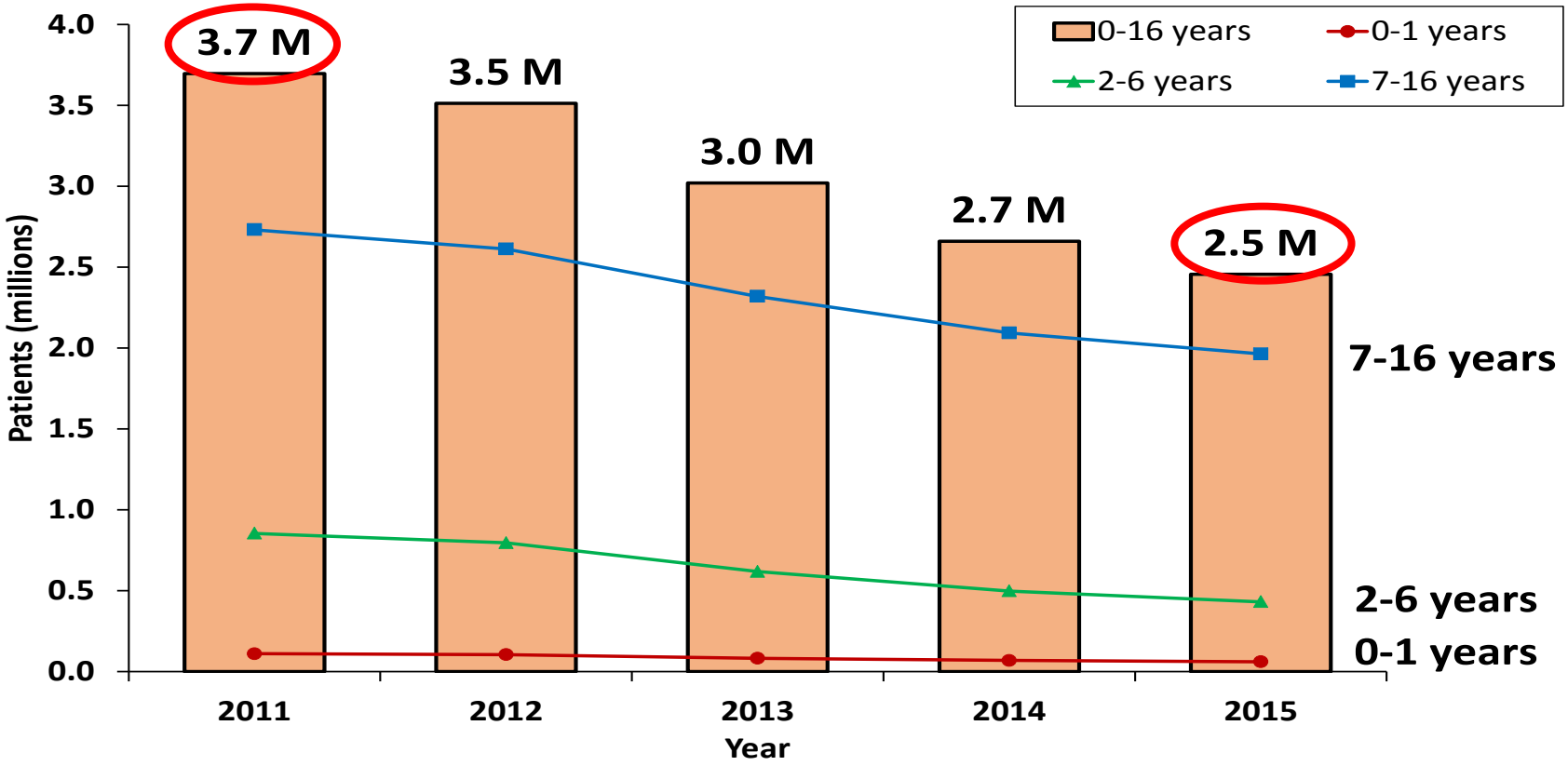
U.S. FOOD & DRUG ADMINISTRATION

Patient-Level Data 2011-2015

Symphony Health Solutions' Integrated Dataverse® Database

Pediatric Utilization: Patient-Level Data

National estimates of total pediatric patients (0-16 years*) who received dispensed prescriptions for opioid analgesics** from U.S. outpatient retail pharmacies



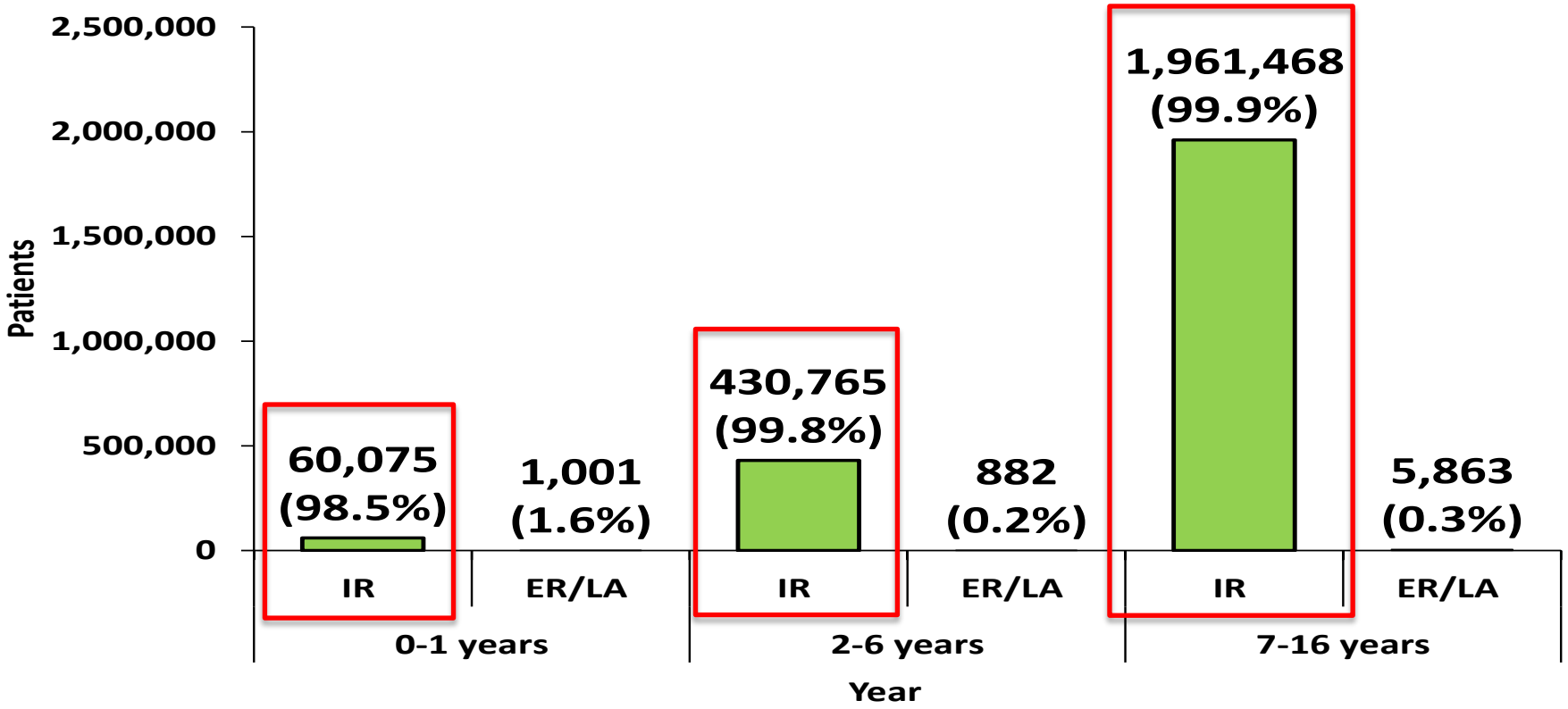
Source: Symphony Health Solutions' Integrated Dataverse® (IDV). Years 2011-2015. Data extracted August 2016.

**Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years old (16 years and 11 months).*

***Data included opioid analgesics with oral, transdermal, and nasal formulations.*

Pediatric Patients:
IR and ER/LA Opioid Analgesics

National estimates of pediatric patients by patient age* who received prescriptions dispensed for IR or ER/LA opioid analgesics** from U.S. outpatient retail pharmacies in 2015



Source: Symphony Health Solutions' Integrated Dataverse® (IDV). Year 2015. Data extracted August 2016.
**Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years old (16 years and 11 months).*
***Data included opioid analgesics with oral, transdermal, and nasal formulations.*

Pediatric Utilization:
Top Dispensed Opioid Analgesics

National estimates of pediatric patients by patient age* who received prescriptions dispensed for the top IR or ER/LA opioid analgesics** from U.S. outpatient retail pharmacies in 2015

	0-1 years		2-6 years		7-16 years	
Product	**Patients**	**%**	**Patients**	**%**	**Patients**	**%**
IR Opioid Analgesics	**60,075**	***100.0%***	**430,765**	***100.0%***	**1,961,468**	***100.0%***
Hydrocodone-Acetaminophen	27,967	*46.6%*	181,566	*42.1%*	934,918	*47.7%*
Codeine-Acetaminophen	19,821	*33.0%*	197,495	*45.8%*	721,016	*36.8%*
ER/LA Opioid Analgesics	**1,001**	***100.0%***	**882**	***100.0%***	**5,863**	***100.0%***
Oxycodone ER	19	*1.9%*	21	*2.4%*	1,765	*30.1%*
Fentanyl transdermal	294	*29.4%*	599	*67.9%*	1,628	*27.8%*
Morphine	23	*2.3%*	48	*5.4%*	1,537	*26.2%*
Methadone	645	*64.4%*	208	*23.6%*	613	*10.5%*

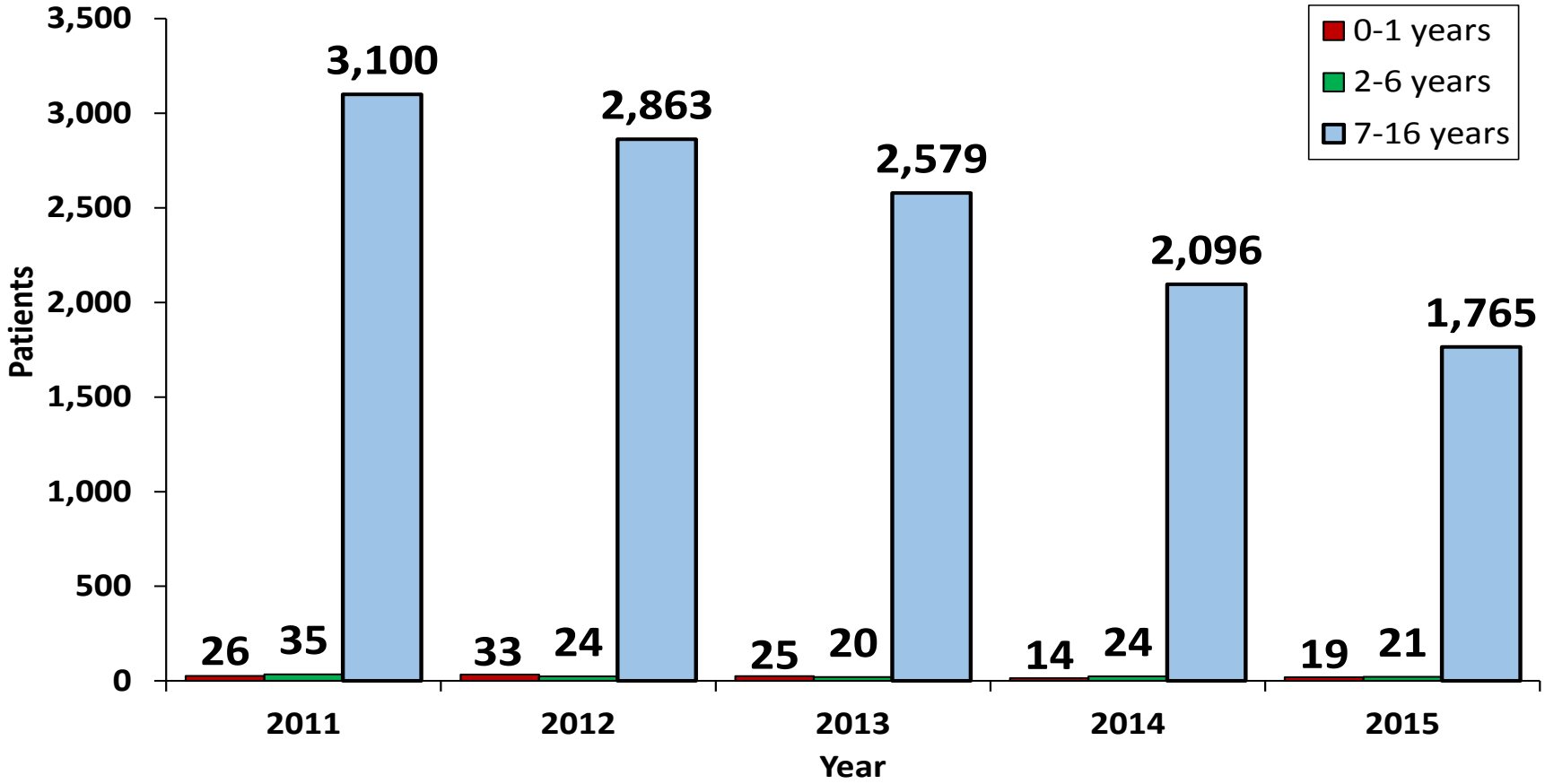
Source: Symphony Health Solutions' Integrated Dataverse® (IDV). Year 2015. Data extracted August 2016.

**Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years old (16 years and 11 months).*

***Data included opioid analgesics with oral, transdermal, and nasal formulations.*

Pediatric Patient-Level Data: Oxycodone ER

National estimates of pediatric patients by patient age* who received prescriptions dispensed for oxycodone ER from U.S. outpatient retail pharmacies



Source: Symphony Health Solutions' Integrated Dataverse® (IDV). Years 2011-2015. Data extracted August 2016.
**Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years old (16 years and 11 months).*

Impact of Pediatric Labeling of Oxycodone ER Products on Dispensing

- Objective

  We compared the mean monthly number of unique pediatric patients dispensed one or more oxycodone ER prescriptions for the 12 months before and the nine months after the approval of pediatric labeling for children 11 years and older.

- Study period:

  August 2014 to April 2016

- Data Source

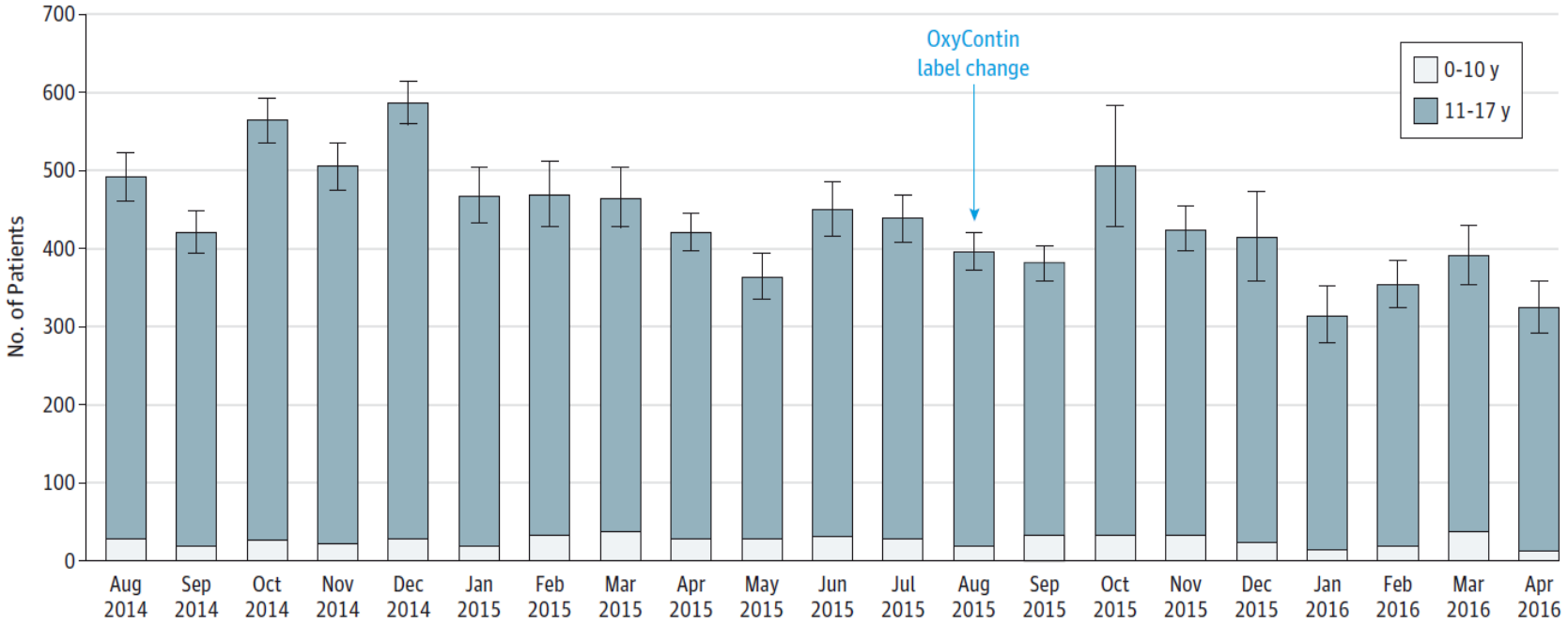
  IMS Health Vector One: Total Patient Tracker

- Method:

  Wilcoxon-Mann-Whitney test

Pediatric Study Results: Oxycodone ER

Nationally Estimated Number of Pediatric Patients Dispensed Oxycodone ER Prescriptions from Retail Pharmacies, August 2014-April 2016



The error bars represent 95% CIs for the total pediatric population dispensed extended-release oxycodone prescriptions.

Children accounted for 0.17% or less of all patients dispensed oxycodone ER in each month of the study period.

Reference: Xu J, Gill R, Cruz M, Staffa J, Lurie P (2016). "Effect of US Food and Drug Administration-Approved Pediatric Labeling on Dispensing of Extended Release Oxycodone in the Outpatient Retail Setting." *JAMA Pediatrics (in press).*

Duration of Use Data

Symphony Health Solutions'
Integrated Dataverse® Database

Duration of Use: Methods

- Products
  - Immediate-Release Opioid Analgesics:
    - Hydrocodone-acetaminophen, codeine-acetaminophen, and oxycodone IR
  - Extended-release/Long-Acting Opioid Analgesics:
    - Oxycodone ER, morphine ER, fentanyl transdermal, and methadone
- Time period: 2015
- Data were obtained from a sample of patients with dispensed prescriptions for selected opioid analgesics from outpatient pharmacies

Duration of Use: Methods, Continued

Defining duration of use

- Duration of use: sum of treatment episodes (days)
  - Treatment episodes refer to a time period that a patient had uninterrupted therapy with an opioid analgesic
    - Grace period of 50% of the days' supply of the last prescription was applied to account for delays in medication refilling
  - Duration of a treatment episode refer to the sum of days' supply of all prescriptions
  - Days' supply is determined and estimated by pharmacists at the time of first dispensing

Duration of Use Data

Duration of therapy for selected IR and ER/LA opioid analgesics dispensed from U.S. outpatient pharmacies to a sample of pediatric patients* ages 0-16 years** in 2015

		Days of Therapy	
Products	**Number of patients**	**Median**	**Mean**
IR Opioid Analgesics			
Hydrocodone-Acetaminophen IR	950,290	6.0	7.3
Codeine-Acetaminophen IR	679,447	5.0	6.6
Oxycodone IR	79,117	6.0	9.4
ER/LA Opioid Analgesics			
Oxycodone ER	1,412	11.0	26.1
Morphine ER	1,325	13.0	36.0
Methadone oral	1,130	31.0	77.0
Fentanyl transdermal	529	31.0	69.8

Source: Symphony Health Solutions Integrated Dataverse (IDV), 2015, Extracted July 2016.

*excludes patients with cash or unspecified prescriber specialty prescriptions

***Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years old (16 years and 11 months).*

Duration of Use Data

During 2015:

- ER/LA Opioid Analgesics*:
  - ~80% of children who were dispensed oxycodone ER or morphine ER had a duration of therapy of <31 days
  - ~50% of children who were dispensed methadone or fentanyl transdermal had a duration of therapy of <31 days
- IR Opioid Analgesics*:
  - >90% of children who were dispensed hydrocodone-acetaminophen, codeine-acetaminophen, or oxycodone IR had a duration of therapy of <2 weeks

Source: Symphony Health Solutions Integrated Dataverse (IDV), 2015, Extracted July 2016.

*excludes patients with cash or unspecified prescriber specialty prescriptions

Prescriber Specialties

IMS Health, National Prescription Audit™ Database

Top Prescriber Specialties

During 2015:

- IR opioid analgesic dispensed prescriptions:
  - 0-1 years (N = 69,707 prescriptions): Pediatrics* at ~32%
  - 2-6 years (N = 487,710 prescriptions): Dentists at ~19%
  - 7-16 years (N = 2,415,455 prescriptions): Dentists at ~29%

- ER/LA opioid analgesic dispensed prescriptions:
  - 0-1 years (N = 1,909 prescriptions): Pediatrics* at ~52%
  - 2-6 years (N = 1,480 prescriptions): Pediatrics* at ~33%
  - 7-16 years (N = 11,806 prescriptions): Pediatrics* at ~35%

Source: IMS Health, National Prescriptions Audit™. Year 2015. Data extracted June 2016.

*Pediatrics include general pediatricians and pediatric subspecialties.

Diagnoses Data

Encuity Research, LLC., TreatmentAnswers™
with Pain Panel Database

Top Diagnoses Data from Physician Surveys: IR Opioid Analgesics

During 2015:

- 0-1 years (N = 99,000 drug use mentions):
  - Hernia (ICD-10 K40.9 and K43.9) at ~52.5%
- 2-6 years (N = 495,000 drug use mentions):
  - Injuries and burns (ICD-10 S42.x-T30.0) at ~39%
- 7-16 years (N = 1,956,000 drug use mentions):
  - Injuries and burns (ICD-10 S00.x-T25.0) at ~53%

Source: Encuity Research, LLC., TreatmentAnswers™. Year 2015. Data extracted June 2016.

Limitations

- Patient and prescription data
  - No linkage between a dispensed prescription and a diagnosis
  - No medical charts available for validation, (e.g. patient DOB)
  - Dispensing trends may not apply to non-retail or mail-order/specialty settings
- Duration of use data
  - Sample population
  - Data were analyzed for one calendar year; therefore, duration of use may be underestimated
  - All analyses were conducted at the active moiety and formulation level (e.g. oxycodone ER), product-level variations, product switching and concurrent use were not assessed

Limitations, Continued

- Office-based physician survey data
  - May not capture prescribing data from subspecialty prescribers in inpatient or clinic settings
  - A diagnosis mention does not necessarily result in a prescription being generated
  - For data with small sample sizes, data may not be generalizable to the pediatric population

Summary

- Opioid analgesics were prescribed and dispensed to pediatric patients of all ages
- In 2015, ~2.5 million pediatric patients (4% of total 66.5 million patients of any age) were dispensed opioid analgesics
- Total outpatient pediatric opioid analgesic utilization declined since 2011
- Outpatient pediatric utilization of oxycodone ER declined since 2011 and since the recent changes of Oxycontin label

Summary, Continued

- ~98.5% or more of pediatric patients were dispensed IR opioid analgesics annually
- ~1.6% or less of pediatric patients were dispensed ER/LA opioid analgesics annually
- Utilization of IR opioid analgesics were for shorter duration than ER/LA opioid analgesics
- Hernia was the top diagnosis associated with the use of IR opioid analgesics in children 0-1 years
- Conditions associated with injuries and burns were the top diagnoses associated with the use of IR opioid analgesics in children 2-6 years and 7-16 years

Thank you

Current Approach to Studying Opioid Analgesics in Pediatric Patients

STEVEN GALATI M.D.
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CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee, the Drug Safety and Risk Management Advisory Committee, and the Pediatric Advisory Committee, Sept. 15-16, 2016

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

Overview

- Currently available opioid analgesics with pediatric labeling
- Completed and outstanding WRs (written requests) and PREA PMRs (post-marketing requirements)
- How FDA came to our current approach to advise Sponsors on study requirements for opioid analgesics in pediatric populations
- Current approach to pediatric study design

Pediatric Assessment Post-Marketing Requirements: PREA

- Opioids with pediatric information in labeling:
  - Actiq (fentanyl citrate)
  - Buprenorphine injection
  - Carisoprodol, aspirin and codeine
  - Codeine/acetaminophen
  - Duragesic patch (fentanyl)
  - Lortab (hydrocodone and acetaminophen)
  - Meperidine tablet
  - OxyContin (oxycodone)
- As discussed by Dr. Pham, some of the more commonly prescribed opioids in children do not have any specific pediatric information in labeling:
  - Oxycodone immediate-release
  - Methadone
  - Oxycodone/acetaminophen
  - Morphine extended-release

Currently Pending PREA Requirements

- Buprenorphine (Belbuca, Butrans)
- Codeine tablets and solution
- Fentanyl (Ionsys)
- Hydrocodone (Hysingla, Zohydro ER)
- Hydromorphone (Dilaudid HP Injection, Exalgo,)
- Morphine immediate release tablets
- Morphine/naltrexone (Embeda)
- Oxycodone/acetaminophen (Xartemis XR)
- Oxycodone/naloxone (Targiniq)
- Oxycodone oral solution
- Oxymorphone (Opana and Opana ER)
- Tapentadol (Nucynta and Nucynta ER)

Written Requests

- 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

- FDA has issued WR for the following opioids:
  - Buprenorphine (Butrans) – 2011
  - Fentanyl
    - Actiq – 2006 (completed)
    - Duragesic – 2001 (completed)
  - Oxycodone (Oxycontin) – 2011(completed)
  - Tapentadol (Nucynta) – 2015
  - Tramadol (Ultram)– 1999
  - Morphine (referred to NIH)

OxyContin Written Request (WR)

- Extended-release (ER) form approved 1995
- Current formulation approved 2010 (NDA 22272)
- WR issued in 1999 w/3 amendments (changes at later times)
  - Efficacy supplement submitted in response to WR December 2014
  - 3 studies as part of the supplement
- The efficacy supplement was approved August 2015 with a pediatric indication added to labeling
  - Opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent

OxyContin Post-Marketing Requirements (PMRs)

- Novel PMRs were put in place to understand the impact of OxyContin's approval in 2015
- FDA determined the Applicant was required to assess this impact as well as safety through the following PMRs:
  - Study 1:
    - Assess risks of respiratory depression, overdose, misuse, accidental exposure and med errors in opioid tolerant patients aged 11-17 and children younger than approved age range or do not meet criteria for opioid tolerance
    - Analysis of postmarket adverse events described above on all pediatric ages
  - Study 2:
    - National drug utilization study to characterize use of OxyContin in pediatrics
    - Data from study will provide denominator for study 1 to assess risk

Previous FDA Opioid Analgesic Study Requirements

- For many years, efficacy, safety and pharmacokinetic (PK) studies were required for all age groups for all indications
- Few studies were conducted, few of these were completed
- Therefore, obtaining useful data in a more efficient manner are necessary
  - E.g., extrapolation of efficacy from adult studies

Extrapolation

- Introduced in the 1994 Pediatric Labeling Rule (59 Fed. Reg. 64240)
- According to 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."

Importance of Extrapolation

- Children are a vulnerable population and require additional safeguards in studies (e.g., inability to consent or communicate symptoms as well as adults, developing organ systems)
- Extrapolating efficacy when possible is important because there are a limited number of pediatric patients available to enroll
  - Extrapolating efficacy allows studies to be smaller and enroll less patients because more patients are needed to study efficacy than to study safety and PK

Limitations to Extrapolation

- If a product has a novel mechanism
- E.g., if exposure of drug is lower in children when compared to adult, then it is unclear of extrapolation of efficacy from adults is appropriate
    - FDA recommends Sponsors collect pain scores and rescue usage in PK/safety studies to provide context

Scientific Basis for Extrapolation in Pain

- December 2009, FDA convened a workshop of leaders in pediatric pain, pediatric clinical studies, pediatric ethics and pediatric drug development
- Discussed the development of the central nervous system, maturation of metabolic pathways, physiology of opioid receptors
- Discussed different approaches for acute and chronic pain studies in children that do not increase risk of pain or delayed treatment to patients
- Discussed available science to support extrapolation for analgesic drug classes

Scientific Basis for Extrapolation in Pain

- The workshop was later translated into a publication[1]
- After the workshop, FDA assessed the information discussed and decided how to apply the latest science to the regulatory approach for studying analgesics, including opioids and nonopioids

[1] Berde CB et al. Pediatric Analgesic Clinical Trial Designs, Measures, and Extrapolation: Report of an FDA Scientific Workshop. Pediatrics. Vol. 2 2012 Feb;129, p. 354-64.

Pediatric Population Enrollment

- Populations for studying opioids in pediatrics are reflected in the language used in the respective indications below
- For immediate-release (IR) opioid analgesics:
  - Must have acute pain that is severe enough to require treatment with an opioid
- For extended-release (ER) opioid analgesics:
  - Must have chronic pain that is severe enough to require treatment with an opioid around-the-clock
- In both cases, alternative treatments are inadequate to manage the pain or cannot be tolerated by the patient, and the risks associated with an opioid are balanced by the need for treatment of the pain such that treatment with an opioid is warranted

Enrollment Challenges

- The preferred randomized parallel-group, placebo-controlled analgesic clinical trial utilized in adults poses ethical concerns when enrolling children
  - Placebo in children is problematic - no potential benefit
  - Children cannot express discomfort or inadequate pain relief at the level of an adult
- Parents may be reluctant to enroll their child for concern that they will be harmed, receive less effective treatment or need to undergo extensive blood sampling
- Enrolling a sufficient number of patients to provide adequate statistical power is a major challenge
  - Relatively few patients in some pain populations especially for the youngest patients (e.g., neonates) and for chronic pain

Current Approach for Pediatric Opioid Studies

- Immediate-release (IR) opioid analgesic products
  - Ages 0 to < 2 years of age: Efficacy, safety and pharmacokinetics
  - Ages 2 to < 17 years of age: Safety and pharmacokinetics with extrapolation of efficacy from adult studies

- Extended-release (ER) opioid analgesic products
  - Ages 0 to < 7 years of age: Waived due to low prevalence of subjects with relevant conditions in this age range (i.e., chronic pain)
  - Ages 7 to < 17 years of age: Safety and pharmacokinetics with extrapolation of efficacy from adult studies

Pediatric Study Design

- Acute Pain (IR):
  - E.g., population post-surgery requiring opioid level of treatment
  - Continue to use standard of care and measure difference in cumulative rescue (study drug vs. placebo) with integration of IR rescue integrated in study design
  - Solves some of ethical/practical issues – still use double-blind study and placebo but children still have access to standard pain relief
- Chronic Pain (ER):
  - Aged 7 to < 17 years of age requiring around-the-clock opioids
  - May include but are not limited to orthopedic injuries, surgeries with prolonged pain expected, inflammatory bowel disease, sickle cell disease crises, inflammatory arthritides, post-traumatic neuropathic pain and bone disease pain
  - Multiple-dose, open-label study (PK and safety) since efficacy may be extrapolated from adults

Conclusions

- For years, FDA has been working to develop a rational approach to inform prescribers about opioids for the treatment of pain in children
- Through scientific rationale, FDA's approach to studying opioids in pediatrics has evolved
- FDA encourages Sponsors to collect data as efficiently as possible to add knowledge about this population to benefit pediatric public health

Clinical Pharmacology Considerations for Pediatric Studies of Opioid Drug Products

Srikanth C. Nallani, Ph.D.

Clinical Pharmacology Reviewer

Office of Clinical Pharmacology (OCP)

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee, the Drug Safety and Risk Management Advisory Committee, and the Pediatric Advisory Committee
September 15-16, 2016

Outline

- Pediatric study planning and Efficacy extrapolation
  - FDA Opinion
  - Expert opinion: Berde C.B. et al (2012), Pediatrics 129(2):354-364.
- General clinical pharmacology considerations for pediatric studies.
  - FDA's Draft guidance on pediatric studies for drugs and biological products.
- Pharmacokinetics (PK)-only approach in pediatric patients where full extrapolation of efficacy is applicable.
  - Opioid immediate-release (IR) and Extended-release long-acting (ERLA) products
- Approach to collect PK in pediatric patients under the age of two years.

Some Conclusions by Berde C.B. et al. 2012 Pediatrics 129(2): 354-364

- Analgesic trials in pediatrics are challenging and require a delicate balance between scientific, ethical, and practical concerns.
- There are biological, empirical, and experiential bases to justify extrapolation of efficacy from studies in adults to children aged 2 years for μ-opioids, local anesthetics, NSAIDs, and acetaminophen.
- Safety data may be collected both during the performance of PK and *dose-ranging studies.*

General Clinical Pharmacology Considerations for Pediatric Studies.

- Agency's Draft Guidance for Industry "General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products" 2014 (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm425885.pdf).

377 If there is no currently used pediatric dose, if there is insufficient PK information about a
378 currently used pediatric dose, or if the currently used pediatric dose in the same clinical context
379 would not be expected to match adult exposure, then a PK study should be performed to identify
380 the pediatric dose that will provide similar exposure to adults. This PK study should be
381 conducted before any additional pediatric clinical studies are initiated to ensure the optimal dose
382 for these studies. Before conducting a PK study, simulations should be performed to identify the
383 dose expected to achieve an appropriate target exposure (e.g., the observed adult drug exposure)
384 in the same clinical context.

General Clinical Pharmacology Considerations for Pediatric Studies

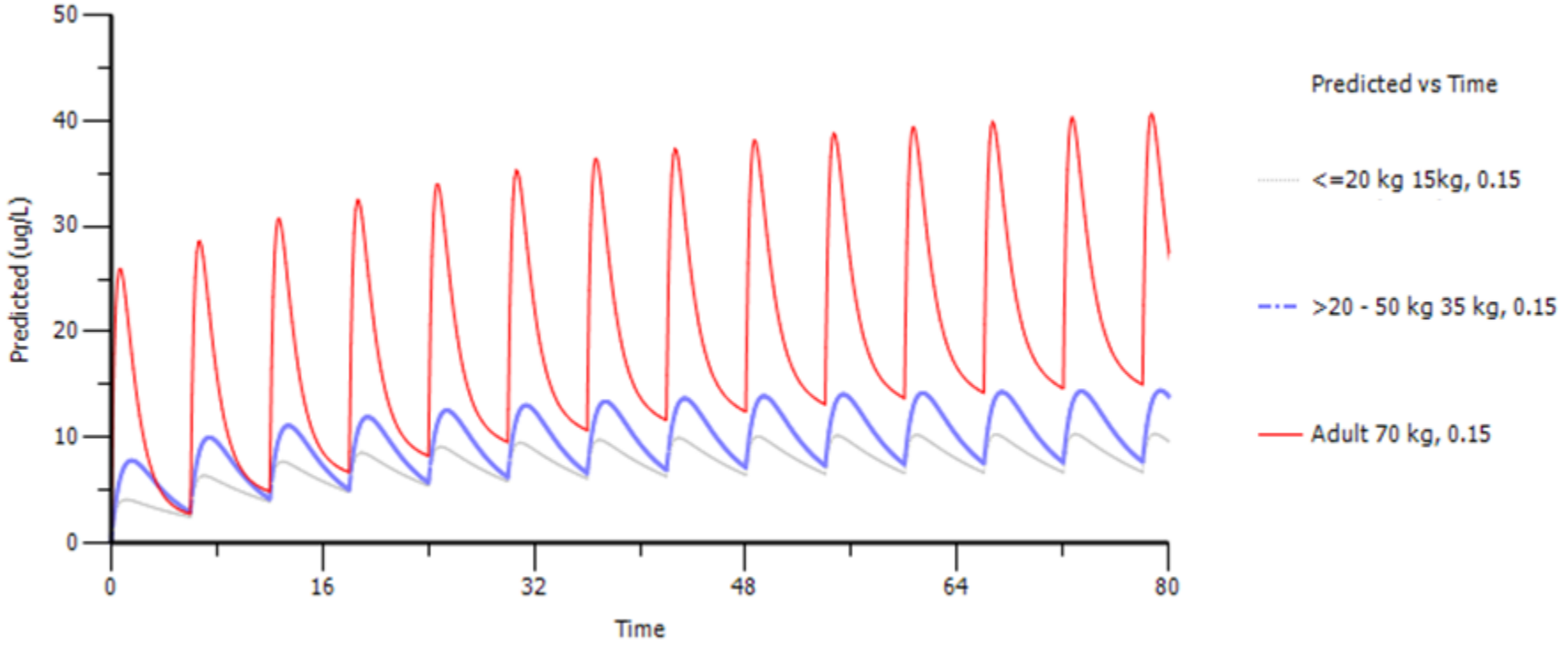
- Conduct of Simulations prior to pediatric studies
  - Leverage PK data from previously completed studies in adults
    - Most opioid IR have published data on adults and pediatric patients.
    - Opioid ERLA clinical pharmacology programs
      - Traditional PK (most common)
      - Population PK plan
  - Understand physiological covariates (body weight, age, sex, etc.) that might help explain the variability in pharmacokinetic parameters.

Conduct Simulations Prior to Actual Pediatric PK and Safety Studies

- Simulations prior to pediatric studies
  - PK parameters for pediatrics may be estimated from adult PK studies.
  - Check if the opioid IR or opioid ERLA product PK might be similar for adolescent patients compared to adults.
  - Important to consider practice-based guidelines established by pain societies and hospitals.
- Example for Opioid A where the assumed adult dose is 0.15 mg/kg oral dose according to the product label.
  - Assumption: Pediatric PK data is available for Opioid A in publications or past clinical experience of the NDA program.
  - Assumption: Data is available on clearance, volume of distribution and absorption rate constant (for oral route).
    - For opioid A, body weight is an important covariate (explains significant inter-individual variability)
    - The relationship is curvilinear $((WEIGHT/70)^{0.75}$

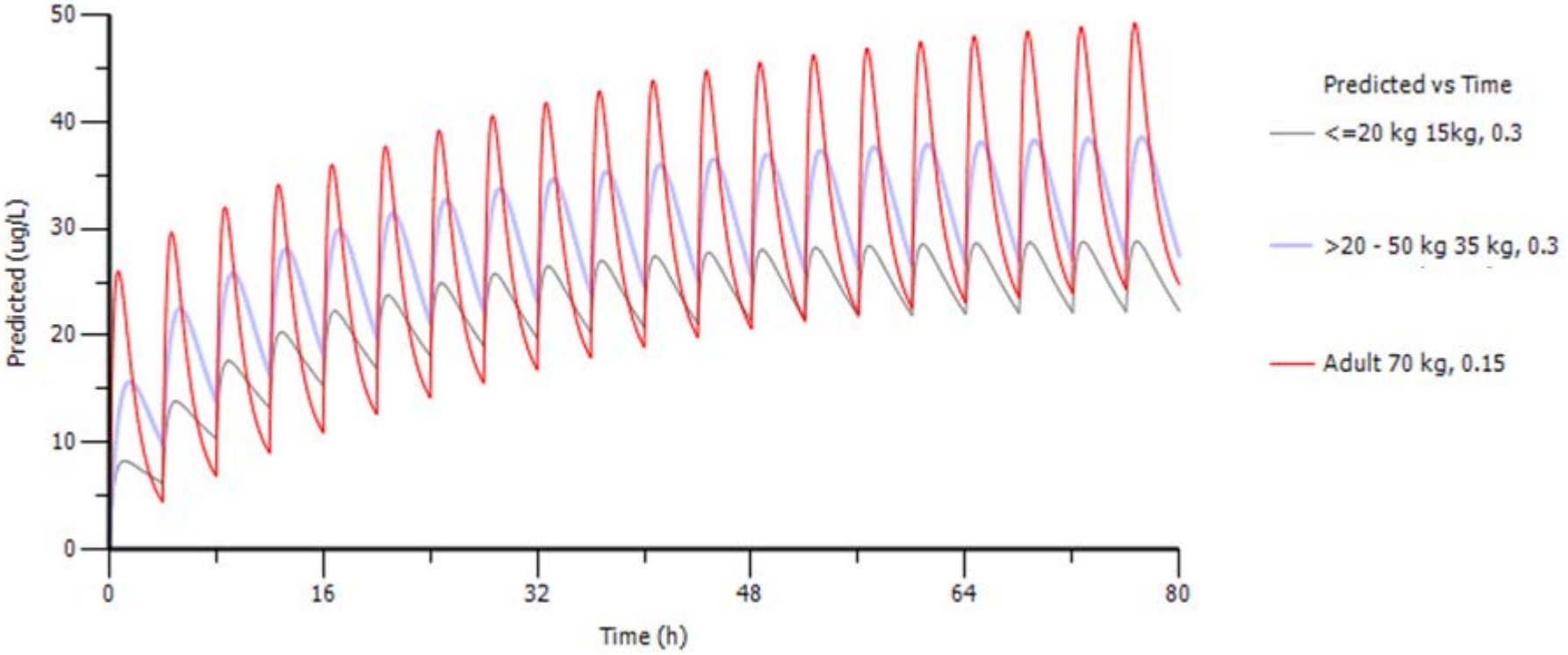
Simulations – Scenario A

- Every 6 hour dosing simulations
  - Pediatric patients (35 kg or 15 kg) and adults (70 kg) receiving oral opioid A every 6 hours dosed at 0.15 mg/kg



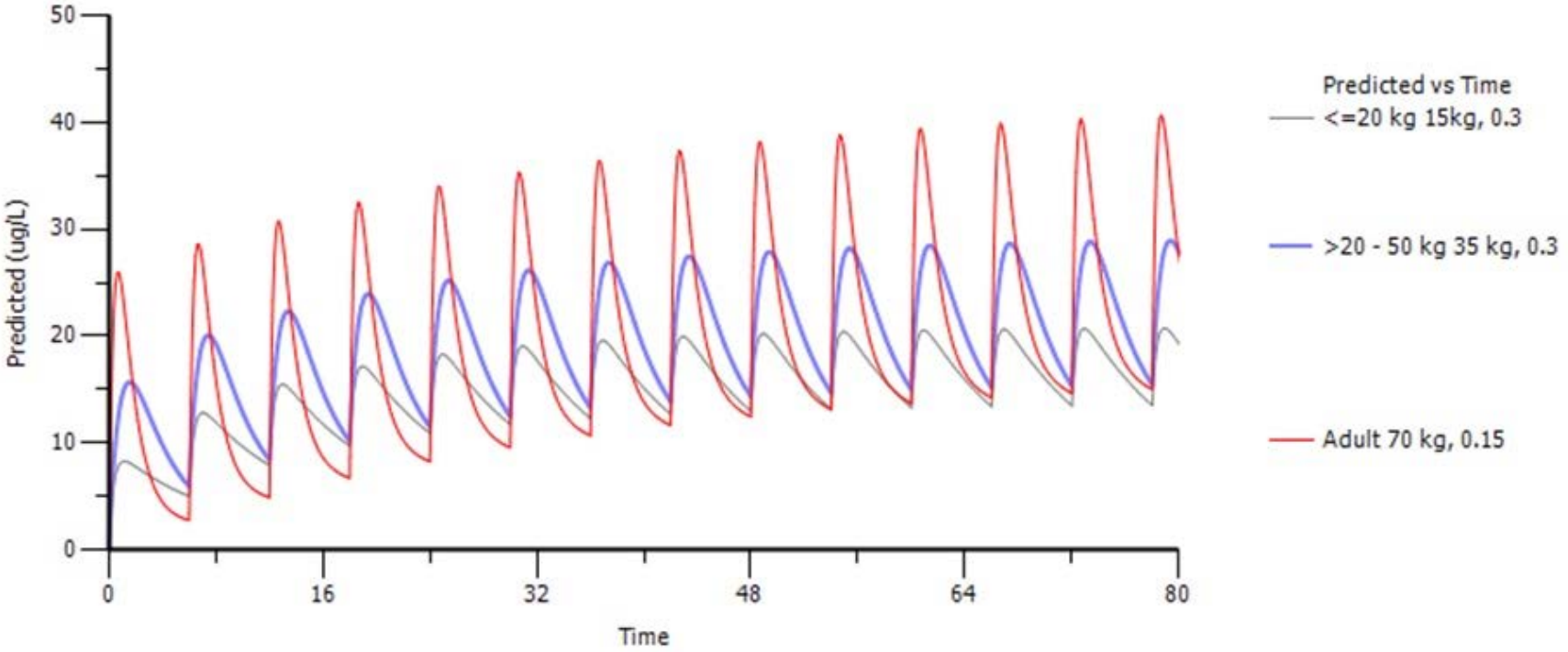
Simulations –Scenario B

- Oral opioid A simulation after **every 4 hours** dosing
  - Pediatric patients (35 kg or 15 kg) receiving 0.3 mg/kg
  - Compared with adults (70 kg) receiving 0.15 mg/kg



Simulations - Scenario C

- Every **6 hour** dosing simulations for opioid A
  - Pediatric patients (35 kg or 15 kg) receiving 0.3 mg/kg
  - Compared with adults (70 kg) receiving 0.15 mg/kg



Simulations Summary

- Pharmacokinetic Simulations can help support selection of initial dose of opioids.
- Important points while considering results of simulations
  - Most opioids in the market have clinical experience published.
  - Is there clinical experience with the Opioid IR product or ERLA product at the dose supported by simulations?
    - Are there regional differences in use of a given opioid in specific hospitals for specific pain conditions (post-op vs cancer pain, etc.)?

Pediatric Plan: Clinical Pharmacology Considerations

- Age
  - Opioid IR - Pediatric patients 2 – 17 years of age.
  - Opioid IR - Pediatric patients Birth to 2 years of age.
  - Opioid ERLA products - Only pediatric patients 7 – 17 years of age.
- Sample size calculation
- Number of blood samples play a critical role in pediatric PK studies.
  - Population PK: Justify blood sampling using a sparse sampling strategy which is aimed at minimizing number of blood draws.
  - Population PK: The sampling strategy should adequately identify a blood sampling scheme that will capture absorption characteristics (important for ERLA opioids), in addition to clearance and volume of distribution.
  - Traditional PK: Justification of timing of blood samples during absorption phase, peak plasma (Cmax) levels, and in the elimination phase (to calculate AUC0-tau/AUCss) should be based on adult PK data or any known pediatric PK data available.

Pediatric Plan: Clinical Pharmacology Considerations

- It is very important to estimate PK parameters in pediatric PK studies with precision.
  - Wang et. al. 2012 discusses methodology and considerations for pediatric PK studies.
  - Main emphasis on characterization of clearance (Cl) and volume of distribution (Vd)
    - Ka or Absorption rate may be important for opioid ERLA products.

Pediatric Plan: Clinical Pharmacology Considerations

- Single-dose study: PK evaluation of a single dose of an opioid IR or ERLA product may be conducted.
  - The opioid IR or ERLA PK should be linear and dose-proportional in adults and therefore single dose PK can be predictive of multiple dose PK.
  - The single-dose PK data must be used, by nonparametric superposition or compartmental methods, to predict doses required in pediatric patients to achieve plasma exposure comparable to adult subjects.
- Multiple-dose study: Pediatric patients that will require opioid ERLA use for more than two days may be dosed up to steady-state (as known in adults).
  - The goal of such a multiple-dose PK study is to confirm that the dose selected in pediatric patients will achieve plasma opioid exposure that is comparable to adults.

Pediatric Plan: Clinical Pharmacology Considerations

- The safety study should utilize doses derived from the aforementioned predictions.
- Sponsors are recommended to follow the above paradigm and submit the information to justify dose-selection prior to conducting a study.
- These safety studies must include additional clinical safety considerations laid out in other presentations.