APS Clinical Trials Shared Interest Group

- Neil Singla, MD, SIG Chair
- SIG provides a forum for researchers to discuss analgesic clinical trials with other experts
- APS-Conference on Analgesic Trials (APS-CAT):

  May 17, 2017, Pittsburgh PA (Day 1 of APS Annual Meeting)

- Today's webinar:

Ellen Fields, MD

Development of Opioids in Pediatric Patients:

Conclusions from the FDA's Recent Advisory Committee, and the Latest Agency Thinking on Studying Opioids in Children

Disclosures: Neil Singla, MD

Chairman, APS Clinical Trials SIG

- Dr. Singla is the Chief Scientific Officer of **Lotus Clinical Research, LLC**. Lotus is an analgesic CRO and research site that receives study grants from multiple pharmaceutical companies for the performance of clinical trial related services (enrollment of study subjects, performance of CRO services, subject education, trial methodology optimization, etc.)
- Dr. Singla and the members of his nuclear family do not have financial interests (including stocks, bonds, options, etc.) in any pharmaceutical company and do not have a financial stake in the outcome of any clinical study.
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  - Astellas Pharma
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  - Grifols, Inc.
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  - Vertex Pharmaceuticals

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Development of Opioids in Pediatric Patients:

Conclusions from the FDA's Recent Advisory Committee, and the Latest Agency Thinking on Studying Opioids in Children

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Disclaimer

- The views expressed in this presentation are mine and should not be attributed to the Food and Drug Administration
- I have no conflicts of interest or relevant financial relationships to disclose.

Topics

- Pediatric Drug Development
- Pediatric analgesic development
- Pediatric analgesic study requirements
- Opioid analgesics and pediatric patients
- Advisory Committee Meeting
- Moving forward

Pediatric Drug Development
General Principles

- Children should have access to products that have been appropriately evaluated
- Thoughtful drug development and inclusion of children in trials is critical to pediatric health

Current 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
- Six months of marketing exclusivity granted if the terms of the WR are met

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

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

Pediatric Analgesic Drug Development

- Unmet needs in pediatric pain management
- Very few analgesics with pediatric indications or labeling, including opioids
- Most analgesic use in pediatric patients is off-label
- Although pediatric studies have been required by law since 2003, few analgesic studies have been completed
- Most infants and children are healthy and experience brief pain episodes, but some have severely painful conditions (i.e, epidermolysis bullosa, OI, cancer, metabolic/neurologic dis, sickle cell)

Analgesics with Pediatric Labeling or Indications

Acetaminophen, Aspirin, NSAIDs

- Oral APAP (≥2 y)
- IV APAP from birth
- ASA
- Ibuprofen (≥ 6 m)

NSAIDS for JIA indication

- Celecoxib
- Diflunisal
- EtodolacXL
- Indomethcin
- Ketorolac
- Mefenamic acid
- Meloxicam
- Naproxen
- Oxaprozin
- Tolmetin

Opioids

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

Combination Products

- **Codeine/APAP (≥ 3 y)**
- **Hydrocodone/APAP (≥2 y)**
- Pentazocine/APAP
- Dihydrocodeine/ASA/Caffeine
- Codeine/ASA/Butalbital/Caffeine
- Oxycodone/Ibuprofen
- Pentazocine/Naloxone
- Carisoprodol/ASA/Codeine
- Butalbital/APAP
- Butalbital/APAP/Caffeine

Analgesics without Pediatric Labeling

NSAIDS

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

Combination Products

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

Single-Entity 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
- Buprenorphine transdermal
- Butorphanol
- Levorphanol
- Nalbuphine
- Pentazocine

Study Requirements for Pediatric Analgesics

Pre 2010

- Pharmacokinetic, efficacy and safety studies for almost all analgesics, all age groups
- But industry could not enroll
  - Sponsors reluctant to conduct randomized, double-blind trials to assess efficacy
  - Ethical concerns of IRBs and investigators re use of placebo, allowing children to experience more than mild pain
  - Enrollment challenges: parents, study sites, investigators
  - Limited number of patients
  - Neonates: painful procedures, emotional impact on parents

FDA Scientific Workshop-2009

- **Are efficacy studies necessary? Can we extrapolate from adults?**
- FDA-sponsored Pediatric Analgesic Clinical Studies Scientific Workshop
  - Leading pediatric analgesic clinical trial design experts and pediatric clinical pain experts
  - Discussed which analgesic drug classes could have efficacy extrapolated from adults to children based on available scientific and medical support
    - What ages?
  - For analgesic drug classes where extrapolation is inappropriate, discussed alternative study designs

Legislation allows for Extrapolation of Efficacy in Pediatric Patients

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.

*21CFR §355c

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 fewer patients

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Pediatric Analgesic Clinical Trial Designs, Measures, and Extrapolation: Report of an FDA Scientific Workshop

Charles B. Berde, Gary A. Walco, Elliot J. Krane, K. J. S. Anand, Jacob V. Aranda, Kenneth D. Craig, Carlton D. Dampier, Julia C. Finkel, Martin Grabois, Celeste Johnston, John Lantos, Alyssa Lebel, Lynne G. Maxwell, Patrick McGrath, Timothy F. Oberlander, Laura E. Schanberg, Bonnie Stevens, Anna Taddio, Carl L. von Baeyer, Myron Yaster and William T. Zempsky

Pediatrics; originally published online January 16, 2012;
DOI: 10.1542/peds.2010-3591

Consensus

Since 2010

- 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 or ER analgesics
  - Waive studies in patients less than 7 years due to small numbers

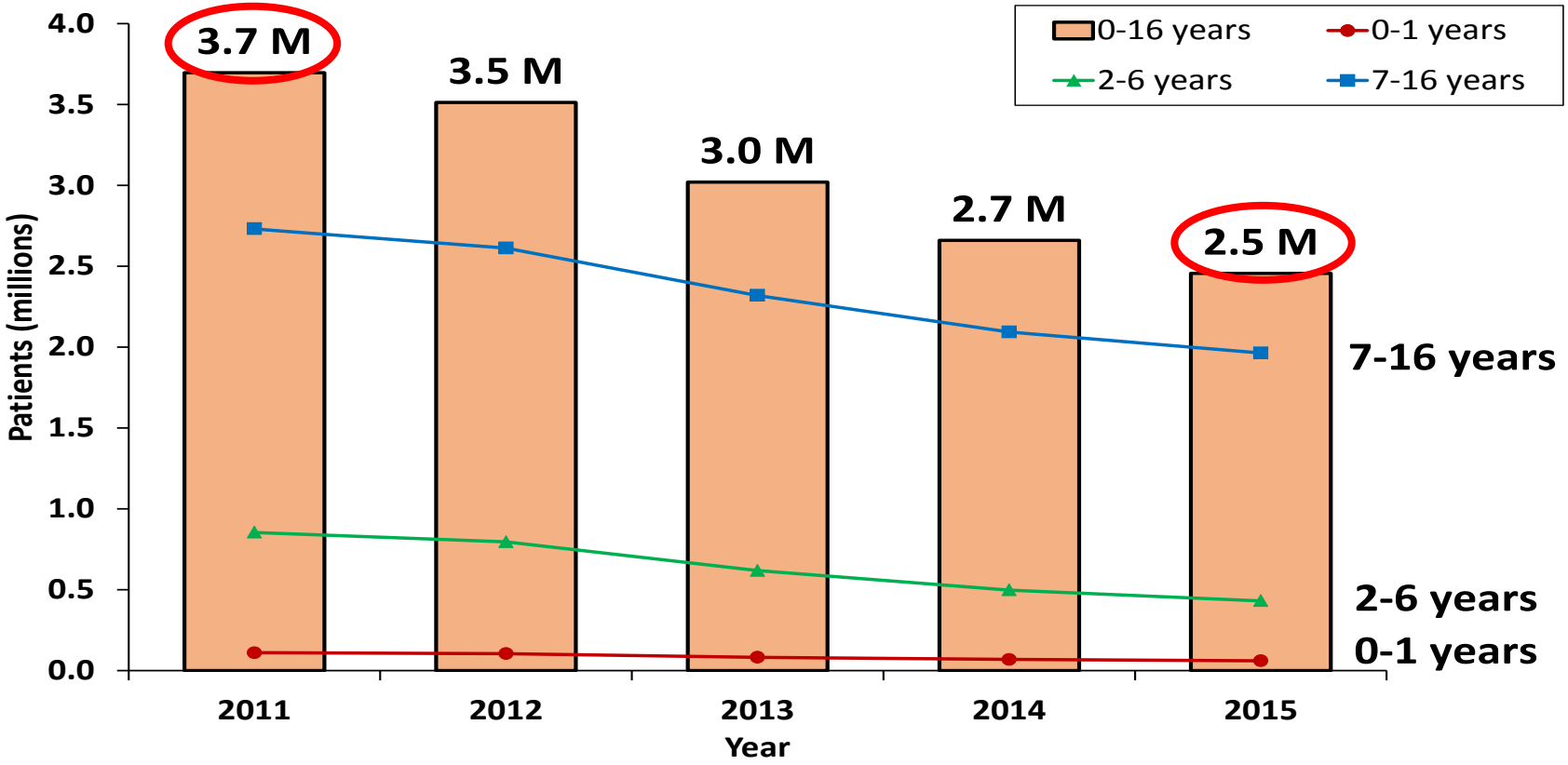
Alternate Study Designs

- Patients <2 years old
- Encourage use of immediate-rescue designs, using opioid-sparing as primary endpoint rather than pain intensity measure
- Particularly useful
  - neonates and infants where there are limitations in pain assessments made by surrogates (parents, investigators)
  - Evaluation of post op pain by using NCA or PCA rescue as primary endpoint for oral analgesic

Use of Opioids in Pediatric Patients

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



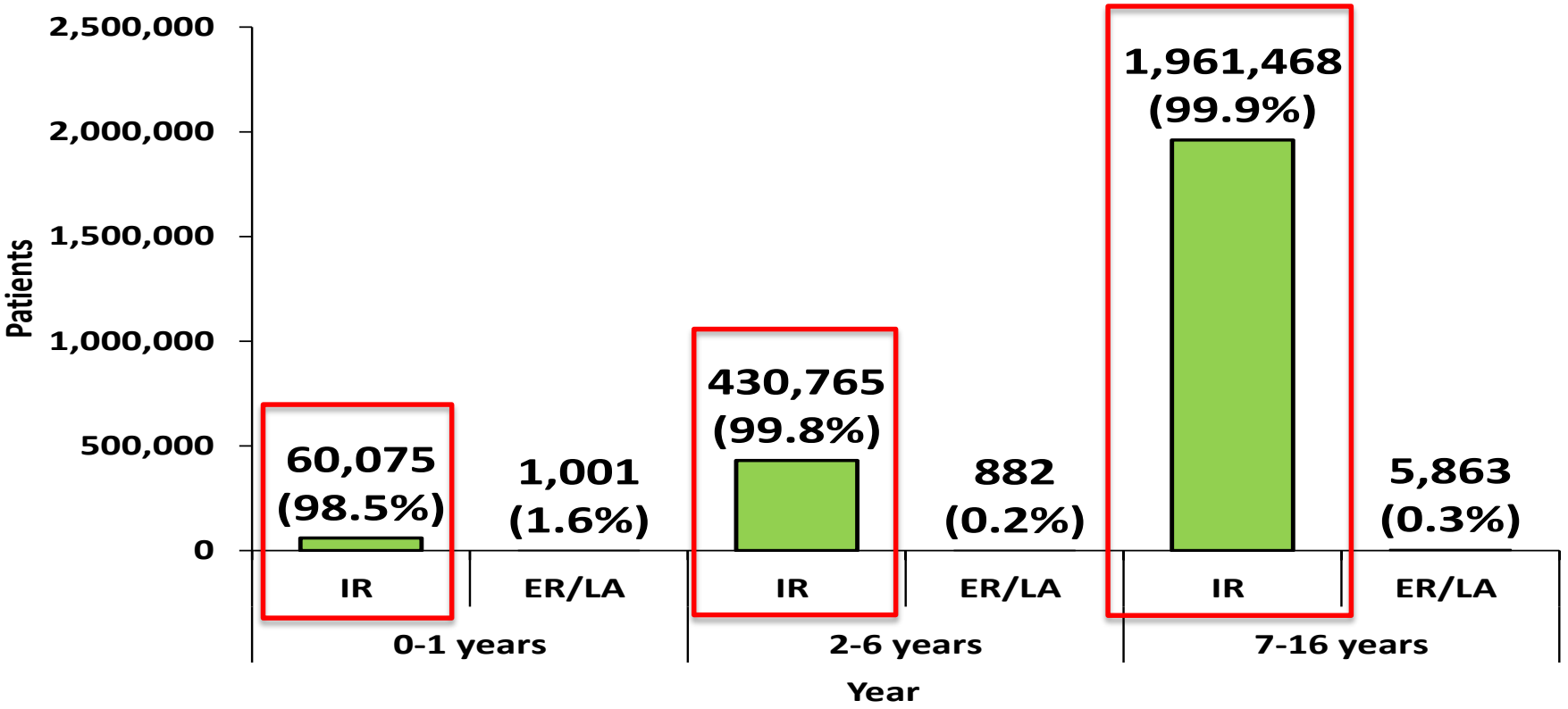
Source: Symphony Health Solutions' Integrated Dataverse® (IDV). Years 2011-2015. Data extracted August 2016.

**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.*

Opioid Utilization

- 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

OxyContin

- Purpose of study was to describe the PK and safety of OxyContin in pediatric patients requiring treatment with an extended-release opioid analgesic
- Pediatric indication approved August 2015
  - 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
- **Approval did not create novel uses for OxyContin in pediatric patients-but provided data in patients who require this treatment**

- http://www.fda.gov/Drugs/NewsEvents/ucm456973.htm

OxyContin

----------INDICATIONS AND USAGE----------

OXYCONTIN is an opioid agonist indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in:

- Adults; and
- 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.

Limitations of Use

- Because of the risks of addiction, abuse and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve OXYCONTIN for use in patients for whom alternative treatment options (e.g. non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1)
- OXYCONTIN is not indicated as an as-needed (prn) analgesic. (1)

OxyContin Post-Marketing Requirements

- Novel PMRs were put in place to further understand the impact of pediatric indication for OxyContin
- The Sponsor is required to assess the safety and use of Oxycontin in pediatric patients in two postmarketing studies:
  - 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

Negative Public Reaction

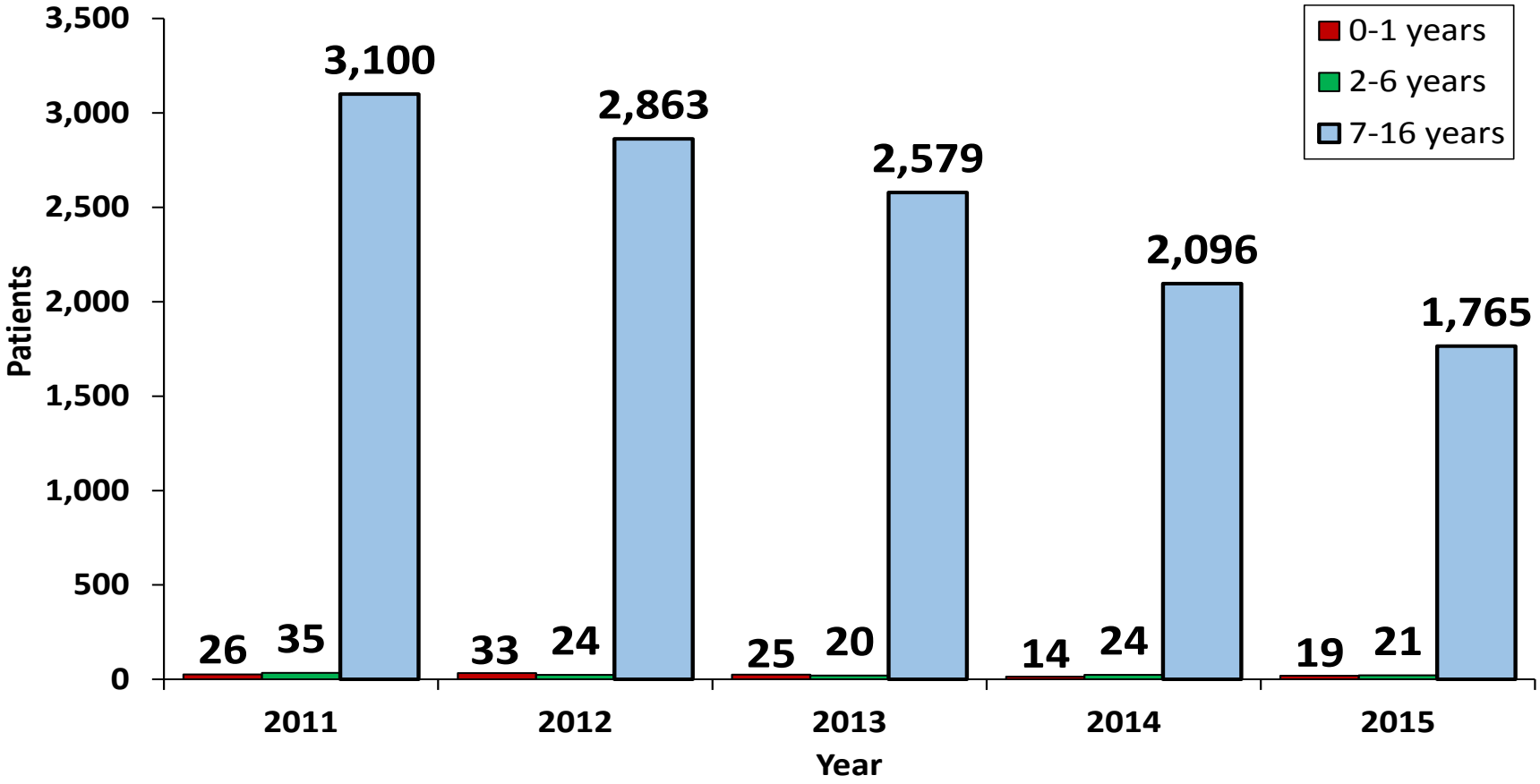
“FDA must revisit OxyContin decision”

“Absolutely incomprehensible that FDA approved OxyContin for children”

“FDA should be absolutely ashamed of itself for this reckless act.”

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).*

Advisory Committee

Continued Challenges

- Sponsors have trouble enrolling pediatric patients into trials

  Reluctance of investigators, study sites and IRBs
  - Too few patients, especially youngest patients and chronic pain
  - Parental concerns
  - Ethical and logistical concerns-neonates (blood sampling, use of placebo and unnecessary pain, emotional impact on parents)
- Cannot complete trials in a reasonable period of time: Oxycontin-4 years
- Public misunderstanding regarding the use and approval of opioids in pediatric patients

Advisory Committee- September, 2016

- Part of the Commissioner's Opioid Action Plan
- Obtain advice on the development of opioid analgesics in the pediatric population
- Three committees
  - Anesthetic and Analgesic Drug Products, Drug Safety and Risk Management, and Pediatric Advisory Committees
- FDA and outside speakers
- http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm486848.htm

Presentations

- FDA
  - Pediatric legislation, use of opioids, current labeling including OxyContin, clinical pharmacology, study design, ethics
- Outside Speakers
  - Importance of treatment of pain in pediatric patients
  - Use of opioids in pediatric patients
  - Identification of pediatric populations requiring opioid treatment
  - Ethics of prescribing opioids in children (benefit/risk)
  - Risk of abuse and misuse in adolescents
  - Challenges of conducting studies in pediatric patients

Highlights

- General
  - **Data is needed to inform labeling and use of opioids in pediatric patients**
  - There are pediatric patients who require opioid analgesics for a variety of conditions
  - Untreated or poorly treated pain in children can have lasting, profound, and irreversible effects, sensitizing to greater risk of chronic pain in the future
  - Need to consider risk/benefit to patients when prescribing opioids
  - Pediatric patients are vulnerable to drug use and addiction due to ongoing brain development. Proper prescribing, patient selection, education is crucial
  - Approvals of opioids in pediatric patients will be accompanied by post marketing requirements to assess the safety of these products in children

Highlights

- **Which pediatric patients are currently treated with opioid analgesics?**
  - Chronic pain conditions or pain requiring treatment for two or more weeks:
    - Cancer, end of life care, post op pain after extensive surgeries such as orthopedic procedures on spine, cardiothoracic procedures, critical illness, mechanical ventilation, complex regional pain syndrome, burns
  - Acute pain conditions, short-term use
    - post op pain, injury, trauma, burns/dressing changes, sickle cell pain crises (intermittent use)
- Very important to select an appropriate pediatric patient population who requires treatment with an opioid to enroll in studies
    - for ERLA opioids, require treatment for at least 2 weeks

Highlights

- **What are the study requirements for opioids?**
  - Acute pain/IR opioids
    - >2 yo: extrapolate efficacy from adults, PK and OL safety studies only
    - birth-2 years: PK, safety, and efficacy; “add-on” design
  - Chronic pain/ERLA opioids
    - 7-16 years: extrapolate efficacy, PK and OL safety only ,
    - No studies required <7 years of age, too few patients

Highlights

- Additional considerations opioid studies
  - Include only types of pain expected to respond to opioids
  - Carefully document reason for opioid treatment in each patient
  - Collect information on use of rescue analgesics and pain assessments to inform efficacy even in OL studies
  - For studies of ERLA opioids
    - enroll as many patients as possible with cancer related pain, however due to relatively small number in this category, no minimum requirement
    - patients should generally be started on IR opioids to ensure tolerability
    - include patients expected to require opioids for at least 2 weeks

Highlights

- **The importance of starting dose selection**
  - Conduct PK simulations prior to studies in pediatric patients
  - Conduct single dose and multiple dose PK studies to confirm doses can match adult exposure of the formulation
  - Conduct safety study(ies) to confirm doses that product matching adult exposures are safe.
  - Refer to AC slides for additional detail

Highlights

- Challenges remain
  - Enrollment, few patients, parental concerns, investigator concerns, study sites
  - Studies in patients < 2 years old, especially < 6 month olds
  - Completing studies in timely manner
  - Measurement of pain, particularly in youngest patients

- Research needs
  - Long-term behavioral outcomes from opioid use in childhood including misuse and abuse
  - Long-term impact of chronic illness with associated pain or painful procedures on pediatric patients
  - Efficacy of multimodal therapies for the treatment of pain in children

Moving Forward

- There are major information gaps regarding the use opioid analgesics in pediatric patients that must be filled
- There is no evidence that appropriate labeling of opioids children increases use in this population
- Clinical trials are needed to improve how opioid analgesics are prescribed to children with acute and chronic pain
- Strongly recommend that sponsors discuss their pediatric study plans with the Agency early in product development
- Open to discussing innovative approaches
- Applications for pediatric labeling for opioids will be taken to advisory committee

Useful References

Pediatric AC Information:

- http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm486848.htm
- Analgesic guidance for Industry:

http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm384691.pdf

- Clinical Pharmacology and Pediatric Studies draft guidance for Industry

http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm425885.pdf

- "Pediatric analgesic clinical trial designs, measures, and extrapolation: report of an FDA scientific workshop," Berde, Walco, Krane, et. al.

https://www.ncbi.nlm.nih.gov/pubmed/22250028

Thank you


FDA
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ADMINISTRATION