FDA Briefing Document

Joint Meeting of Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee

September 14, 2017
DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought clinical and pharmacokinetic data to this Advisory Committee in order to gain the Committee’s insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.
### Background Materials

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DATE: August 14, 2017

FROM: Sharon Hertz, MD
        Director
        Division of Anesthesia, Analgesia, and Addiction Products
        Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members and Invited Guests
     Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)
     Drug Safety and Risk Management Advisory Committee (DSaRM)

RE: Overview of the September 14, 2017 AADPAC/DSaRM Joint Advisory Committee Meeting to Discuss NDA 21306

At this joint meeting of AADPAC and DSaRM, we will be discussing a study conducted by Purdue Pharma (the Applicant) in pediatric patients receiving Butrans (buprenorphine) Transdermal System, and whether the data from this study supports adding information about Butrans to the pediatric section of the labeling, without adding an indication for use in this population. The study was conducted in response to a postmarketing requirement under the Pediatric Research and Equity Act (PREA) to assess the use of Butrans in pediatric patients. Butrans was approved in 2010 for the management of moderate-to-severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time. The indication was updated in 2016 according to the extended-release/long-acting opioid analgesic class labeling change to the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate.

PREA requires pediatric assessments of new drugs and biological products for all new active ingredients, indications, dosage forms, dosing regimens, and routes of administration. The pediatric assessments are conducted to assess the safety and effectiveness of a drug or biologic for the claimed indications in all relevant pediatric subpopulations, and to support dosing and
administration for which the drug or biologic product is safe and effective. In other words, the purpose of the pediatric assessments under PREA is not to in any way broaden the use of the product, but to obtain data that will support the safe and effective use in pediatric patients that already use or could benefit from their use.

There was general misunderstanding of the addition of a new pediatric indication to OxyContin for use in pediatric patients ages 11-17 in 2015. There was a lack of knowledge that OxyContin was already being used off label in pediatric patients and concern that the indication would expand use. However, the requirement that pediatric patients be tolerant to a minimum of 20 mg of oxycodone per day actually restricts use to a narrower population than in adults. The primary intent of the approval was to add to labeling the data collected in the studies to better inform safe and effective dosing in appropriately selected pediatric patients. In September 2016, a joint advisory committee meeting was held comprised of the Anesthetic and Analgesic Drug Products Advisory Committee, the Drug Safety and Risk Management Advisory Committee, and the Pediatric Advisory Committee. The committee was asked to provide the Agency with advice about whether opioid analgesics should be studied in pediatric patients, and if so, to provide advice about the conduct of those studies. The committees sent a strong message that there are pediatric patients who require opioid analgesics for a variety of painful conditions and for whom the benefit of treatment with opioid analgesics outweighs the risks, and that clinical trials are needed to inform the safe and effective prescribing of opioid analgesics to children. The committees also expressed that as pediatric patients are vulnerable to drug use and addiction due to ongoing brain development, proper prescribing, patient selection, and education are crucial to optimize safety into this population.

Children experience pain in a number of settings and the imperative to relieve their suffering is no less great than for adults. Most of the analgesic products used to manage pain in children, opioid and non-opioid, do not have pediatric efficacy, safety, or dosing information because they have not been studied in children. The serious public health problem associated with the misuse and abuse of prescription opioid analgesics and the problems of addiction, overdose, and death must always be kept in mind when discussing opioid analgesics. However, it is critically important to address the medical needs of children, which includes providing clinicians age-appropriate information about the efficacy, safety, and pharmacokinetics of the products they use.

At this meeting you will hear presentations from the Applicant describing their pediatric development program and study for Butrans. Presentations from FDA will include a summary of the 2016 pediatric opioid analgesic advisory committee meeting, and review of and conclusions regarding the study of Butrans in pediatric patients.

We are asking that you provide your expertise, your experience, and your best insights in order to help us make a reasonable and responsible decision regarding this application. Your advice
and recommendations will be essential in assisting us with addressing this complex and critical public health concern. We are grateful that you have agreed to join us for this important discussion and look forward to seeing you at the meeting.

**Draft Discussion Points**

1. Discuss any concerns you have regarding the use of Butrans in pediatric patients.

2. Discuss whether there is adequate data to support adding information about the pediatric study to the labeling of Butrans.
AC Backgrounder: Butrans in Pediatric Patients

Product Information

Butrans is a transdermal system that delivers buprenorphine, a partial mu-opioid agonist and kappa-opioid antagonist, to the bloodstream. Butrans (also called BTDS) is indicated in adults 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. The currently available patch strengths of Butrans include 5, 7.5, 10, 15, and 20 mcg/hour. Each Butrans patch is intended to be worn for seven days.

Buprenorphine is currently marketed as an analgesic and for medication assisted therapy for opioid use disorder. The buprenorphine moiety was first approved in 1981 as an injectable formulation with an indication of relief of moderate to severe pain. This formulation is also approved in children down to two years of age. In 2002, the buprenorphine moiety was approved for the treatment of opioid addiction. Buprenorphine is currently available as a buccal film, sublingual tablet, and a subdermal implant for opioid dependence, and as an injectable formulation, transdermal patch, and buccal film for pain.

Regulatory History, PREA Requirement, Evolving Policy Around Pediatric Opioid Studies

Butrans was approved on June 30, 2010 in adults for the management of moderate-to-severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time. With the 2016 opioid class labeling, the indication was changed to the management of pain severe enough to require daily, around-the-clock, long-term opioid...
treatment for which alternative treatment options are inadequate. At the time of approval, the pediatric study requirement for ages birth through six years was waived because necessary studies were impossible or highly impracticable since the numbers of pediatric patients meeting the indication were too small in number to make pediatric studies feasible. The pediatric study was deferred for ages seven through sixteen years because the product was ready for approval in adults. The deferred pediatric study required under the Pediatric Research Equity Act (PREA) was a pharmacokinetic and safety study for the treatment of moderate-to-severe chronic pain requiring continuous, around-the-clock opioid treatment for an extended period of time in pediatric patients ages seven through sixteen. The Agency had determined that for opioid analgesics, efficacy could be extrapolated from adults to pediatric patients as young as 2 years old because of similarity of the underlying disease process and the exposure response to buprenorphine in adults and pediatric patients. Therefore, the study to fulfill the PREA requirement could be an open-label design assessing pharmacokinetics and safety.

The FDA provided guidance during the development of the pediatric protocol. Key pieces of advice from FDA to the Sponsor included: 1. While a four-week treatment duration was acceptable for the pharmacokinetic aspect of the study, additional patients must be studied to provide the necessary long-term safety data and, 2. The Sponsor would need 40 completers with at least 6-months of exposure to assess safety. As discussed below, certain of these recommendations have evolved over the period of time since the approval of Butrans.

Butrans was approved in mid-2010 when the Division was reevaluating the policy for studies of opioids in the pediatric population. While FDA had been requiring such studies under the Pediatric Research Equity Act (PREA) since 2003, the available data circa 2010 revealed difficulties in enrollment of pediatric pain studies along with other issues. In 2009, FDA convened a panel of pediatric pain and clinical trial experts to discuss this issue. The experts published their findings (Berde et al Pediatric Analgesic Clinical Trial Designs, Measures, and Extrapolation: Report of a FDA Scientific Workshop. Pediatrics 2012;129(2):354-S12). Pertinent to this application, since 2010, FDA has been waiving studies for patients under age 7 years and requiring safety and pharmacokinetic studies in patients age 7 to <17 years.

As data on pediatric studies of opioids has accumulated, FDA also convened an Advisory Committee in September, 2016 to obtain advice on the development of opioid analgesics in the pediatric population. A full description of this meeting can be found at:

https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm486848.htm

Highlights of the Committee’s discussion pertinent to this application include:

- Data informing labeling and use of opioids in pediatric patients are needed, as there are pediatric patients for whom the benefit of opioid treatment for pain outweighs the risks.
- For pediatric studies of extended-release/long-acting (ERLA) opioids:
  - Patients enrolled in studies should be expected to require treatment with opioids for at least two weeks.
  - Studies should include only types of pain expected to respond to opioids.
The reason for opioid treatment should be carefully documented for each patient.

- It is important to collect information on the use of rescue analgesics and pain intensity, even in open-label studies.

- Enrollment of as many patients as possible with cancer-related pain is desirable, however, there is no minimum requirement for oncology patients in these studies as it is difficult to enroll them in analgesic studies.

**Study BUP3031**

The Applicant submitted one study in children (BUP3031), to fulfill their PREA requirement.

Study BUP3031 was an open-label, multicenter, multiple-dose study of the safety and pharmacokinetics (PK) of Butrans in patients aged 7 to 16 years, inclusive, who required continuous around-the-clock opioid analgesia for moderate-to-severe persistent pain.

Eligibility criteria included patients aged 7 to 16 years with malignant and/or nonmalignant moderate-to-severe pain requiring or anticipated to require continuous, around-the-clock, opioid treatment for at least 2 weeks, based on the investigator’s judgment. Patients with post-operative pain were allowed if at least 48 hours had elapsed since the end of surgery. Patients may have been opioid-naïve or opioid-experienced. Patients who were opioid-naïve or were receiving 10 mg/day oral morphine or equivalent (MEQ) or less during the five consecutive days prior to the initiation of BTDS treatment were required to be inpatients at the initiation of BTDS treatment and remain hospitalized for the first 48 hours of treatment.

All patients in the younger age group (aged 7 to 11 years) initiated treatment with BTDS 2.5 mcg/hour; all patients in the older age group (aged 12 to 16 years) initiated treatment with BTDS 5 mcg/hour. If the starting dose did not seem to be controlling the patient’s pain, short-acting rescue opioids were permitted during this time at the discretion of the investigator.

The dose of BTDS was allowed to be adjusted upward or downward as needed throughout the study. During the treatment period, patients may have used supplemental short-acting opioid (other than buprenorphine) or non-opioid medications. The study permitted treatment for up to 26 weeks.

**Efficacy**

This was an open-label study with pain assessments completed once daily during the first four weeks of the study and weekly thereafter. It was not designed to assess efficacy however, data were collected for informational purposes.

The PK samples were drawn up to 5 times during the first 4 weeks of the study at the following timepoints:

- 18 to 24 hours after the application of the first BTDS patch (visit 3)
- End of week 1 (visit 4)
- 2 to 3 days after the end of week 1 (visit 5)
- End of week 2 (visit 6)
- End of week 4 (visit 8) or at discontinuation prior to visit 8.
A completer was defined as a patient who met any of the following conditions: (1) the patient completed at least 2 weeks of study drug dosing, did not meet any of the discontinuation reasons described in the protocol, and did not need additional treatment with opioid medication for pain relief at the minimum study drug dose (BTDS 2.5 mcg/hour) or equivalent; (2) the patient completed the entire 24 weeks of study drug dosing; or, (3) the patient completed at least 2 weeks of study drug dosing and was being tapered down from his or her current BTDS dose in order to switch from BTDS to other opioid analgesic medication(s) and did not meet any of the discontinuation reasons.

Safety Monitoring
Vital signs (blood pressure, respiratory rate, pulse rate, and temperature) and SpO2 were recorded at: screening; before and after initial BTDS application; and before and after any up-titration. ECGs, including a 24-hour Holter Monitor at screening, were conducted throughout the study.

Results

Exposure:
A total of 41 patients were exposed to at least one dose of Butrans, 6 patients in the 7 to 11 year age group and 35 patients in the 12 to 16 year age group. The mean and median age in the younger stratum was 10.3 years and 11 years, respectively. For the older stratum, the mean and median were 14.5 and 15.0, respectively. Overall, 37 patients (90%) received treatment for at least 2 weeks and 31 patients (76%) received treatment for at least 4 weeks. The duration of exposure was less for the 7 to 11 year age group with only 3 patients (50%) treated for at least 2 weeks and one patient treated for at least 4 weeks. Exposure to the highest dose (20 mcg/h) was limited to the older age group with 13 subjects exposed to at least one dose, 10 subjects for at least 2 weeks and 6 subjects for at least 4 weeks. The majority of patients who discontinued did so for adverse events (11/18).

The primary conditions for study entry were the following: low back pain (8), migraine headaches (6), sickle cell disease (6), surgical procedure\(^1\) (4), musculoskeletal pain (complex regional pain syndrome) (1), abdominal pain (3), Epstein Barr antibody positive (1), chronic foot pain (neuroma/osteomyelitis) (1), amniotic band syndrome (chronic osteomyelitis/right club foot) (1), knee arthritis (1), Crohns Disease (1), oral Crohns with mouth ulcers (1), pelvic pain (1), diffuse scleroderma (1), joint pain (1), juvenile rheumatoid arthritis (1), generalized rheumatologic pain (1), avascular necrosis of both hips (patient also had sickle cell disease but this was not included as primary diagnosis) (1) and gunshot wound right lower extremity (1). It is noted that none of the subjects had pain due to cancer. Although patients with pain due to cancer are often appropriate for treatment with opioids, traditionally these patients are difficult to recruit into pain studies due to their primary focus on treating the cancer and the restriction of not being eligible to participate in more than one study at a time.

As described in the preceding paragraph, some of the pediatric patients enrolled in this study had painful conditions that are not commonly associated with the use of ERLA opioid analgesics.

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\(^1\) Includes: hemipelvectomy; pectus Nuss procedure; GSW hip (open reduction/internal fixation of right femoral neck fracture); lower extremity crush injury (open reduction/internal fixation lower extremity fasciotomy)
Two clinical investigator inspections were conducted as a routine part of the review process. Medical records for the seven patients enrolled at one site were collected and reviewed to provide details around the coded diagnoses. All of patients enrolled had complex medical histories. One patient was coded with fibromyalgia, one with EBV-related neuralgia, and the remainder had migraine or chronic headache. Two of the patients had pain so debilitating that they could not attend school. All patients had been previously treated with a variety of non-narcotic drugs used for pain and migraine such as gabapentin, pregabalin, fioricet, clonidine, topirimate, divalproex sodium, verapamil, NSAIDs, cyclobenzaprine, propranolol, tricyclic antidepressants, corticosteroids, ergots, botulinum toxin injections, and milnacipran. Several patients had comorbid psychiatric conditions, particularly depression, for which some were on SSRIs. Other patients were on trazodone or benzodiazepines for insomnia. The number of discrete non-narcotic analgesics tried before enrollment in the study ranged from 1 to 14 with most patients having tried at least 7 non-opioid drugs. Of the five patients with migraine, two had not been treated with a triptan. With regard to prior opioid therapy, six out of seven patients had prior exposure to tramadol and three were on scheduled vs. prn tramadol. The one patient who had never taken tramadol had failed butorphanol nasal spray. Case summaries for these seven patients can be found in the Appendix.

Pharmacokinetics
The clinical pharmacology team reviewed the data and concluded that the final population PK model provided an adequate description of the pediatric PK data and can be used to perform simulations to identify the “target” pediatric BTDS dose which can match the steady-state exposures in adults following the recommended starting dose of BTDS 5 mcg/hr.

Safety
There were no deaths in any patients who received Butrans during Study BUP3031. Of the 41 patients treated with BTDS, eight patients (20%) experienced treatment-emergent serious adverse events (SAEs). Butrans was not considered to be the cause of any of the SAEs but may have exacerbated the SAE of hypomnolence in an 11-year-old girl with a history of sickle cell disease who had similar episodes before starting and after stopping Butrans. The most frequently reported treatment-emergent adverse events were consistent with the known opioid and transdermal patch adverse event profile and included local application site conditions, nausea, somnolence, dizziness, headache, constipation, and vomiting. Overall the safety profile for Butrans in pediatric patients was generally consistent with adults but the number of patients and exposure were limited.

ECG and ECG-related Adverse Events
Buprenorphine can cause QTc prolongation. The Butrans label includes a warning not to exceed a dose of 20 mcg/hour. In a thorough QT study conducted in adults in 2009, there was no clinically meaningful effect on mean QTc with a Butrans dose of 10 mcg/hour but a Butrans dose of 40 mcg/hour prolonged mean QTc by a maximum of 9.2 (90% CI: 5.2-13.3) msec.

The ECG data systematically collected as routine surveillance for this pediatric study and AEs potentially related to QT prolongation were evaluated by the Division of Cardiovascular and Renal Products (DCRP). DCRP opined that the data do not suggest a signal for QTc interval prolongation. However, five patients were discontinued for ECG-related adverse events, such as QT prolongation, mild sinus tachycardia, first degree atrio-ventricular block, and QRS complex
prolongation. In three of five of those patients, the facts of the case suggested the possibility of a drug-related event at doses lower than that specified in the labeling. DCRP opined that the current labeling adequately describes the risk of QT prolongation. DCRP further recommended that a description of this study should include a description of the ECG-adverse events and the doses of BDTS when they occurred. Plasma levels of buprenorphine did not clearly correlate with these events.

DISCUSSION

In response to a postmarketing requirement under PREA, the Applicant completed and submitted a study in 41 pediatric patients. The study was conducted in pediatric patients age 7 to 16 years, inclusive, with the vast majority of the patients at the upper end of the age range and few (6) between the ages of 7 and 11 years. It is important to note that, since the approval of Butrans and the design phase of the study currently under review, the clinical trial experience with opioids in the pediatric population has grown and policy has evolved with that experience. Since the time of the initial Butrans PREA requirement, the recommended size of the safety database has increased from 40 patients to approximately 125 patients for the 12 to 17 year age group and 50 patients for the 7 to 11 year age group.

No new safety signals were identified in this small study. However, while the aggregate, surveillance ECG data revealed no evident risk in the patients enrolled, three patients experienced ECG-related adverse events for which the contribution of Butrans could not be excluded.

We also note that some of the pain diagnoses used to meet selection criteria for this study do not generally reflect the currently accepted indications for the use of ERLA opioids in the pediatric population. Our review of individual cases at one site showed that the patients enrolled generally had few other therapeutic options. However, as recommended by the 2016 Advisory Committee, it is important that Applicants’ carefully document a justification for the use of opioids in studies of opioids in the pediatric population.

Given the small database size, there are not sufficient data to fully describe the safety profile of Butrans in pediatric patients in the 7 to 16 year age group. We recommend that Butrans not receive an indication in pediatric patients ages 7 to 16 for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate.
APPENDIX
NB: Due to redaction of personally identifying information in the medical records, it is not possible to know the exact date any subjects were enrolled or dosed in Study 3031. Some records contain references to this study and a gross estimation of the timing of the study compared to medical events and medication use can be inferred but not with certainty.

Patient 1
This is a 12 year-old female with attention deficit disorder who presented with leg pain, paresthesias, and dysesthesias. Records for her painful condition date to approximately 10 months prior to study enrollment. A workup including MRI, CT, and plain radiographs reveal no organic etiology for her symptoms. A complement and rheumatoid factor were normal. She was eventually diagnosed with fibromyalgia. She was on extended-release methylphenidate for her ADD. She was tried on gabapentin (10 months) and scheduled-dose tramadol (6 months) prior to enrollment in the study.

Patient 2
This is a 10 year old female with pain felt to be a sequelae of Epstein-Barr Virus infection. Records for her painful condition date to approximately 3 months prior to study enrollment. This diagnosis was made after an extensive rheumatology and imaging workup. She had been tried on pregabalin, cyclobenzaprine, amitryptiline, nortriptyline, and prn and scheduled-dose tramadol (at least two months) and had intractable pain. She was offered duloxetine or the Butrans study and chose to enroll in the study. On Butrans, her PR interval lengthened and Butrans was discontinued. She later started a fentanyl patch.

Patient 3
This is a 14-year-old female with migraine, depression, asthma, and anxiety. It is not possible to determine when she was enrolled or dosed in Study 3031 although the last record refers to adolescent pain studies so it is likely that the preceding records predated her study participation. Upon initial evaluation by the investigator, she had complained of a continuous headache for 8 weeks. She was tried on a large number of analgesics including: topiramate, nortriptyline, divalproex sodium, verapamil, prednisone, ketorolac, diclofenac, gabapentin, pregabalin, amitryptiline, imipramine, propranolol, tramadol (scheduled dose). A workup including lumbar puncture and CNS imaging was negative. She became homebound and had multiple emergency department visits. She was tried on a course of dihydroergotamine mesylate (DHE) and had botulinum toxin injections for cervical dystonia.

Patient 4
This is a 16 year-old male with migraine and asthma. His records date to approximately six months prior to study entry. He had been tried on DHE treatment, ketorolac, divalproex sodium, prn tramadol (6 months), prednisone, rizatriptan, celecoxib, meloxicam, and fioricet prior to study enrollment.

Patient 5
This is a 15 year-old female who presented with headache, asthma, and, presumably, allergic rhinitis. Later notes indicate that she was diagnosed with hereditary angioedema at some point. Findings also included hand tremor and left arm numbness. It is not possible to estimate when
she enrolled in Study 3031. The analgesics in the medical record are pregabalin, cyclobenzaprine, topiramate, naproxen, DHE, tramadol prn, propranolol, fioricet. She had two MRIs as a part of her workup. Notes indicate that she was missing school.

Patient 6
This is a 12 year-old male with migraine and obesity. It is not possible to ascertain when he started the study although a note three months into the available records indicates that he was on a study of a patch. He had been tried on naproxen, ketorolac, divalproate, fioricet, DHE, tramadol prn, triptan (not specified), amitryptiline, and propranolol. He was out of school for some of the period the medical records cover.

Patient 7
This is a 15 year-old female with headache, presumed migraine. She had been seen by the investigator for at least 6 months prior to study enrollment. She had been tried on rizatriptan, burorphanol nasal spray, Topiramate, prednisone, and gabapentin.
MEMORANDUM

DATE: August 10, 2017

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Director, Division of Clinical Pharmacology 2
Office of Clinical Pharmacology, OTS, CDER, FDA

TO: Chair, Members and Invited Guests
Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)
Drug Safety and Risk Management Advisory Committee (DSaRM)

RE: Summary of Clinical Pharmacology for Butrans (buprenorphine) Transdermal System
Summary of Clinical Pharmacology Data for Butrans (buprenorphine) Transdermal System

Butrans is a partial opioid agonist and approved for the indication of the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. At the time of approval, the pediatric study requirement was waived for ages birth through 6 years because necessary studies were impossible or high impracticable due to the small number of patients in this age group that would require treatment with an extended-release or long-acting opioid analgesic. A postmarketing study requirement (PMR) under the Pediatric Research and Equity Act (PREA) was deferred for ages 7 through 16 years because the product was ready for approval in adults. The deferred pediatric study, PMR 1655-1, was entitled “a pharmacokinetic and safety study for the treatment of moderate-to-severe chronic pain requiring continuous, around-the-clock opioid treatment for an extended period of time in pediatric patients ages 7 through 16.” In this efficacy supplement, the Applicant submitted a pediatric study BUP3031 to fulfill PMR 1655-1.

The full extrapolation of efficacy from adequate and well-controlled studies in adults to the pediatric population may be considered a reasonable approach if there is evidence to support the following in both adult and pediatric populations: (a) similar disease progression (b) similar response of the disease to treatment, (c) similar exposure-response or concentration-response relationship and (d) measureable drug or active metabolite concentrations that are predictive of the clinical response. Additional pediatric pharmacokinetic studies to identify the appropriate dosage and pediatric safety studies may still be needed. For a chronic pain indication for drug classes with well characterized mechanisms of action, e.g., µ-opioid agonists, local anesthetics, NSAIDS etc., it has been determined that efficacy may be extrapolated down to 2 years of age while additional pharmacokinetic (PK) studies to characterize the appropriate dose as well as safety studies are required. On the contrary, for drugs with novel mechanisms of action or not well-established efficacy in adults, pediatric efficacy trials are required in addition to the safety and PK studies.

In principle, the key elements of a full extrapolation approach are (1) to identify the appropriate pediatric dosage or dosing regimen and (2) to establish safety at that dose. In general, dosage and administration in pain indications includes a starting dose that is followed by titration to a maintenance dose (with a maximum recommended dose) that provides adequate analgesia and has a reasonable safety profile. The appropriate “target” pediatric dosage or dosing regimen is defined as one which results in an exposure range or distribution that is comparable to that observed in adults. Prior to conducting a pediatric pharmacokinetic study to adequately

2 Pediatric analgesic clinical trial designs, measures, and extrapolation: report of an FDA scientific workshop. (Pediatrics.129(2):354-64, February 2012)
characterize the “target” dosage, modeling and simulation (M&S) may serve as a powerful tool to leverage available information including adult data and knowledge of the impact of age-related developmental and body size changes on PK in the pediatric population.

In response to their PREA requirements, the Applicant conducted Study BUP3031, an open-label, multicenter study to evaluate the safety, pharmacokinetics and efficacy of buprenorphine transdermal system (BTDS) for the treatment of moderate-to-severe chronic pain requiring continuous, around-the-clock opioid treatment for an extended period of time in pediatric patients in ages (inclusive) 7 through 16. A total of 41 patients received treatments with 6 patients in the younger age cohort of 7-11 years and 35 patients in the older age cohort of 12 -16 years. The treatment period was up to 24 weeks and PK blood samples were drawn at five time points: 18-24 hours after the application of the first BTDS patch, end of week 1, 2 to 3 days after the end of weeks 1, 2 and 3 or at discontinuation, if it happened prior to the last scheduled draw. All patients in the younger age cohort initiated treatment with BTDS 2.5 mcg/hr, while patients in the older age cohort initiated treatment with BTDS 5 mcg/hr. The dose of BTDS was adjusted upward or downward as needed throughout the study and the maximum allowed dose in the study was BTDS 20 mcg/hr. The adult starting dose in opioid-naïve patients is 5 mcg/hr and the maximum dose is 20 mcg/hr.

The final buprenorphine pediatric PK analysis dataset, which included 38 subjects (n = 3 with plasma buprenorphine concentrations that were not quantifiable) and a total of 151 plasma concentrations, was used to characterize the population PK of transdermal buprenorphine in pediatric patients. Owing to the sparsely sampled PK data, small sample size, and the complexity of the absorption process involved with the patch formulation, prior information from a previously developed adult population PK model was used for all of the parameters except for CL/F, which was estimated based on the pediatric PK data. Overall, the final population PK model provided an adequate description of the pediatric PK data and could be used to perform simulations to identify the “target” pediatric BTDS dose which matches the steady-state exposures in adults following the recommended starting dose of BTDS 5 mcg/hr. A summary of buprenorphine exposure in study BUP3031 in the younger age cohort (7 to 11 years) at a BTDS dose of 2.5 mcg/hr and the older cohort (12 to 16 years) at a BTDS dose of 5 mcg/hr is provided in Table 1. In general, observed buprenorphine concentrations in Study BUP3031 were within the range of concentrations previously observed in adults. Although age is often used as a cutoff, body weight was found to be the most important factor influencing buprenorphine pharmacokinetics following administration of BTDS in pediatric patients. Therefore, weight-based dosing recommendations could be derived to match pediatric exposure to adults.

The current Butrans label contains a table summarizing buprenorphine pharmacokinetics in a study of healthy adults and is reproduced in Table 2.
### Table 1 Exposures of Buprenorphine at Steady-state in Younger Age Cohort (7-11 Years) Receiving at A 2.5 mcg/hr Dose And Older Age Cohort (12-16 Years) at A 5 mcg/hr Dose

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<th>Age Cohort</th>
<th>Pediatric subjects 7-11 years (n=5) following BTDS 2.5 mcg/hr (Median (Range))</th>
<th>Pediatric subjects 12-16 years (n=33) following BTDS 5 mcg/hr (Median (Range))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine Steady State Exposures [AUCss (ng.h/ml)]</td>
<td>15.7 (12.3, 23.2)</td>
<td>18.9 (13.3, 30.3)</td>
</tr>
</tbody>
</table>

### Table 2 Pharmacokinetic Parameters of Butrans in Healthy Subjects, Mean (%CV)

<table>
<thead>
<tr>
<th>Single 7-day Application</th>
<th>AUC&lt;sub&gt;inf&lt;/sub&gt; (pg.h/mL)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUTRANS 5 mcg/hour</td>
<td>12087 (37)</td>
<td>176 (67)</td>
</tr>
<tr>
<td>BUTRANS 10 mcg/hour</td>
<td>27035 (29)</td>
<td>191 (34)</td>
</tr>
<tr>
<td>BUTRANS 20 mcg/hour</td>
<td>54294 (36)</td>
<td>471 (49)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multiple 7-day Applications</th>
<th>AUC&lt;sub&gt;tau,ss&lt;/sub&gt; (pg.h/mL)</th>
<th>C&lt;sub&gt;max,ss&lt;/sub&gt; (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUTRANS 10 mcg/hour, steady-state</td>
<td>27543 (33)</td>
<td>224 (35)</td>
</tr>
</tbody>
</table>
Guidance for Industry

How to Comply with the Pediatric Research Equity Act

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions on the content of the draft document contact Grace Carmouze, 301-594-7337 or Leonard Wilson, 301-827-0373.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
September 2005
Procedural
Guidance for Industry

How to Comply with the Pediatric Research Equity Act

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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September 2005
Procedural
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GUIDANCE FOR INDUSTRY\textsuperscript{1}

How to Comply with the Pediatric Research Equity Act

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This draft guidance provides recommendations on how to interpret the pediatric study requirements of the Pediatric Research Equity Act (Public Law 108-155) (PREA). PREA amends the Federal Food, Drug, and Cosmetic Act (the Act) by adding section 505B (21 U.S.C. 355B). PREA requires the conduct of pediatric studies for certain drug and biological products.\textsuperscript{2} Specifically, PREA requires new drug applications (NDAs) and biologics licensing applications (BLAs) (or supplements to applications) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment unless the applicant has obtained a waiver or deferral (see section 505B(a) of the Act). It also authorizes FDA to require holders of applications for previously approved marketed drugs and biological products who are not seeking approval for one of the changes enumerated above (hereinafter "marketed drugs and biological products") to submit a pediatric assessment under certain circumstances (see section 505B(b) of the Act).

\textsuperscript{1} This guidance has been prepared by the PREA Working Group at the Food and Drug Administration (FDA).

\textsuperscript{2} For purposes of this guidance, references to "drugs" and "drug and biological products" includes drugs approved under section 303 of the Act (21 U.S.C. 355) and biological products licensed under 351 of the Public Health Service Act (PHSA) (42 U.S.C. 262) that are drugs.

Paperwork Reduction Act Public Burden Statement: According to the Paperwork Reduction Act of 1995, a collection of information should display a valid OMB control number. The draft guidance contains information collections approved as OMB Nos. 0910-0001 (expires May 31, 2008) and 1910-0433 (expires March 31, 2007). In addition, the time required to complete this information collection is estimated to average from 8 to 50 hours per response, including the time to prepare and submit an application containing required studies or request a waiver from such studies.
Although PREA applies to both new applications (or supplements to applications) and already marketed drugs and biological products, this guidance will only provide recommendations on NDAs and BLAs (or supplements to an already approved application) for drugs and biological products under section 505B(a) of the Act. Issues under section 505B(b) of the Act related to already marketed drug and biological products for which the sponsor is not seeking one of the enumerated changes may be addressed in future guidance.

This guidance addresses the pediatric assessment, the pediatric plan (see section V.A), waivers and deferrals, compliance issues, and pediatric exclusivity provisions.

FDA’s guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

On December 3, 2003, the Pediatric Research Equity Act (PREA) was signed into law. PREA is the most recent of more than a decade of legislative and regulatory attempts to address the lack of pediatric use information in drug product labeling. In PREA, Congress codified many of the elements of the Pediatric Rule, a final rule issued by FDA on December 2, 1998 (63 FR 66632), and suspended by court order on October 17, 2002.

Under the Pediatric Rule, approval actions taken or applications submitted on or after April 1, 1999, for changes in active ingredient, indication, dosage form, dosing regimen, or route of administration were required to include pediatric assessments for indications for which sponsors were receiving or seeking approval in adults, unless the requirement was waived or deferred. The Pediatric Rule was designed to work in conjunction with the pediatric exclusivity provisions of section 505A of the Act (21 U.S.C. 355a), an incentive signed into law to encourage sponsors or holders of approved applications to voluntarily perform the pediatric studies described in a Written Request issued by FDA, in order to qualify for an additional 6 months of marketing exclusivity.

1 For purposes of this guidance, the term "pediatric assessment" describes the required submissions under PREA that contain data, primarily from required pediatric clinical studies, that are adequate to assess safety and effectiveness and support dosing and administration for claimed indications in all relevant pediatric populations (section 505B(a)(1) and (2) of the Act). Generally, the terms "pediatric assessment" and "pediatric studies" are used interchangeably.

2 The Pediatric Rule was codified at 21 CFR 314.55 and 601.27, with additional amendments to 21 CFR 201, 312, 314, and 601.

5 FDA issues Written Requests for pediatric studies under 21 U.S.C. 355a.
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On January 4, 2002, the Best Pharmaceuticals for Children Act (BPCA) (Public Law 107-109) was enacted. The BPCA reauthorized and amended the pediatric exclusivity incentive program of section 505A and created new mechanisms for funding pediatric studies that sponsors or holders of approved applications declined to conduct voluntarily. On April 24, 2002, FDA issued an advance notice of proposed rulemaking (ANPRM) soliciting comments on the most appropriate ways to update the Pediatric Rule in a manner consistent with other mechanisms for obtaining studies created by the BPCA.

On October 17, 2002, the U.S. District Court for the District of Columbia held that FDA had exceeded its statutory authority when issuing the Pediatric Rule and the court suspended its implementation and enjoined its enforcement (Association of Am. Physicians & Surgeons, Inc. v. FDA, 226 F. Supp. 2d 204 (D. D.C. 2002)). When the Court enjoined FDA from enforcing the Pediatric Rule in October 2002, the ANPRM was also rendered obsolete.

As noted above, PREA codified elements of the suspended Pediatric Rule and attempted to fill gaps left by the Pediatric Rule’s suspension.

III. OVERVIEW — REQUIREMENTS OF PREA

A. PREA Statutory Requirements

PREA requires all applications (or supplements to an application) submitted under section 505 of the Act (21 U.S.C. 355) or section 351 of the Public Health Service Act (PHSA) (42 U.S.C. 262) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment unless the applicant has obtained a waiver or deferral (section 505B(a) of the Act). It also authorizes FDA to require holders of approved NDAs and BLAs for marketed drugs and biological products to conduct pediatric studies under certain circumstances (section 505B(b) of the Act).

In general, PREA applies only to those drugs and biological products developed for diseases and/or conditions that occur in both the adult and pediatric populations. Products intended for pediatric-specific indications will be subject to the requirements of PREA only if they are initially developed for a subset of the relevant pediatric population.

B. Scope of Requirements

1. Applications Affected by PREA

Because section 4(b) of PREA makes the legislation retroactive, all approved applications for new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration submitted on or after April 1, 1999 (including those approved when the Pediatric Rule was suspended), are subject to PREA. Under PREA, holders of such approved applications that did not previously include pediatric assessments, waivers, or deferrals must submit their pediatric assessments or requests for waiver or deferral (section 4(b)(2)(B) of
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PREA states, "Unless the Secretary requires otherwise by regulation, this section does not apply to any drug for an indication for which orphan designation has been granted under section 526." FDA has not issued regulations applying PREA to orphan-designated indications. Thus, submission of a pediatric assessment is not required for an application to market a product for an orphan-designated indication, and waivers are not needed at this time. However, if only one indication for a product has orphan designation, a pediatric assessment may still be required for any applications to market that same product for the non-orphan indication(s).


Because PREA applies only to applications (or supplements to applications) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, and because an abbreviated new drug application (ANDA) submitted under section 505(j) of the Act for a duplicate version of a previously approved drug product does not involve such changes, PREA does not impose pediatric assessment requirements on ANDAs for generic drugs. However, ANDAs submitted under an approved suitability petition under section 505(j)(2)(C) of the Act for changes in dosage form, route of administration, or new active ingredient in combination products are subject to the pediatric assessment requirements that PREA imposes. If clinical studies are required under PREA for a product submitted under an approved suitability petition and a waiver is not granted, that application is no longer eligible for approval under an ANDA.

Because PREA is retroactive, all approved and pending ANDAs submitted on or after April 1, 1999 (when the Pediatric Rule became effective) and prior to December 3, 2003 (when PREA was enacted) under suitability petitions for changes in dosage form, route of administration, or active ingredient in combination products are subject to PREA. Although some ANDAs submitted under suitability petitions after April 1, 1999, and prior to December 3, 2003, would not have been approved as ANDAs had PREA been in effect at the time of approval, PREA’s retroactivity does not require FDA to revoke those previous approvals. Instead, as with NDAs and BLAs, holders of approved and pending ANDAs submitted under suitability petitions between April 1, 1999 and December 3, 2003, who have not already obtained waivers, must submit postapproval pediatric studies or a request for a waiver or deferral of the pediatric assessment requirement (section 505B(a)(2) of the Act). If a waiver request is denied for a product already submitted or approved in an ANDA based upon a suitability petition during this time frame, FDA will require the applicable studies as postmarketing studies.

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6 Section 526 is codified at 21 U.S.C. 360bb.
IV. THE PEDIATRIC ASSESSMENT

A. What Is the Pediatric Assessment? (Section 505B(a)(2) of the Act)

Under PREA, the pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required, and other data that are adequate to:

- Assess the safety and effectiveness of the drug or the biological product for the claimed indications in all relevant pediatric subpopulations
- Support dosing and administration for each pediatric subpopulation for which the drug or the biological product has been assessed to be safe and effective

B. When to Submit the Pediatric Assessment in Compliance with PREA

Under PREA, a pediatric assessment must be submitted at the time an application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration is submitted to the Agency, unless the requirement for the assessment has been deferred or waived. If a deferral has been granted, the pediatric assessment will be due on or before the date specified by the Agency (section 505B(a)(3) of the Act).

As noted above, PREA is retroactive and requires pediatric assessments for all applications submitted between April 1, 1999, and the present. To address potential gaps in pediatric information for applications approved between April 1, 1999, and the present resulting from, among other things, the suspension of the Pediatric Rule in October 2002, PREA provides for waivers or deferrals in cases where pediatric study requirements were never addressed and for extensions of certain deferrals issued previously under the Pediatric Rule (see Attachment C for a chart of deferral dates under PREA).

If an application previously was granted a waiver of pediatric studies under the Pediatric Rule, the waiver will continue to apply under PREA (section 4(b)(2)(A) of PREA).

C. What Types of Data Are Submitted as Part of the Pediatric Assessment?

The data submitted under PREA will depend on the nature of the application, what is known about the product in pediatric populations, and the underlying disease or condition being treated. PREA does not require applicants to conduct separate safety and effectiveness studies in pediatric patients in every case. PREA states:

If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretary 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.

(Section 505B(a)(2)(B)(i) of the Act.)

If extrapolation from adult effectiveness data is inappropriate, adequate and well-controlled efficacy studies in the pediatric population may nevertheless be required. Additional information, such as dosing and safety data, could also be important to support pediatric labeling decisions.

PREA further provides, "A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group" (section 505B(a)(2)(B)(ii) of the Act). Whether or not pediatric studies in more than one age group are necessary depends on expected therapeutic benefit and use in each age group, and on whether safety and effectiveness data from one age group can be extrapolated to other age groups. As with the use of adult data, the extrapolation may be supplemented with data to define dosing and safety for the relevant age groups.

Applicants should contact the appropriate review division to discuss the types of pediatric studies needed to complete their pediatric assessments.

V. THE PEDIATRIC PLAN AND SUBMISSIONS

A. When to Develop a Pediatric Plan

A Pediatric Plan is a statement of intent that outlines the pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that the applicant plans to conduct. The plan should also address the development of an age-appropriate formulation. Furthermore, it should address whether and, if so, under what grounds, the applicant plans to request a waiver or deferral under PREA. Applicants are encouraged to submit their pediatric plans to the Agency as early as possible in the drug development process and to discuss these plans with the Agency at critical points in the development process for a particular drug or biologic.

Early consultation and discussions are particularly important for products intended for life-threatening or severely debilitating illnesses. For these products, FDA encourages applicants to discuss the pediatric plan at pre-investigational new drug (pre-IND) meetings and end-of-phase 1 meetings. For products for life-threatening diseases, the review division will provide its best judgment at the end-of-phase 1 meetings on whether pediatric studies will be required under PREA and, if so, whether the submission will be deferred until after approval. In general, studies of drugs or biological products for diseases that are life-threatening or severely debilitating in pediatric patients and that lack adequate therapy could begin earlier than studies of other products because the urgency of the need for the products may justify early trials despite the relative lack of safety and effectiveness information.
Contains Nonbinding Recommendations

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For products that are not intended for treatment of life-threatening or severely debilitating illnesses, applicants are encouraged to submit and discuss the pediatric plan no later than the end-of-phase 2 meeting. Information to support any planned request for a waiver or deferral of pediatric studies also should be submitted as part of the background package for this meeting. The review division will provide its best judgment about (1) the pediatric assessment that will be required for the product, (2) whether its submission can be deferred, and (3) if deferred, the date studies will be due. In addition, if relevant, FDA encourages applicants to include a discussion of their intent to qualify for and the studies needed to earn pediatric exclusivity (see section VIII for a discussion of PREA and pediatric exclusivity).

When a decision to waive or defer pediatric studies is made at key meetings, the minutes from those meetings reflecting the decision generally will be provided to applicants for their records. Alternatively, a separate letter may be sent to the applicant conveying FDA’s decision to either waive or defer the pediatric assessment. If a deferral of studies is granted at the time of the meeting, a due date for submission generally will also be included in the meeting minutes or separate letter.

B. What Ages to Cover in a Pediatric Plan

PREA requires, unless waived or deferred, the submission of a pediatric assessment for certain applications for the claimed indications in all relevant pediatric populations. As discussed in section VI, PREA authorized FDA to waive assessments when: 1) the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and 2) is not likely to be used in a substantial number of pediatric patients (section 505B(a)(4)(A)(iii) of the Act). Thus, PREA requires the pediatric assessment to evaluate safety and effectiveness for the claimed indication(s) for each age group in which the drug or biological product is expected to provide a meaningful therapeutic benefit over existing therapies for pediatric patients or is likely to be used in a substantial number of pediatric patients.

Under PREA, a drug or biological product is considered to represent a meaningful therapeutic benefit over existing therapies if FDA estimates that (1) “if approved, the drug or biological product would represent a significant improvement in the treatment, diagnosis, or prevention of a disease, compared with marketed products adequately labeled for that use in the relevant pediatric population,” or (2) “the drug or biological product is in a class of products or for an indication for which there is a need for additional options” (section 505B(c) of the Act). Improvement over marketed products might be demonstrated by showing (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) enhancement of compliance; or

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7 PREA does not define a “substantial number.” In the past, FDA generally has considered 50,000 patients to be a substantial number of patients (see, for example, October 27, 1997, DHHS Public Meeting on FDA’s Proposed Regulations to Increase Pediatric Use Information for Drugs and Biologics). The Agency, however, will take into consideration the nature and severity of the condition in determining whether a drug or biological product will be used in a substantial number of pediatric patients.
(4) safety and effectiveness in a new subpopulation for which marketed products are not currently labeled.

The BPCA defines "pediatric studies" or "studies" to include studies in all "pediatric age groups (including neonates in appropriate cases)" in which a drug is anticipated to be used (section 505A(a) of the Act). For purposes of satisfying the requirements of PREA, the appropriate age ranges to be studied may vary, depending on the pharmacology of the drug or biological product, the manifestations of the disease in various age groups, and the ability to measure the response to therapy. In general, however, the pediatric population includes patients age "birth to 16 years, including age groups often called neonates, infants, children, and adolescents" (21 CFR 201.57(f)(9)).

The complex medical state of neonates and infants makes it critical to evaluate drugs specifically for their use. The Agency is also aware that trials in neonates and infants pose special ethical issues. FDA generally will require studies in neonates and infants under PREA if the drug represents an important advancement and use in these age groups for the approved indication is anticipated. However, it is possible that partial waivers for these specific age groups might be appropriate under certain circumstances when "necessary studies are impossible or highly impracticable," or when "there is evidence strongly suggesting that the drug or biologic product would be ineffective or unsafe in that age group" (section 505B(a)(4)(B)(i) and (ii) of the Act).

C. Must the Sponsor Develop a Pediatric Formulation?

PREA requires pediatric assessments to be gathered "using appropriate formulations for each age group for which the assessment is required" (section 505B(a)(2)(A) of the Act). Under PREA, applicants must submit requests for approval of the pediatric formulation used in their pediatric studies, and failure to submit such a request may render the product misbranded (section 505B(d) of the Act). FDA interprets the language "request for approval of a pediatric formulation" to mean that applicants must submit an application or supplemental application for any not previously approved formulation(s) used to conduct their pediatric studies. Where appropriate, applicants may need to begin the development of a pediatric formulation before initiation of pediatric clinical trials.

PREA does, however, specifically authorize FDA to waive the requirement for pediatric studies in one or more age groups requiring a pediatric formulation if the applicant certifies and FDA finds that "the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed" (section 505B(a)(4)(B)(iv) of the Act). This exception is limited to the pediatric groups requiring that formulation (section 505B(a)(4)(C)). FDA believes that this partial waiver provision will generally apply to situations where the applicant can demonstrate that unusually difficult technological problems prevented the development of a pediatric formulation. In certain cases, the Agency may seek appropriate external expert opinion (e.g., from an advisory committee) to assess whether a waiver should be granted (see section VI.A and B for more detailed information on waivers).
D. When to Initiate Pediatric Studies

As discussed in section V.A, applicants may initiate pediatric studies of drugs and biologics for life-threatening diseases for which adequate treatment is not available earlier in development than might occur for less serious diseases. The medical need for these products may justify early pediatric trials despite a relative lack of safety and effectiveness data. In some cases, pediatric studies of a drug or biological product for a life-threatening disease may begin as early as phase 1 or phase 2, when the initial safety data in adults becomes available.

The Agency recognizes that in certain cases scientific and ethical considerations will dictate that pediatric studies should not begin until after approval of the drug or biological product for use by adults — for example, where a product has not shown any benefit over other adequately labeled products in the class, the therapeutic benefit is likely to be low, or the risks of exposing pediatric patients to the new product may not be justified until after the product’s safety profile is well established in adults after initial marketing.

The Agency recommends that for products with a narrow therapeutic index, the nature of the disease in the pediatric population to be studied and the context in which the drug will be used should factor into the decision on when to initiate the studies in the affected pediatric patient population. For example, studies for an oncology drug product with a narrow therapeutic index might be conducted in children with a life-threatening cancer at an earlier stage in the drug development process than studies for a new aminoglycoside antimicrobial used to treat acute pyelonephritis infections in children. In the latter case, there are several therapeutic options available, so the investigational drug would likely be studied in children after the approval in adults for this condition.

E. What Information Must Be Submitted to FDA

Pediatric studies of drugs conducted under an investigational new drug application (IND) are subject to the rules governing INDs, including the content and format requirements of 21 CFR 312.23 and the IND safety and annual reporting requirements described in 21 CFR 312.32 and 312.33, respectively.

- When study reports are submitted as part of an application or supplement to an application, the content and format must meet the relevant general requirements for submission (see 21 CFR 314.50 for NDA requirements and 21 CFR 601.2 for BLA requirements).

VI. WAIVERS AND DEFERRALS

A. What Is a Waiver?

PREA authorizes FDA to waive the requirement to submit the pediatric assessment, based on established criteria, for some or all pediatric age groups. FDA can grant a full or partial waiver of the requirements on its own initiative or at the request of an applicant. If an applicant requests
a waiver, the applicant should provide written justification for the waiver and evidence to support the request.

B. How to Apply for a Waiver

1. Criteria for Full Waiver (Section 505B(a)(4)(A) of the Act)

On FDA’s initiative or at the request of an applicant, FDA will grant a full waiver of the requirement to submit pediatric assessments if the applicant certifies and FDA finds one or more of the following:

(a) Necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed) (section 505B(a)(4)(A)(i) of the Act).

Another example is a drug or biological product for an indication that has extremely limited applicability to pediatric patients because the pathophysiology of these diseases occur for the most part in the adult population. FDA would be likely to grant a waiver for studies on products developed for the treatment of these conditions without requiring applicants to provide additional evidence of impossibility or impracticability. For a list of adult-related conditions that may be candidates for a disease-specific waiver, see Attachment A, Sample Waiver Request Form.

(b) There is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups (section 505B(a)(4)(A)(ii) of the Act).

If a waiver is granted based upon evidence that the drug is unsafe or ineffective in pediatric populations, the applicant must include this information in the labeling for the drug or biological product (section 505B(a)(4)(D) of the Act).

(c) The drug or biological product (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and (2) is not likely to be used in a substantial number of pediatric patients (section 505B(a)(4)(A)(iii) of the Act).

2. Criteria for Partial Waiver (Section 505B(a)(4)(B) of the Act)

On its own initiative or at the request of an applicant, FDA will grant a partial waiver of the requirement to submit pediatric assessments for a drug or biological product with respect to a specific pediatric age group, if the applicant certifies and FDA finds evidence of one or more of the following:

(a) Necessary studies are impossible or highly impracticable (because, for example, the number of patients in that age group is so small or patients in that age group are geographically dispersed) (section 505B(a)(4)(B)(i) of the Act).
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(b) There is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in that age group (section 505B(a)(4)(B)(ii) of the Act). If a partial waiver is granted based on evidence that the drug is unsafe or ineffective in pediatric populations, the applicant must include this information in the labeling for the drug or biological product (section 505B(a)(4)(D) of the Act).

(c) The drug or biological product (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group and (2) is not likely to be used by a substantial number of pediatric patients in that age group (section 505B(a)(4)(B)(iii) of the Act).

(d) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed (section 505B(a)(4)(B)(iv) of the Act). If a waiver is granted on the basis that it is not possible to develop a pediatric formulation, the waiver shall cover only the pediatric groups requiring that formulation (section 505B(a)(4)(C) of the Act).

3. Information in a Waiver Request

As noted in section V, discussions with FDA on developing pediatric plans and initiating pediatric studies should occur early in the drug development process. If an applicant believes a full or partial waiver of the pediatric studies requirement is warranted, FDA strongly encourages the applicant to request the waiver at the earliest appropriate time. This guidance includes a sample Waiver Request to assist applicants in providing sufficient information for FDA to determine whether to grant a waiver request (Attachment A). However, the information necessary to support any particular waiver will be determined on a case-by-case basis.

To request a waiver, we recommend an applicant provide:

- Product name, applicant name, and indication
- Age group(s) included in waiver request
- Statutory reason(s) for requesting a waiver, including reference to the applicable statutory authority (i.e., one of 2(a)-(d) in Attachment A)
- Evidence that the request meets the statutory reason(s) for waiver of pediatric assessment requirements
- Applicant Certification

4. Waiver Decision

The Agency will grant a waiver request if FDA determines that any of the criteria for a waiver enumerated in the statute have been met. As noted above, if a full or partial waiver is granted "because there is evidence that a drug or biological product would be ineffective or unsafe in
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pediatric populations, this information shall be included in the labeling for the drug or biological product" (section 505B(a)(4)(D) of the Act).

As discussed in section V, for waivers agreed to at the end-of-phase 2 meetings, the meeting minutes will document the waiver of pediatric assessment requirements. Full or partial waiver documentation (meeting minutes or a letter from FDA) should be submitted in the Clinical Data Section of the NDA or BLA and noted in Form FDA-356h under the "Pediatric Use" part of item 8, and also under item 20, "Other." Under "Other," the applicant should identify the location (volume and page number) of the waiver documentation in the NDA or BLA submission.

Decisions to waive the requirement for submission of pediatric assessments that are made early in the pre-approval development period (e.g., end-of-phase 1 or end-of-phase 2 meetings) reflect the Agency’s best judgment at that time. If, prior to approval, the Agency becomes aware of new or additional scientific information that affects the criteria on which the waiver decision was based, the Agency may reconsider its earlier decision. A waiver decision becomes final once issued in the approval letter for an NDA, BLA, or supplement.

C. What Is a Deferral?

A deferral acknowledges that a pediatric assessment is required, but permits the applicant to submit the pediatric assessment after the submission of an NDA, BLA, or supplemental NDA or BLA. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all of the pediatric studies until a specified date after approval of the drug or issuance of the license for a biological product for adult use (section 505B(a)(3) of the Act).

D. How to Apply for a Deferral

1. Criteria for Deferral (Section 505B(a)(3) of the Act)

FDA may defer the timing of submission of some or all required pediatric studies if it finds one or more of the following:

- The drug or biological product is ready for approval for use in adults before pediatric studies are complete (section 505B(a)(3)(A)(i) of the Act).

- Pediatric studies should be delayed until additional safety or effectiveness data have been collected (section 505B(a)(3)(A)(ii) of the Act).

OR

- There is another appropriate reason for deferral (section 505B(a)(3)(A)(iii) of the Act) (e.g., development of a pediatric formulation is not complete).
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In addition, to obtain a deferral the applicant must submit certification of the reason(s) for deferring the assessments, a description of the planned or ongoing studies, and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time (section 505B(a)(3)(B)(i)-(iii) of the Act).

2. Information in a Deferral Request

FDA has provided a sample Deferral Request checklist to assist applicants in providing sufficient information for FDA to determine whether to grant a deferral request (Attachment B). To request a deferral, we recommend an applicant provide:

- Product name, applicant name, and indication
- Age group(s) included in deferral request
- Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request (e.g., studies have already been completed in other age groups and need not be deferred)
- Reason(s) for requesting a deferral
- Evidence justifying that the proposed product meets the criteria for deferral of the pediatric assessment requirement
- Description of planned or ongoing studies
- Evidence that planned or ongoing studies are proceeding
- Projected date for the submission of the pediatric assessment (deferral date)
- Applicant certification

3. Deferral Decision

The decision to defer and the deferral date will be determined on a case-by-case basis. Considerations used in determining whether and how long to defer submission of the pediatric assessment may include:

- The need for the drug or biologic in pediatric patients
- Availability of sufficient safety data to initiate pediatric trials
- The nature and extent of pediatric data needed to support pediatric labeling
- The existence of substantiated difficulties in enrolling patients
- Evidence of technical problems in developing pediatric formulations

As discussed in section V.A, the meeting minutes or a separate letter will document the deferral of pediatric assessments agreed to at the end-of-phase 2 meetings. For a deferral granted during the pre-approval development period, it is possible that FDA may reevaluate the length of the deferral closer to the time of approval, taking into account any new information obtained while the product was in development and information reviewed in the NDA or BLA. The pediatric assessments deferred under PREA are required postmarketing studies subject to the annual status
reporting and information disclosure provisions of 21 CFR 314.81(b)(2)(vii)(a) and (b) and 21 CFR 601.70.

VII. COMPLIANCE WITH PREA

If a pediatric assessment or a request for approval of a pediatric formulation is not submitted by an applicant in accordance with the statutory requirements, the drug or biological product may be considered misbranded solely because of that failure and subject to relevant enforcement action (section 505B(d)(1) of the Act). The failure to submit a pediatric assessment or request for waiver or deferral will not be the basis for withdrawing approval of a drug under section 505(e) of the Act or the revocation of a license for a biological product under section 351 of the PHSA (section 505B(d)(2) of the Act). However, the Agency could bring injunction or seizure proceedings if a product is found to be misbranded under these provisions.  

VIII. PREA AND PEDIATRIC EXCLUSIVITY

It is the Agency’s policy to offer applicants the opportunity to qualify for pediatric exclusivity under section 505A of the Act for studies required and conducted under PREA. Under that policy, however, FDA will not issue a Written Request for or grant pediatric exclusivity for studies that have been submitted to the Agency before the Written Request is issued. Therefore, an applicant seeking to qualify for pediatric exclusivity should obtain a Written Request for studies from FDA before submitting the pediatric studies to satisfy PREA. (Note that for marketed drugs and biological products, the Agency is required to issue a Written Request prior to requiring studies under PREA (section 505B(b)(3) of the Act)). To qualify for pediatric exclusivity, the pediatric studies conducted to satisfy the requirements of PREA must also satisfy all of the requirements for pediatric exclusivity under section 505A of the Act (see sections 505A(d) and 505A(h) of the Act).

In addition, there is a noteworthy distinction between the scope of the studies requested under the pediatric exclusivity provisions and what is required under PREA. For pediatric exclusivity under the Act, FDA’s authority to issue a Written Request extends to the use of an active moiety for all indications that occur in the pediatric population, regardless of whether the indications have been previously approved in adults or approval for those indications is being sought in adults (see section 505A(a), which refers only to "information relating to the use of a new drug in the pediatric population"). Under PREA, on the other hand, a pediatric assessment is required only on those indications included in the pending application (section 505B(a), which addresses "the safety and effectiveness of the drug or biological product for the claimed indications"). To learn more about eligibility for pediatric exclusivity, applicants should consult the guidance for industry entitled Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act or should contact the relevant review division.

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IX. ADDITIONAL INFORMATION

A. Additional Information Concerning PREA

General information about complying with PREA can be obtained from the Division of Pediatric Drug Development (DPDD), 301-594-7337 or 301-827-7777, e-mail pdit@cdr.fda.gov. Additional pediatric information is available at http://www.fda.gov/cder/pediatric.

Specific information about the types of pediatric studies that must be conducted and requirements for submission of assessments for your drug product can be obtained from the appropriate review division.

B. Additional Information Concerning Pediatric Exclusivity

General information and the latest statistical information regarding pediatric exclusivity are located at http://www.fda.gov/cder/pediatric. You can also refer to the guidance for industry on Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act.
ATTACHMENT A — SAMPLE WAIVER REQUEST

1. Identify pediatric age group(s) included in your waiver request.

2. With regard to each age group for which a waiver is sought, state the reason(s) for waiving pediatric assessment requirements with reference to applicable statutory authority (i.e., one of the options (a)-(d) listed below — choose all that apply):
   (a) Studies are impossible or highly impractical (because, for example, the number of pediatric patients is so small or geographically dispersed). If applicable, please check from the following list of adult-related conditions that may qualify the drug product for disease-specific waivers:

   - Age-related macular degeneration
   - Alzheimer’s disease
   - Amyotrophic lateral sclerosis
   - Arteriosclerosis
   - Infertility
   - Menopause symptoms
   - Osteoarthritis
   - Parkinson’s disease
   - Other (please state and justify)

   - Basal cell and squamous cell cancer
   - Breast cancer
   - Colorectal cancer
   - Endometrial cancer
   - Hairy cell cancer
   - Lung cancer (small cell and non-small cell)
   - Oropharynx cancers (squamous cell)
   - Ovarian cancer (non-germ cell)
   - Pancreatic cancer
   - Prostate cancer
   - Renal cell cancer
   - Uterine cancer

   (b) The product would be ineffective or unsafe in one or more of the pediatric age group(s) for which a waiver is being requested.

   (c) The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

   (d) Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. Please document previous attempts to make a pediatric formulation and describe reasons for failure.

3. Provide evidence that the statutory reason(s) for waiver of pediatric studies have been met (not necessary if a 2(a) category is checked).

4. Applicant certification.
Attachment B — Sample Deferral Request

Product name:
IND/NDA/BLA number (as applicable):
Applicant:
Indications(s):

(NOTE: If drug is approved for or you are seeking approval for more than one indication, address the following for each indication.)

1. What pediatric age group(s) are included in your deferral request?

2. Reason(s) for requesting deferral of pediatric studies (address each age group separately and for each age group — choose all that apply):
   (a) Adult studies completed and ready for approval
   (b) Additional postmarketing safety data needed (describe)
   (c) Nature and extent of pediatric data needed (explain)
   (d) Evidence provided of technological problems with development of a pediatric formulation
   (e) Difficulty in enrolling pediatric patients (provide documentation)
   (f) Other (specify)

3. What pediatric age group(s) is/are not included in your deferral request?

4. Reason(s) for not including the pediatric age group(s) listed in number 3 in the deferral request (address each excluded age group separately and for each such age group — choose all that apply):
   (a) Adequate pediatric labeling exists
   (b) Studies completed in the specified age group
   (c) Requesting a waiver
   (d) Currently conducting pediatric studies that will be submitted with application
   (e) Other (specify)

5. Has a pediatric plan been submitted to the Agency?
   • If so, provide date submitted.
   • If not, provide projected date pediatric plan is to be submitted.

6. Suggested deferred date for submission of studies.
ATTACHMENT C — COMPLIANCE DATES FOR APPLICATIONS SUBJECT TO PREA

<table>
<thead>
<tr>
<th>Categories of Application</th>
<th>Expected Date of Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application or supplement submitted between 4/1/99 and 12/3/03, no waiver or deferral was granted and no studies were submitted</td>
<td>Immediate unless FDA specifies later date</td>
</tr>
<tr>
<td>Application or supplement submitted between 4/1/99 and 10/17/02, studies were deferred to a date after 4/1/99, but no studies were submitted</td>
<td>Deferral date + 411 days</td>
</tr>
<tr>
<td>Application or supplement submitted between 10/17/02 and 12/3/03 and approved after 12/3/03, studies were deferred</td>
<td>Immediate unless later date is specified in deferral letter</td>
</tr>
<tr>
<td>Applications submitted after 12/3/03, studies were deferred</td>
<td>Date specified in deferral letter</td>
</tr>
</tbody>
</table>

The dates in the chart are relevant as follows:

- **4/1/99**: The date the Pediatric Rule became effective
- **10/17/02**: The date that implementation and enforcement of the Pediatric Rule was suspended by court order
- **12/3/03**: The date that PREA was enacted
General Clinical Pharmacology
Considerations for Pediatric Studies for Drugs and Biological Products
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document, contact (CDER) Gilbert J. Burckart at 301-796-2065.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2014
Clinical Pharmacology
General Clinical Pharmacology
Considerations for Pediatric Studies for Drugs and Biological Products
Guidance for Industry

Additional copies are available from:
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Email: druginfo@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2014
Clinical Pharmacology
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General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products

Guidance for Industry

This draft guidance, when finalized, will represent the Food and Drug Administration’s (FDA’s) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This draft guidance is intended to assist those sponsors of new drug applications (NDAs), biologics license applications (BLAs) for therapeutic biologics, and supplements to such applications who are planning to conduct clinical studies in pediatric populations. Effectiveness, safety, or dose-finding studies in pediatric patients involve gathering clinical pharmacology information, such as information regarding a product’s pharmacokinetics and pharmacodynamics pertaining to dose selection and individualization. This guidance addresses general clinical pharmacology considerations for conducting studies so that the dosing and safety information for drugs and biologic products in pediatric populations can be sufficiently characterized, leading to well-designed trials to evaluate effectiveness.¹

In general, this draft guidance focuses on the clinical pharmacology information (e.g., exposure-response, pharmacokinetics, and pharmacodynamics) that supports findings of effectiveness and safety and helps identify appropriate doses in pediatric populations. This guidance also describes the use of quantitative approaches (i.e., pharmacometrics) to employ disease and exposure-response knowledge from relevant prior clinical studies to design and evaluate future pediatric studies. The guidance does not describe: (1) standards for approval of drug and biological products in the pediatric population, (2) criteria to allow a determination that the course of a disease and the effects of a drug or a biologic are the same in adults and pediatric populations, or (3) clinical pharmacology studies for vaccine therapy, blood products, or other products not

¹ This draft guidance has been prepared by the Pediatric Working Group of the Office of Clinical Pharmacology in conjunction with the Pediatric Subcommittee of the Medical Policy Coordinating Committee (MPCC) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.
² For purposes of this guidance, references to “drugs” and “drug and biological products” includes drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act or Act) (21 U.S.C. 355) and biological products licensed under 351 of the Public Health Service Act (PHSA) (42 U.S.C. 262) that are drugs.
regulated by the Center for Drug Evaluation and Research.

FDA’s guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

During the past two decades, the Food and Drug Administration (FDA) has worked to address the problem of inadequate pediatric testing and inadequate pediatric use information in drug and biological product labeling. The Food and Drug Administration Modernization Act of 1997 (the Modernization Act) addressed the need for improved information about drug use in the pediatric population by establishing incentives for conducting pediatric studies on drugs for which exclusivity or patent protection exists. Congress subsequently passed the Best Pharmaceuticals for Children Act (BPCA) in 2002 and the Pediatric Research Equity Act (PREA) in 2003. Both BCPA and PREA were reauthorized in 2007. In 2012, BPCA and PREA were made permanent under Title V of the Food and Drug Administration Safety and Innovation Act (FDASIA).

Under BPCA, sponsors of certain applications and supplements filed under section 505 of the FD&C Act and under section 351 of the Public Health Service Act can obtain an additional six months of exclusivity if, in accordance with the requirements of the statute, the sponsor submits information responding to a Written Request from the Secretary relating to the use of a drug in the pediatric population. Under PREA, sponsors of certain applications and supplements filed under section 505 of the FD&C Act or section 351 of the Public Health Service Act are required to submit pediatric assessments, unless they receive an applicable waiver or deferral of this requirement. If applicable, sponsors must submit a request for a deferral or waiver as part of an initial pediatric study plan (section 505B(e) of the FD&C Act) (see section V of this guidance).

The FD&C Act requires a description of pediatric study data in labeling arising from study data

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3 Public Law No. 105-115, 111 Stat. 2296 (Nov. 21, 1997).
7 Public Law No. 112-144, 126 Stat. 993 (July 9, 2012).
submitted in response to a Written Request under BPCA and/or data from studies required under
PREA, whether the findings are positive, negative, or inconclusive. The PREA requirements
are triggered by the submission of an application or supplement for a drug for a new active
ingredient, new indication, new dosage form, new dosing regimen, or new route of
administration under Section 505 of the FD&C Act or Section 351 of the PHS Act. If a full or
partial waiver is granted under PREA because there is evidence that the drug would be
ineffective or unsafe in pediatric populations, the information must be included in the product’s
labeling.

This guidance deals with the clinical pharmacology considerations of any planned pediatric
study, whether or not it is conducted pursuant to BPCA or PREA.

III. CLINICAL PHARMACOLOGY CONSIDERATIONS

There are several recognized approaches to providing substantial evidence to support the safe
and effective use of drugs in pediatric populations, including (1) evidence from adequate and
well-controlled investigations of a specific pediatric indication different from the indication(s)
approved for adults; (2) evidence from adequate and well-controlled investigations in pediatric
populations to support the same indication(s) approved for adults; or (3) evidence from adequate
and well-controlled studies in adults and additional information in the specific pediatric
population. The first approach generally requires a full pediatric development program. The
second approach above generally involves the use of prior disease and exposure-response
knowledge from studies in adults and relevant pediatric information to design and, in some cases,
analyze new pediatric studies. For the third approach, the assumption is that the course of the
disease and the effects of the drug are sufficiently similar in the pediatric and adult populations
to permit extrapolation of the adult efficacy data to pediatric patients (Dunne, Rodriguez et al.
2011). If the third approach is taken, there would ordinarily be a pediatric study to determine a
dose in the pediatric population that provides a drug exposure similar to the exposure that is
effective in adults. If there is a concern that exposure-response relationships might be different
in pediatric patients, studies relating blood levels of drug to pertinent pharmacodynamic effects
other than the desired clinical outcome (exposure-response data for both desired and undesired
effects) for the drug in the pediatric population might also be important. For all three

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13 See Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological
approaches, the extent of the required pediatric safety studies may take into consideration prior experience with similar drugs in pediatric populations, the seriousness of the adverse events in adults or in pediatric populations, when this information is available, and the feasibility of conducting studies in pediatric patients.

Clinical pharmacology studies in the pediatric population should be conducted in patients receiving therapy for a particular indication, or in rare instances, in those who are at risk for the condition of interest. The identification of the appropriate ages to study and decisions on how to stratify data by age are drug-specific and require scientific justification, taking into consideration developmental biology and pharmacology.

The Center for Drug Evaluation and Research generally divides the pediatric population into the following groups:\(^{14}\)

- Neonates: birth up to 1 month;
- Infants: 1 month up to 2 years;
- Children: 2 up to 12 years; and
- Adolescents: 12 years up to 16 years.\(^{15}\)

The measurement or prediction of a drug or biologic’s pharmacokinetics (exposure) and pharmacodynamics (response) is essential to the clinical pharmacology assessment. It is important to describe the exposure-response relationship of a drug or biologic in the pediatric population. In some instances, knowledge of pharmacogenetic differences, which can affect a product’s exposure, may also be required.

**A. Pharmacokinetics**

Pharmacokinetic measures, such as area under the curve (AUC) and maximum concentration \(C_{\text{max}}\) and parameters such as clearance (CL), half-life, and volume of distribution, reflect the absorption (A), distribution (D), and excretion (E) of a drug or biologic from the body. Drugs may be eliminated in the unchanged (parent) form, or undergo metabolism (M) to one or more active and inactive metabolites. The overall set of processes is often referred to as ADME, which ultimately determines systemic exposure to a drug and its metabolites after drug

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\(^{14}\) See the final rule on Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of “Pediatric Use” Subsection in the Labeling, 59 FR 64240, 64241-42, (December 13, 1994). Pediatric age groups are described in the preamble to this final rule, which revised the *Pediatric Use* subsection of the labeling for human prescription drugs to provide for the inclusion of more complete information about the use of a drug or biological product in pediatric populations.

\(^{15}\) Sponsors should address the entire age range but need not use these specific age categories. If physiologic categories or groupings based upon systems ontogeny are used, they should be supported with scientific and developmental data.
administration. This systemic exposure, reflected in plasma drug or metabolite concentrations, or both, is generally correlated with both beneficial and adverse drug effects. All drugs and biologics show inter- and intra-individual variability in PK measures and parameters. In the pediatric population, growth and developmental changes in factors influencing ADME can also lead to changes in PK parameters. The PK of a drug or biologic is typically evaluated over the entire pediatric age range in which the agents will be used (Kauffman and Kearns 1992; Kearns 2000). Special areas of importance in planning pediatric PK studies are discussed in the following paragraphs.

• Absorption

Developmental changes in the pediatric population that can affect absorption include effects on gastric acidity, rates of gastric and intestinal emptying, surface area of the absorption site, gastrointestinal drug-metabolizing enzyme systems, gastrointestinal permeability, biliary function, and transporter expression. Similarly, developmental changes in skin, muscle, and fat, including changes in water content and degree of vascularization, can affect absorption patterns of drugs delivered by intramuscular, subcutaneous, or percutaneous absorption (Yaffe and Aranda 2010).

• Distribution

Distribution of a drug or biologic can be affected by changes in body composition, such as changes in total body water and adipose tissue, which are not necessarily proportional to changes in total body weight. Plasma protein binding and tissue binding changes arising from changes in body composition with growth and development may also influence distribution. Differences between pediatric patients and adults in blood flow to an organ, such as the brain, can also affect the distribution of a drug or biologic in the body.

• Metabolism

Drug metabolism commonly occurs in the liver, but may also occur in the blood, gastrointestinal wall, kidney, lung, and skin. Developmental changes in metabolizing capacity can affect both bioavailability and elimination, depending on the degree to which intestinal and hepatic metabolic processes are involved (Leeder 2004). Although developmental changes are recognized, information on drug metabolism of specific drugs in newborns, infants, and children is limited. Both rates of metabolite formation and the principal metabolic pathway can be different in pediatric patients compared to adults and within the pediatric population. In vitro studies performed early in drug development may be useful in focusing attention on
metabolic pathways in both adults and pediatric patients.\textsuperscript{16}

• Excretion

Drug excretion by the kidney is the net result of glomerular filtration, tubular secretion, and tubular reabsorption. Because these processes mature at different rates in the pediatric population, age can affect the systemic exposure of drugs when renal excretion is a dominant pathway of elimination. The maturation of other excretory pathways, including biliary and pulmonary routes of excretion, is also important.

• Protein Binding

Protein binding to a drug or its metabolites may change with age and concomitant illness. In certain circumstances, an understanding of protein binding may be needed to interpret the data from a blood level measurement and to determine appropriate dose adjustments (Kearns, Abdel-Rahman et al. 2003). In vitro plasma protein binding studies can determine the extent of binding of the parent and the major active metabolite(s) and identify specific binding proteins, such as albumin and alpha-1 acid glycoprotein.

• Clearance

Clearance of drugs or biologic products as a function of age is generally a valuable parameter for determining the dose for each age group in the pediatric population, and drug clearance has provided a valuable tool in the assessment of pediatric clinical pharmacology studies (Rodriguez, Selen et al., 2008). Plasma clearance can be defined as the volume of plasma which is completely cleared of drug in a given time period.

• Additional Factors

Growth and developmental changes in the pediatric population will create substantial changes in ADME. PK measures and parameters for a drug or biologic may need to be described as a function of age and be related to some measure of body size, such as height, weight, or body surface area (BSA) (Kearns, Abdel-Rahman et al. 2003). The maturational changes in systems affecting ADME, such as membrane transporters and metabolizing enzymes, should be taken into consideration in choosing age groups and doses to study in the pediatric population.

B. Pharmacodynamics

Sponsors should collect and analyze both PK and, whenever possible, pharmacodynamics (PD) data in pediatric studies to determine how the two are linked (i.e., the PK-PD or exposure-response relationship). Pharmacodynamics may include the effect of the drug on biomarkers or clinical endpoints for both effectiveness and safety. These measurements may allow a better understanding of whether the PK-PD relationships of the drug or biologic in pediatric patients are similar to those observed in adults, and may aid in deriving rational dosing strategies in pediatrics.

If the clinical endpoint cannot be measured directly because the effect is delayed or rare, then the selection of an appropriate biomarker to substitute for the clinical efficacy or toxicity endpoint is essential. In many cases, biomarkers are first evaluated in an adult population, in which case the support for the use of the biomarker in a pediatric population depends on evidence that the disease pathophysiology and pharmacologic response in pediatric patients is sufficiently similar to adults.

C. Pharmacogenetics

Genetic differences that clinically affect both exposure and response are increasingly documented, but the relationship between genomic profiles and developmentally regulated gene expression has not been extensively studied in pediatric populations. Some of the difficulties in obtaining specific pharmacogenetic information in pediatric patients have been reviewed (Leeder 2004). Nevertheless, if drug exposure in a pediatric clinical pharmacology study is dependent on a well-known pharmacogenomic biomarker (e.g., cytochrome P4502D6), obtaining patient DNA may provide additional information for the interpretation of the PK and PD results.

IV. ETHICAL CONSIDERATIONS

FDA-regulated clinical investigations are governed, in part, by the institutional review board (IRB) regulations at 21 CFR Part 56 and the human subject protections at 21 CFR Part 50. Pediatric subjects who are enrolled in FDA-regulated clinical pharmacology studies must be afforded the additional safeguards found at 21 CFR Part 50, Subpart D. These safeguards restrict the allowable risk to which a pediatric subject may be exposed in a clinical investigation based

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on whether the proposed intervention or procedure offers a prospect of direct clinical benefit to
the individual child. Clinical pharmacology studies generally do not provide a direct clinical
benefit to individual pediatric subjects, and must therefore present no more than minimal risk (21
CFR 50.51) or a minor increase over minimal risk (21 CFR 50.53). Exceptions to this general
rule may include, for example, dose-monitoring studies that directly benefit individual pediatric
subjects by ensuring that serum levels of a drug remain within a therapeutic range. Under such
circumstances, a clinical pharmacology study may be approvable by an IRB under 21 CFR
50.52. Before initiation of the clinical trial, an IRB must approve the proposed trial under the
requirements of 21 CFR 50 subpart D.\textsuperscript{19} However, FDA has an independent responsibility to
assess the compliance of the proposed clinical trial under 21 CFR 50 subpart D. Failure of a
proposed clinical trial to be in compliance with 21 CFR Part 50, Subpart D, may be sufficient
grounds for FDA to impose a clinical hold because the investigation could present an
unreasonable and significant risk of illness or injury (21 CFR 312.42(b)).

The assessment under 21 CFR Part 50, Subpart D of a clinical pharmacology protocol depends
on whether the experimental drug or biologic is being administered (1) solely for the purposes of
obtaining pharmacokinetic data or (2) in such a way that it offers the enrolled child a prospect of
direct clinical benefit. The following two paragraphs discuss these two cases, respectively. In
both cases, administration of an experimental drug or biological product is always considered to
represent more than minimal risk and thus is not approvable by an IRB under 21 CFR 50.51. For
IRB approval under 21 CFR 50.53, an enrolled child must have a disorder or condition that is the
focus of the clinical investigation. For IRB approval of a clinical investigation under 21 CFR
50.52, an enrolled child must have a prospect of direct clinical benefit from administration of the
investigational product. Thus, only patients with a therapeutic need for the investigational drug
product can be enrolled in such trials. Consequently, healthy pediatric subjects (i.e., without a
disorder or condition which is the focus of the research) cannot be enrolled in clinical
pharmacology studies absent a determination by the Commissioner, after consultation with a
panel of experts in pertinent disciplines and opportunity for public review and comment, that the
conditions in 21 CFR 50.54 (which allows clinical investigations to proceed that present an
opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare
of children) are met.\textsuperscript{20}

\textit{Case 1: IRB review of a clinical pharmacology study using pediatric human subjects under 21
CFR 50.53.}

\textsuperscript{19} See 21 CFR 56.109(h) and 21 CFR 56.111(c).

\textsuperscript{20} See \textit{Guidance for Clinical investigators, Institutional Review Boards, and Sponsors Process for Handling
Referrals to FDA Under 21 CFR 50.54}, December 2006, available at
When the experimental drug or biologic is being administered solely for the purpose of obtaining pharmacokinetic data, both the experimental drug administration and the pharmacokinetic sampling must present no more than a minor increase over minimal risk (21 CFR 50.53(a)). In addition, pediatric subjects may be exposed to such risks if, among other criteria, the intervention or procedure is likely to yield generalizable knowledge about the subjects’ disorder or condition that is of vital importance for the understanding or amelioration of that disorder or condition (21 CFR 50.53(c)). Thus, for a clinical investigation to be approved by an IRB under this category, the enrolled pediatric subject must have a disorder or condition. A condition may include being “at risk” for the disease. In addition, sufficient empirical data regarding the risks of the proposed interventions or procedures need to be available to ascertain that the risks are no more than a minor increase over minimal risk (21 CFR 50.53(a)). The available adult data including dose-response data may be considered for this purpose. Even if the risk is thought to be low, if there are not enough data to adequately characterize the risk, then the intervention or procedure cannot be considered to present no more than a minor increase over minimal risk because the risks of the intervention or procedure would not be known with sufficient accuracy. In addition, the risks of the blood and/or fluid sampling procedures need to be no more than a minor increase over minimal risk. An example of a clinical pharmacology study that may be conducted under 21 CFR 50.53 is the pharmacokinetics of a single dose of an over-the-counter cough and cold product. To be enrolled in such a study, a child may either be symptomatic from an upper respiratory infection (URI) or be at risk for a future URI based on the presence of criteria such as the frequency of past infections, number of people living in the home, or exposure to others in a preschool or school setting.


The experimental drug administration may present more than a minor increase over minimal risk as long as this level of risk exposure is justified by a sufficient prospect of direct clinical benefit to the subjects (21 CFR 50.52(a)). For example, dose-monitoring studies that directly benefit individual pediatric subjects by ensuring that serum levels of a drug remain within a therapeutic range would fall under 21 CFR 50.52. In this case, pharmacokinetic studies of investigational products must be done in children who have a therapeutic need for the drug or biologic, and the drug or biologic must be administered using a dosing regimen that offers a sufficient prospect of direct clinical benefit to justify the risks (21 CFR 50.52(a)). In such studies, the limited venipunctures that may be required to obtain specimens for pharmacokinetic analyses are generally considered either minimal risk or a minor increase over minimal risk, and therefore may be approvable absent a prospect of direct benefit (21 CFR 50.51 and 50.53). This approach to the analysis of clinical pharmacology trials is called a component analysis of risk, whereby the interventions that do and do not offer a prospect of direct benefit in any given protocol must be
analyzed separately.21
Adequate information from clinical pharmacology studies to support pediatric dosing is critical
to the development of ethically sound confirmatory trials. For example, pivotal trials of
antihypertensive agents may have failed to demonstrate efficacy in the pediatric population as a
result of inadequate pediatric dosing (Benjamin, Smith et al., 2008; Rodriguez, Selen et al.,
2008). FDA considers the public health need for adequate pediatric dosing in its assessment of
the ethical propriety of proposed studies. For further information, investigators and IRBs may
refer to the American Academy of Pediatrics Guidelines for the Ethical Conduct of Studies to
Evaluate Drugs in Pediatric Populations (Shaddy and Denne, 2010) or the International
Conference on Harmonization (ICH) Guidance for Industry E6 Good Clinical Practice:
Consolidated Guidance (ICH E6), which contains a section on nontherapeutic studies in special
populations.22

V. THE PEDIATRIC STUDY PLAN DESIGN AND POINTS TO CONSIDER

Under Section 505B(e)(1) of the FD&C Act, a sponsor who will be submitting an application for
a drug or biological product that includes a new active ingredient, new indication, new dosage
form, new dosing regimen, or new route of administration is required to submit an initial
pediatric study plan (PSP). A pediatric study plan (PSP) outlines the pediatric study or studies
that the applicant plans to conduct.23

The submission of the initial PSP is intended to encourage sponsors to consider pediatric studies
early in product development and, when appropriate, begin planning for these studies. The

21 See National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research,
Research Involving Children: Report and Recommendations of the Commission for the Protection of Human
Subjects of Biomedical and Behavioral Research, (43 FR 2084, 2086 (Jan. 13, 1978)); Guidance for Industry: Acute
Bacterial Otitis Media: Developing Drugs for Treatment, September 2012, available at
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070947.pdf; and
Preamble to the Final Rule on the Additional Safeguards for Children in Clinical Investigations of Food and Drug
See also the ICH Guidance for Industry: E11 Clinical Investigation of Medicinal Products in the Pediatric
23 See section 505B(e)(2)(B) of the FD&C Act; 21 U.S.C. 355(e)(2)(B) and the draft Guidance for Industry-
Pediatric Study Plans: Content and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric
initial PSP must include “(i) an outline of the pediatric study or studies that the applicant plans to conduct (including, to the extent practicable, study objectives and design, age groups, relevant endpoints, and statistical approach); (ii) any request for a deferral, partial waiver, or waiver...if applicable, along with any supporting information; and (iii) other information specified in the regulations” promulgated by the FDA. When designing the pediatric clinical studies, sponsors should be mindful that modeling and simulation, and pharmacologic considerations, are often critical for the successful completion of a study. Modeling and simulation using all of the information available should therefore be an integral part of all pediatric development programs. The following sections are critically important when developing the clinical pharmacology components of a pediatric study plan.

A. Approaches to Pediatric Studies

In addition to the usual considerations of PK (i.e., drug exposure), PD (i.e., effect on biomarker or clinical endpoint), and exposure-response relationships that may be different from those of adults, a pediatric drug development program should consider the time course of development of the drug metabolizing enzyme(s), drug excretory systems, and transporters specific to the drug being studied. This is probably best achieved by characterizing the PK of the drug across the appropriate pediatric age range. Based on the availability and reliability of the information about such factors, the pediatric study planning and extrapolation algorithm in the Appendix of this guidance illustrates the different approaches in conducting pediatric clinical studies.

PK Only Approach (i.e., full extrapolation): This approach is appropriate when it is reasonable to assume that children, when compared to adults, have (1) a similar progression of disease; (2) a similar response of the disease to treatment; (3) a similar exposure-response or concentration-response relationship; and (4) the drug (or active metabolite) concentration is measureable and predictive of the clinical response. 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

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25 Further information about the content of the initial PSP can be found in the draft Guidance for Industry: Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans (Footnote 23).
population, and experience with the drug, or other drugs in its therapeutic class, in the disease or condition or related diseases or conditions.\textsuperscript{28}

If there is no currently used pediatric dose, if there is insufficient PK information about a currently used pediatric dose, or if the currently used pediatric dose in the same clinical context would not be expected to match adult exposure, then a PK study should be performed to identify the pediatric dose that will provide similar exposure to adults. This PK study should be conducted before any additional pediatric clinical studies are initiated to ensure the optimal dose for these studies. Before conducting a PK study, simulations should be performed to identify the dose expected to achieve an appropriate target exposure (e.g., the observed adult drug exposure) in the same clinical context. The antibacterial therapeutic area is a good example of this approach, where the organism is expected to respond to similar plasma concentrations in adults and pediatric patients. In this case, the study can focus on identifying the doses in the pediatric setting that would result in exposures similar to those attained in adults.

\textbf{PK and PD Approach (i.e., partial extrapolation):} This approach is applicable when the disease and intervention are believed to behave similarly in pediatric patients and adults, but the exposure-response relationship in pediatric patients is either inadequately defined or thought not to be sufficiently similar. To use this approach, the exposure-response relationship in adults should be well-characterized. The goal of such an approach is to characterize and compare the exposure-response relationship in adults and in the pediatric population with the appropriate pediatric doses based on the exposure-response relationships seen in pediatric patients. Clinical measures (e.g., symptoms, signs, outcomes) can be used to select doses, but an appropriate biomarker considered to be related to such an endpoint can also be used, which is usually a biomarker based on adult experience. If there is uncertainty about whether extrapolation of efficacy is appropriate, a single adequate and well-controlled study using a clinical endpoint may be necessary. Additional studies powered to demonstrate efficacy may not be required.

The antiarrhythmic therapeutic area is one example of this approach, where mortality and morbidity studies cannot be ethically conducted in pediatric patients. In the case of antiarrhythmic therapy, the Agency accepted a clinical study assessing the beta adrenergic blocking effects of sotalol on heart rate and the effect on QTc, both of which are acceptable biomarkers in pediatrics, as the basis for labeling information on use of the drug in pediatric patients.

\textbf{PK and Efficacy Approach (i.e., no extrapolation):} If the disease progression is unique to pediatric patients or its progression and/or response to intervention is undefined or dissimilar to that in adults, then the pediatric development program should provide substantial evidence of the

\textsuperscript{28} See Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (Footnote 13).
effectiveness and safety of the drug product in pediatric subjects in one or more clinical studies, usually evaluating more than one dose.\textsuperscript{29} The study objectives are to provide evidence of effectiveness and safety and to characterize the PK and exposure-response relationships to aid in optimizing pediatric dosing strategies. A population PK analysis can be conducted concurrently using PK data from the efficacy study to confirm PK estimates in the age subgroups.\textsuperscript{30}

For the “PK and PD” and “PK and Efficacy” approaches, response data in pediatric studies should be collected and analyzed. Response or PD data may include biomarkers or clinical endpoints for both safety and effectiveness. The specific endpoints for an exposure-response evaluation for each drug or biologic product should be discussed with the Agency.

A dedicated PK study is not always required in every age group. For example, prior experience with dosing in adolescent patients has demonstrated that knowledge of adult dosing and appropriate dose scaling may be sufficient for some drugs with adequate justification. Confirmatory population PK studies may be used to supplement such a program in which a dedicated PK study is not considered essential.

B. Alternative Approaches

In addition to conventional PK studies with intensive blood sampling in pediatric patients, other approaches can be used to obtain useful drug exposure information. Urine and saliva collection are noninvasive, but the interpretation of drug analysis of either is complicated and requires careful consideration before use. Likewise, tissue or cerebrospinal fluid that is being collected for clinical purposes present both an opportunity and a challenge for the appropriate interpretation of these results in understanding the PK of the drug.

When clinical PK studies in pediatric patients are not feasible, there are situations in which interpolation or extrapolation of PK data may be sufficient. PK information in certain pediatric age groups may be gained by interpolating or extrapolating from existing data in adults, data in pediatric patients in other age groups, or both. However, extrapolation of data to very young pediatric patients, particularly neonates, is rarely credible. Significant metabolic differences may exist between neonates and older pediatric patients or adults that can give rise to considerable variability in metabolism and drug disposition. This variability can lead to an altered dose-response relationship. Modeling and simulation can provide another method for reducing residual uncertainty about drug dosing in special pediatric populations.

\textsuperscript{29} See Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (Footnote 13).

C. Pediatric Dose Selection

Selection of an appropriate dose range to be studied is critical in deriving rational dosing recommendations for the pediatric population. Because there may be limited information on the safety of the dose to be administered to a neonate or infant, the dose range in initial studies requires careful consideration. Factors for consideration include (1) similarity of the disease and exposure-response in other studied pediatric groups; (2) the relative bioavailability of the new formulation compared to the previous formulations; (3) the age and developmental stage of the population; (4) the pharmacogenetic characteristics of the drug or biologic; (5) the toxicity of the drug or biologic; and (6) PK data from other pediatric populations. Initial doses are typically normalized to body size (mg/kg) or BSA (mg/m²).

When separate efficacy studies in pediatrics are not conducted (i.e., for the PK only approach described in section V.A above), in general, PK studies in the pediatric population should determine how the dosage regimen should be adjusted to achieve the same level of systemic exposure in adults as defined above. Differences in interpatient variability in these PK measures and/or parameters between age groups or between pediatric and adult patients should be interpreted with regard to their impact on dosing, safety, and/or efficacy. In these instances, the sponsor should specify the criteria by which exposure matching would be acceptable. For example, one approach would be to select the appropriate dosing strategy through simulations that ensure the pediatric exposures are within the range of exposures (e.g., 5th to 95th percentile) shown to be safe and effective in adults.

As science and technology continue to advance, in silico and other alternative modeling study methods may be developed that can provide preliminary data to inform the design and conduct of PK/PD studies for investigational drugs in pediatric populations. For example, the development of a physiologically-based PK (PBPK) in silico model that integrates drug-dependent parameters (e.g., renal clearance, metabolic pathways) and system-dependent parameters (e.g., non-drug parameters such as blood flow rate, protein binding, and enzyme and transporter activities) is one possible approach. PBPK has been used in pediatric drug development programs for (a) planning for a first-in-pediatric PK study, (b) optimizing the study design, (c) verifying the model in specific age groups, (d) recommending starting doses, (e) informing enzyme ontogeny using a benchmark drug, and (f) facilitating covariate analysis for the effects of organ dysfunction or drug interactions in pediatric patients (Leong, Vieira et al. 2012). The model selected should incorporate in vivo PK/PD data obtained in other groups of pediatric and adult patients as well as human volunteer studies, as appropriate.
Reference to the Centers for Disease Control and Prevention (CDC) growth charts provides a preliminary assessment of the weight ranges that can be anticipated within specific age groups. For example, weights can vary 2.5- to 3-fold in healthy children between the 10th percentile at 2 years and 90th percentile at age 6 (10.6 kg to 25.3 kg for males) and between the 10th percentile at 6 years and the 90th percentile at 12 years (17.7 kg to 54 kg in males).

An estimate of the exposure-response relationship across a range of body-size doses (dose/kg or dose/m²) may be important. For the “PK and PD” and “PK and efficacy” approaches discussed in section V.A above, investigation of a range of doses and exposures should allow assessment of those relationships and development of rational dosing instructions.

Where PK/PD data are developed, the dose range should account for observed differences in response between adults and the pediatric population (Benjamin, Smith et al. 2008), both in terms of exposure and response. For example, there is evidence that pediatric populations are on average less sensitive to antihypertensive drugs than the adult population. Therefore, pediatric studies may include exposures greater than the highest drug exposure associated with the approved adult dose, provided that prior data about the exposure-response relationship and safety information justify such an exposure. Studies of distinctly different ranges of exposure are desirable to provide sufficient information for the calculation of an optimal dose.

D. Pediatric Dosage Formulation

Pediatric formulations that permit accurate dosing and enhance adherence (i.e., dosing regimen, palatability) are an important part of pediatric clinical pharmacology studies. If there is a pediatric indication, an age-appropriate dosage formulation must be made available for pediatric patients. One way to fulfill this requirement is to develop and test a pediatric formulation and seek approval for that formulation.

If the sponsor demonstrates that reasonable attempts to develop a pediatric formulation have failed, the sponsor should develop and test an age-appropriate formulation that can be prepared by a pharmacist in a licensed pharmacy using an FDA-approved drug product and commercially available ingredients. If the sponsor conducts the pediatric studies using such a formulation,
the following information should be provided in the study report:

- A statement on how the selected final concentration was optimized to help ensure that the doses can be accurately measured with commercially available dosing devices;
- A statement that the volume to be prepared is appropriate to be dispensed for a course of therapy for one patient, unless there are safety factors that necessitate decreasing the volume to be prepared;
- A listing of all excipients, including diluents, suspending agents, sweeteners and flavoring agents, and coloring agents;
- Information on containers (designated containers should be readily and commercially available to retail pharmacies) and storage requirements (if possible the most user friendly storage condition [room temperature] should be evaluated and or studied); and
- Testing results on formulation stability, not to exceed the expiration date of the original drug product lot from which the pediatric formulation is derived.

The bioavailability of any formulation used in pediatric studies should be characterized in relation to the adult formulation. If needed, a relative bioavailability study comparing the age-appropriate formulation to the approved drug should be conducted in adults. Potential drug-food or vehicle interactions should be considered, such as those that have been reported with apple juice (Abdel-Rahman, Reed et al. 2007), in these study designs.

Extended-release dosage forms or combination products produced for adults should be made available for pediatric patients as an age-appropriate formulation when it is appropriate to do so.

E. Sample Size

1. Number of Patients

The precision of PK and exposure-response parameters in the sample size calculation is critical for pediatric studies. Prior knowledge of the disease, exposure, and response from adult and other relevant pediatric data, such as that related to variability, can be used to derive sample size for ensuring precise parameter estimation. The sponsor should account for all potential sources of variability, including inter-subject and intra-subject variability, and differences between the adult and pediatric populations in the final selection of the sample size for each age group.

The distinct age groups to be studied should be chosen based upon what is known about the development of the drug-metabolizing enzymes and excretory mechanisms, and safety considerations. An example of age groups to be studied is provided in the table below. If the drug is intended to be used in newborn infants, the pediatric study plan should specify whether
premature or small for gestational age infants will be included in the study population.

<table>
<thead>
<tr>
<th>Example of age groups to be studied for the drug or biologic product</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 month to &lt;6 months</td>
</tr>
<tr>
<td>6 months to &lt;24 months</td>
</tr>
<tr>
<td>2 years to &lt;6 years</td>
</tr>
<tr>
<td>6 years to &lt;12 years</td>
</tr>
<tr>
<td>12 years to &lt;17 years</td>
</tr>
</tbody>
</table>

The sponsor should discuss the distribution of the number of patients across each age range and the appropriateness of these age ranges with the Agency, because this will be drug product-specific. Justification should be provided for the sample size selected. For example, one approach would be to prospectively target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for the drug in each pediatric subgroup with at least 80% power. Noncompartmental analysis (NCA) based on rich PK sampling, population PK modeling analysis based on sparse PK sampling, or other scientifically justified methods can be applied to achieve this precision standard (Wang, Jadhav et al. 2012). Conceivably, certain disease states might not allow recruitment of an adequate number of participants to meet the standard, but practical considerations should be taken into account in determining the sample size.

2. Number of Samples Per Patient

In addition to the number of patients, the number of blood samples collected in the clinical pharmacology study to estimate PK measures and parameters for each patient in the study should be carefully considered. The number of samples may be very limited in some pediatric patients such as neonates (for more on collection of blood or plasma samples, see section F below). Clinical study simulations or optimal sampling techniques may be recommended to justify the proposed sampling scheme. Additional sampling for drug or metabolite concentrations is also recommended when an adverse event occurs.

F. Sample Collection

Blood or plasma concentrations of drug or metabolite have been used as supporting evidence of effectiveness or dose selection through exposure-response analyses in pediatric patients. However, the volume and frequency of blood sampling are often of concern in pediatric studies. Blood samples can be obtained by direct venipuncture or through the use of an indwelling intravascular catheter. Because repeated venipuncture may cause discomfort and bruising at the puncture site, an indwelling intravascular catheter should be used when possible. The volume
and frequency of blood sampling can be minimized by using micro-volume drug assays, dried blood spots, and sparse-sampling techniques. These types of assays and analysis are especially relevant when studying neonates (Long, Koren et al. 1987). Modern assay techniques allow small sample volumes to be used to determine drug concentration (Kauffman and Kearns 1992), but data quality may be affected if the sample volume is insufficient to allow for reanalysis when necessary. Blood samples for analysis should be collected from the circulating blood volume and not from reservoir dead space created by catheters or other devices. Sampling technique is critical when using the available pediatric indwelling intravenous catheters. The time of sample collection, proper sample transportation and storage, and sample handling techniques should be documented. The collection of fluids such as cerebral spinal fluid (CSF) or bronchial fluids may be beneficial when samples are being obtained for clinical purposes. Noninvasive sampling procedures, such as urine and saliva collection, may suffice if correlated with outcomes or if the correlation with blood or plasma levels has been documented.

Given the difficulty in collecting blood samples in the pediatric population, special approaches to allow optimal times of sample collection may be useful. The sampling scheme should be planned carefully to obtain the maximum information using the minimum number of samples. If possible, collect additional PK samples when adverse events are observed to understand the relationship between drug exposure and toxicity. Samples for DNA should be collected when appropriate, as discussed in section III of this guidance.35

G. Covariates and Phenotype Data

The sponsor should obtain the following covariates for each pediatric patient: age, body weight, BSA, gestational age and birth weight for neonates, race or ethnicity, sex, and relevant laboratory tests that reflect the function of the organs responsible for drug elimination. Concomitant and recent drug therapy should also be recorded. Sponsors are encouraged to collect DNA samples in pediatric PK studies under the circumstances described in section II, along with appropriate phenotype information to optimize the interpretation of pharmacogenetic findings. For example, when genotype information is obtained for a cytochrome P450 enzyme, the sponsor should look at the influence of genetic mutations on PK, PD, and/or dose-response to determine whether genetically defined subsets of patients may need special dosing considerations.

The sponsor should examine the relationship between the covariates and the PK of the drug or biologic agent of interest. The contribution of weight or BSA and age to the PK variability should be assessed. The following practice for assessing effect of age on pediatric PK, which

is applicable in most cases, is recommended:

- Identify the accurate relationship between PK and body weight or BSA using allometric scaling (Mahmood 2006; Mahmood 2007).

- Analyze the residuals versus age visually, after accounting for the body weight or BSA effect on CL, followed by a more formal analysis exploiting the physiological understanding underlying the CL, if appropriate. Residual is referring to the difference between individual value (treated as predicted value) and the population mean (treated as actual value). Testing for other biologically relevant predictive factors for PK in pediatric patients may be important.

In pediatric PK studies, an estimation of creatinine clearance is recommended because of the challenge with using exogenous markers such as iohexol as an estimate of the glomerular filtration rate (GFR). The modified Schwartz equation, with adjustments for premature infants (Brion, Fleischman et al. 1986), neonates and infants (Schwartz, Feld et al. 1984), and children (Schwartz, Haycock et al. 1976) can be used. The older Schwartz equations may require correction for enzymatic creatinine assays. The Cockcroft-Gault formula should be used to estimate creatinine clearance in adolescents. This formula has been shown to be the best prediction of GFR, as measured by inulin clearance, when compared with the Schwartz and MDRD formulas in adolescents older than 12 years of age (Pierrat, Gravier et al. 2003).

a. Modified Schwartz equation (pediatric patients < 12 years of age):

\[
\text{CrCl (ml/min/1.73 m^2) = (K * Ht) / Scr}
\]

<table>
<thead>
<tr>
<th>Height (Ht) in cm; serum creatinine (Scr) in mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>K (proportionality constant):</td>
</tr>
<tr>
<td>Infant (LBW &lt; 1 year): K=0.33</td>
</tr>
<tr>
<td>Infant (Term &lt;1 year): K=0.45</td>
</tr>
<tr>
<td>Female Child (&lt;12 years): K=0.55</td>
</tr>
<tr>
<td>Male Child (&lt;12 years): K=0.70</td>
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</tbody>
</table>

b. Cockcroft-Gault equation (pediatric patients ≥ 12 years of age):

\[
\text{ClCr (ml/min) = [ (140 - age) x weight in kg] / [ Scr x 72] (x 0.85 if female)}
\]
When studying pediatric patients with impaired renal function, the sponsor should refer to the draft Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling, March 2010, for the general concepts of study design. Newer formulas incorporating cystatin C may be used to estimate GFR in pediatric patients with impaired renal function (Schwartz, Munoz et al. 2009).

If factors affecting the PK of the drug are to be studied (e.g., the effect of a concomitant medication or the presence or absence of a disease), a justification for the numbers of patients with and without those factors in the study should be included.

H. Sample Analysis

An accurate, precise, sensitive, specific, and reproducible analytical method to quantify the drug and metabolites in the biologic fluids of interest is essential. A method that is readily adaptable and that uses only minimum sample volumes should be chosen.

I. Data Analysis

Two basic approaches for performing the PK analysis in pediatric patients can be used; a standard noncompartmental PK approach and a population PK approach.

1. Noncompartmental Analysis

The noncompartmental analysis PK approach involves administering either single or multiple doses of a drug to a relatively small group of patients with relatively frequent blood and urine sample collection. Samples are collected over specified time intervals chosen on the basis of absorption and disposition half-lives, and subsequently assayed for either total or unbound concentrations of drug and relevant metabolites. Noncompartmental analysis can be used to establish PK parameters such as AUC, C<sub>max</sub>, CL, volume of distribution, and half-life, which are descriptive of the concentration of drug or metabolite over time. Data are usually expressed as the means of the relevant measure or parameter and interindividual variances. In this approach, including a sufficient number of patients to give a precise estimate of the mean is essential, as discussed in section V.E. If drug administration and sampling are repeated in a patient in the PK study, some understanding of intra-individual variability in PK parameters can be obtained.

36 When final, this guidance will represent FDA’s current thinking on the topic. Available at http://www.fda.gov/downloads/Drugs/Guidances/UCM204959.pdf.
2. Population Analysis

An alternative approach for analysis in pediatric clinical pharmacology studies is the population approach to PK analysis. Population PK accommodates infrequent (sparse) sampling of blood or plasma from a larger patient population than would be used in a compartmental or noncompartmental analysis PK approach to determine PK parameters. Sparse sampling of blood or plasma is considered more acceptable for pediatric studies, because the total volume of blood sampled can be minimized. Sampling can often be performed concurrently with clinically necessary blood or urine sampling. Because relatively large numbers of patients are studied and samples can be collected at various times of the day and repeatedly over time in a given patient, estimates of both population and individual means, as well as estimates of intra- and inter-subject variability, can be obtained if the population PK study is properly designed.38

Exposure-response analyses predominantly employ a population analysis approach. Individual analysis is generally not recommended unless responses from a wide range of doses from each patient are available. Simultaneous modeling of data across all patients provides the best opportunity to describe the exposure-response relationship.39

J. Clinical Study Report

The clinical study report should follow the ICH E3 guidance on the Structure and Content of Clinical Study Reports for the general content and the format of the pediatric clinical study report. The evaluation of exposure-response relationships and the population PK analyses should be included as stipulated in the Exposure-Response Guidance40 and the Population PK Guidance,41 respectively. In submitting PK information, the sponsor should submit the data illustrating the relationship between the relevant PK parameters (e.g., CL unadjusted and adjusted for body size in the manner described in section VI.G) and important covariates (e.g., age, renal function) in addition to the noncompartmental analysis results.

K. Data Submission

The preferred submission standard for clinical data is the Clinical Data Interchanges Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) standard. Please see the FDA Data

38 For more information on population PK, see the Guidance for Industry: Population Pharmacokinetics (Footnote 30).
39 See the Guidance for Industry: Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications (Footnote 26).
40 See the Guidance for Industry: Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications (Footnote 26).
41 See the Guidance for Industry: Population Pharmacokinetics (Footnote 30).
Standards Council 42 and the CDER Study Data Standards web sites for more information. The sponsor should also submit PK and exposure-response data used for modeling and simulation in an SAS.XPT-compatible format.

Pediatric Study Planning & Extrapolation Algorithm

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

- No to either:
  - Is it reasonable to assume similar exposure-response in pediatrics and adults?
    - No:
      - Is there a PD measurement that can be used to predict efficacy in children?
        - No:
          - Conduct: (Partial extrapolation)
            1. Adequate dose-ranging studies in children to establish dosing.
            2. Safety and efficacy trials at the identified dose(s) in children.
        - Yes:
          - Conduct: (Partial extrapolation)
            1. Adequate dose-ranging study in children to select dose(s) that achieve the target PD effect.
            2. Safety trials at the identified dose(s).
    - Yes:
      - Conduct: (Full extrapolation)
        1. Adequate PK study to select dose(s) to achieve similar exposure as adults.
        2. Safety trials at the identified dose(s).

- Yes to both:
  - Is the drug (or active metabolite) concentration measurable and predictive of clinical response?
    - No:
      - Conduct: (Partial extrapolation)
        1. Adequate dose-ranging studies in children to establish dosing.
        2. Safety and efficacy trials at the identified dose(s) in children.
    - Yes:
      - Conduct: (Full extrapolation)
        1. Adequate PK study to select dose(s) to achieve similar exposure as adults.
        2. Safety trials at the identified dose(s).

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 biologic environment (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.

See the Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (Footnote 13).
REFERENCES


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Subject: Utilization Patterns of Opioid Analgesics in the Pediatric Population

Drug Name(s): Opioid Analgesic Products

Application Type/Number: Multiple

Applicant/Sponsor: Multiple

OSE RCM #: 2015-241

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EXECUTIVE SUMMARY

A joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC), the Drug Safety and Risk Management Advisory Committee (DSaRM), and Pediatric Advisory Committee (PAC) will be held on September 15-16, 2016 to discuss the purpose and the conduct of clinical trials of opioid analgesics in pediatric patients. In preparation for this upcoming joint advisory committee meeting, this review examined the national utilization patterns of opioid analgesics in the pediatric population (0-16 years) from 2011 through 2015 in the U.S. outpatient retail setting. The drug utilization analyses in this review will be used as background information to provide context for the meeting’s discussion.

In the U.S. outpatient retail setting, pediatric patients 16 years of age and younger accounted for approximately 4% (2.5 million patients) of the total 66.5 million patients of any age who received dispensed prescriptions for opioid analgesics in 2015. The majority of pediatric patients were ages 7-16 years. There was a 34% decrease in the number of pediatric patients from 2011 to 2015. Annually within each respective pediatric age group examined, approximately 98.5% or more of patients in each pediatric age group received IR opioid analgesic prescriptions, and 1.6% or less of patients in each pediatric age group received ER/LA opioid analgesic prescriptions throughout the study period. Combination hydrocodone-acetaminophen IR and combination codeine-acetaminophen IR were the most commonly dispensed IR opioid analgesics while methadone, fentanyl transdermal, single-ingredient oxycodone ER, and morphine ER were the most commonly dispensed ER/LA opioid analgesics to pediatric patients with slight variations by patient age. Overall, trends in dispensed prescription data were similar to unique patient utilization data. In 2015, pediatricians were the top prescriber specialty for both IR and ER/LA opioid analgesics in patients ages 0-1 years and for ER/LA opioid analgesics in patients ages 2-6 years and 7-16 years. Dentists were the top prescriber specialty for IR opioid analgesics in patients ages 2-6 years and 7-16 years.

Analyses of duration of use for opioid analgesics were also conducted for the calendar year 2015 in a study sample of patients with claims for prescriptions dispensed from outpatient retail pharmacies. Consistent with dispensed prescription trends above, higher numbers of pediatric patients were dispensed IR opioid analgesics, of which the majority of patients were treated for shorter durations. These data are consistent with dispensing of IR opioid analgesic for the management of pain associated with an acute injury or dental procedure. A small number of pediatric patients were exposed to ER/LA opioid analgesics; of these, patients were treated for longer durations of use compared to the IR opioids. This finding is consistent with ER/LA opioid analgesic utilization in patients with medical illnesses which cause chronic pain. The majority of pediatric patients on ER/LA opioid analgesics had durations of therapy for less than 31 days; a small subset of patients had longer durations of therapy.

Based on U.S. office-based physician survey data, hernia was the top diagnosis associated with the use of IR opioid analgesics in patients ages 0-1 years from outpatient retail setting. Injuries and burns were the top diagnoses reported in patients ages 2-6 years and 7-16 years in association with the use of IR opioid analgesics. Diagnoses associated with the use of ER/LA opioid analgesics were not captured for the pediatric population in this data source most likely due to the low pediatric utilization of these products. These findings are consistent with patterns of pediatric use observed in dispensed prescriptions and duration of use analyses.

The majority of opioid analgesics are currently not labeled for use in children 16 years of age and younger. However, our analyses show that opioid analgesics, both IR and ER/LA products, are prescribed and dispensed to pediatric patients aged 16 years and younger in the outpatient retail setting.

Reference ID: 3988377
Therefore, studies of opioid analgesics in pediatric patients are necessary to inform health care providers of the safe use and proper dosing of opioid analgesics in the management of pain in children.

1 INTRODUCTION

The Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC), the Drug Safety and Risk Management Advisory Committee (DSaRM), and Pediatric Advisory Committee (PAC) joint meeting will be held on September 15-16, 2016. The purpose of this meeting is to discuss the studies of opioid analgesics in children, and the data on safe use and dosing in children who are appropriate for these products and has already received treatment with opioid analgesics on an off-label basis. In preparation for this upcoming meeting, this review provides context and background information on the U.S. outpatient retail utilization patterns for opioid analgesics, both extended-release/long-acting (ER/LA) and immediate-release (IR) opioid analgesics, in the pediatric population (0-16 years) from 2011 through 2015.

1.1 BACKGROUND

Opioid analgesics are an effective option to treat moderate to severe pain. In August 2015, extended-release oxycodone (OxyContin) was approved for use in opioid-tolerant pediatric patients aged 11 years to 16 years with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The addition of the labeling language for pediatric patients for OxyContin has resulted in widespread comments from the public, much of which reflected a misunderstanding of the purpose of studying opioid analgesics and the use of these products in children.

The upcoming joint advisory committee (AC) meeting will provide a forum for FDA and stakeholders to discuss the studies of opioid analgesics in children, to both educate the public, and to obtain advice from the committee on certain aspects of the types of pediatric studies. The studies are not intended to expand the use of opioids in children, but rather to provide data to inform on the safe use and dosing in children who are appropriate for these products and has already received treatment with opioid analgesics on an off-label basis.

2 METHODS AND MATERIALS

Proprietary databases available to the Agency were used to conduct the drug utilization analyses in this review (see Appendix B for full database descriptions).

2.1 PRODUCTS INCLUDED

The following extended-release/long-acting and immediate-release opioid analgesics are included in the analyses of the review. This review focused on opioid analgesic products largely dispensed in the outpatient retail setting. Injectable and suppository formulations of opioid analgesics were excluded as well as opioid-containing Medication-Assisted Therapy (MATs) products and opioid-containing cough/cold products due to the different indications and settings of care.

<table>
<thead>
<tr>
<th>Extended-Release/Long-Acting Formulation (ER/LA)</th>
<th>Immediate-Release Formulation (IR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Buprenorphine Transdermal</td>
<td>• Butorphanol</td>
</tr>
<tr>
<td>• Fentanyl Transdermal</td>
<td>• Codeine</td>
</tr>
<tr>
<td>• Hydrocodone</td>
<td>• Codeine-Acetaminophen</td>
</tr>
<tr>
<td>• Hydromorphone</td>
<td>• Hydrocodone-Acetaminophen</td>
</tr>
</tbody>
</table>

Reference ID: 3988377
The following opioid analgesics were not included in the analyses of the review because they were either not approved or marketed in the U.S. during the study time period.

- As of June 11th, 2016, combination oxycodone-naloxone ER (Targiniq) has not been marketed in the U.S.²
- As of July 2nd, 2016, single-ingredient morphine ER (Morphabond) has not been marketed in the U.S.³
- Single-ingredient oxycodone ER (Xtampza ER) was approved on April 26th, 2016.⁴
- Single-ingredient buprenorphine film (Belbuca) was approved on October 23rd, 2015, but was not marketed in the U.S. until February 22nd, 2016.⁵

2.2 DETERMINING SETTINGS OF CARE

Based on the IMS Health, IMS National Sales Perspectives™ database, approximately 72%, 27%, and 1% of bottles/packages of opioid analgesics were distributed to outpatient retail pharmacies, non-retail settings, and mail-order/specialty settings, respectively, in 2015.⁶ As a result, outpatient retail pharmacy utilization patterns of these opioid analgesics were examined. Data from the mail-order/specialty and non-retail pharmacy settings are not included in this review.

2.3 DATA SOURCES USED

2.3.1 Prescription Data
The IMS Health, National Prescriptions Audit™ database was used to provide national estimates of prescriptions dispensed to pediatric patients for opioid analgesics, stratified by patient age (0-1, 2-6, and 7-16 years), from U.S. outpatient retail pharmacies from 2011 through 2015. The top five prescriber specialties data were also obtained from this database for 2015; prescriptions written by veterinary medicine prescribers were excluded from the prescription analyses to exclude possible non-human use of opioid analgesics.

2.3.2 Patient Data
The Symphony Health Solutions’ Integrated Dataverse® (IDV) database was used to provide national estimates of pediatric patients who received a prescription dispensed for opioid analgesics, stratified by patient age (0-1, 2-6, and 7-16 years), from U.S. outpatient retail pharmacies from 2011 through 2015. To exclude possible non-human use of opioid analgesics such as prescriptions written by veterinary medicine prescribers, we excluded patients who paid cash for dispensed prescriptions written by the following prescriber specialties: All Other, Not Known, Other Specialty, and Other; veterinary medicine prescribers are captured under these specialty categories in this database. Patients were included in the study if they received dispensed prescriptions written by these unspecified specialties and were covered by commercial insurance plans, Medicare Part D, and Medicaid.

2.3.3 Duration of Use
Symphony Health Solutions’ Integrated Dataverse® (IDV) was also used to provide duration of use analyses of the most frequently dispensed IR and ER/LA analgesic opioids in a study sample of pediatric patients ages 0-16 years with dispensed prescription claims from U.S. outpatient pharmacy settings for 2015. Based on the pediatric utilization of the total opioid analgesic market, we selected the most frequently dispensed IR analgesic opioids (products included in the analysis were hydrocodone/acetaminophen, codeine/acetaminophen and oxycodone IR) and ER/LA analgesics opioids (products included in the analysis were oxycodone ER, morphine ER, fentanyl transdermal patches and methadone). For this analysis, patients with cash only or unspecified prescriber specialty prescriptions were excluded.

To determine the duration of use of the most frequently dispensed opioid analgesics, a crude analysis of treatment episodes was conducted. A treatment episode was defined as the period of time that a patient had uninterrupted therapy with a product of interest. The duration of a treatment episode is defined as the number of days between the start and end dates of the episode, which is determined by summing days’ of supply of all prescriptions. The total treatment episode duration is the sum of the days for each episode for a product within the selected study period. Duration of therapy was determined based on a frequency distribution of the therapy durations for each patient for the specified product. Based on the minimum and the maximum therapy duration for each respective patient, patients were divided into 10 equal groups or deciles. To account for patient behavior and short gaps between subsequent prescriptions, we allowed a grace period of 50% of the days’ supply of the last prescription.

2.3.4 Indications for Use
The Encuity Research, LLC., TreatmentAnswers™ with Pain Panel database was used to obtain the common diagnoses associated with the use of opioid analgesics in the pediatric population, stratified by patient age (0-1, 2-6, and 7-16 years), as reported by U.S. office-based physician surveys for 2015. Drug use mentions for diagnoses associated with the use of opioid analgesics were identified using ICD-10-CM codes.

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3 RESULTS

3.1 PRESCRIPTION DATA

Figure 1 below and Tables 1 a-c in Appendix A provide national estimates of total prescriptions dispensed to the pediatric population (0-16 years) for opioid analgesics from U.S. outpatient retail pharmacies. In 2015, approximately 226 million total prescriptions were dispensed for opioid analgesics. Pediatric patients 16 years of age and younger accounted for 1% (3 million prescriptions) of total dispensed prescriptions in 2015. Of the prescriptions dispensed to pediatric patients, 81% of prescriptions (2.4 million prescriptions) were dispensed to patients ages 7-16 years, followed by patients ages 2-6 years at 16% of prescriptions (489,000 prescriptions), and patients ages 0-1 years at 2% of prescriptions (72,000 prescriptions). The total number of prescriptions dispensed to pediatric patients (0-16 years) for opioid analgesics decreased by 35% from 4.6 million prescriptions in 2011 to 3 million prescriptions in 2015.

![Figure 1. National estimates of total prescriptions dispensed to pediatric patients (0-16 years) for opioid analgesics from U.S. outpatient retail pharmacies, years 2011-2015](image)


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

Throughout the examined time period, IR opioid analgesics accounted for 97% or more, and ER/LA opioid analgesics accounted for 3% or less of the total opioid analgesic prescriptions dispensed annually for each pediatric age group.

Among the IR opioid analgesic prescriptions dispensed to patients ages 0-1 years, approximately 47.5%, 32%, and 12% of prescriptions were dispensed for combination hydrocodone-acetaminophen IR, combination codeine-acetaminophen IR, and single-ingredient oxycodone IR, respectively. Among the ER/LA opioid analgesic prescriptions dispensed to patients ages 0-1 years, approximately 83%, 10%, 3%, and 2% of prescriptions were dispensed for methadone, fentanyl transdermal, morphine ER, and single-ingredient oxycodone ER, respectively.

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Among the IR opioid analgesic prescriptions dispensed to patients ages 2-6 years, approximately 45%, 41%, and 7% of prescriptions were dispensed for combination codeine-acetaminophen IR, combination hydrocodone-acetaminophen IR, and single-ingredient oxycodone IR, respectively. Among the ER/LA opioid analgesic prescriptions dispensed to patients ages 2-6 years, approximately 49%, 38%, 6%, and 5% of prescriptions were dispensed for methadone, fentanyl transdermal, morphine ER, and single-ingredient oxycodone ER, respectively.

Among the IR opioid analgesic prescriptions dispensed to patients ages 7-16 years, approximately 46%, 34%, and 7% of prescriptions were dispensed for combination hydrocodone-acetaminophen IR, combination codeine-acetaminophen IR, and combination oxycodone-acetaminophen IR, respectively. Among the ER/LA opioid analgesic prescriptions dispensed to patients ages 7-16 years, approximately 26.5%, 26%, 20%, and 19% of prescriptions were dispensed for morphine ER, single-ingredient oxycodone ER, methadone, and fentanyl transdermal, respectively.

3.2 **Patient Data**

Figure 2 below and Tables 2 a-c in Appendix A provide national estimates of total unique pediatric patients 16 years of age and younger who received prescriptions dispensed for opioid analgesics from U.S. outpatient retail pharmacies. In 2015, approximately 66.5 million total patients received prescriptions dispensed for opioid analgesics. Pediatric patients 16 years of age and younger accounted for 4% (2.5 million patients) of total patients in 2015. Of the total pediatric patients, 80% of patients (2 million patients) were ages 7-16 years, followed by patients ages 2-6 years at 18% (431,000 patients), and patients ages 0-1 years at 2.5% (61,000 patients). The total number of pediatric patients 16 years of age and younger who received prescriptions dispensed for opioid analgesics decreased by 34% from 3.7 million patients in 2011 to 2.5 million patients in 2015. Overall, trends in patient utilization across time were similar to dispensed prescription data.

**Figure 2. National estimates of pediatric patients ages 0-16 years who received dispensed prescriptions for opioid analgesics* from U.S. outpatient retail pharmacies, years 2011-2015**

![Graph showing number of patients (millions) by age group and year from 2011 to 2015.]

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


Reference ID: 3988377
Throughout the examined time period, approximately 98.5% or more of patients in each pediatric age group received IR opioid analgesic prescriptions, and 1.6% or less of patients in each pediatric age group received ER/LA opioid analgesic prescriptions.

Among patients ages 0-1 years who received IR opioid analgesic dispensed prescriptions, approximately 47%, 33%, and 11% of patients received a dispensed prescription for combination hydrocodone-acetaminophen IR, combination codeine-acetaminophen IR, or tramadol IR, respectively. Among patients ages 0-1 years who received ER/LA opioid analgesic dispensed prescriptions, approximately 64%, 29%, 2%, and 2% of patients received a dispensed prescription for methadone, fentanyl transdermal, morphine ER, or single-ingredient oxycodone ER, respectively.

Among patients ages 2-6 years who received IR opioid analgesic dispensed prescriptions, approximately 46%, 42%, and 5.5% of patients received a dispensed prescription for combination codeine-acetaminophen IR, combination hydrocodone-acetaminophen IR, or single-ingredient oxycodone IR, respectively. Among patients ages 2-6 years who received ER/LA opioid analgesic dispensed prescriptions, approximately 68%, 24%, 5%, and 2% of patients received a dispensed prescription for fentanyl transdermal, methadone, morphine ER, or single-ingredient oxycodone ER, respectively.

Among patients ages 7-16 years who received IR opioid analgesic dispensed prescriptions, approximately 48%, 37%, and 9% of patients received a dispensed prescription for combination hydrocodone-acetaminophen IR, combination codeine-acetaminophen IR, or tramadol IR, respectively. Among patients ages 7-16 years who received ER/LA opioid analgesic dispensed prescriptions, approximately 30%, 28%, 26%, and 10.5% of patients received a dispensed prescription for single-ingredient oxycodone ER, fentanyl transdermal, morphine ER, or methadone, respectively.

### 3.3 Duration of Use

Table 3 in Appendix A shows an analysis of the median and mean duration of therapy in days in pediatric patients 0-16 years of age for the most frequently dispensed IR (hydrocodone/acetaminophen, codeine/acetaminophen, oxycodone IR) and ER/LA analgesic opioids (oxycodone ER, morphine ER, fentanyl transdermal patches and methadone). All patients in a study sample with prescription claims for the selected opioids dispensed from outpatient retail pharmacies for year 2015 were included in the analysis.

Amongst IR opioid analgesics, the median treatment episode duration was 6 days for hydrocodone/acetaminophen, 5 days for codeine/acetaminophen, and 6 days for oxycodone IR. The corresponding mean treatment episode duration was slightly higher at 7.3 days for hydrocodone/acetaminophen, 6.6 days for codeine/acetaminophen and 9.4 days for oxycodone IR.

Amongst ER opioid analgesics, the median treatment episode duration ranged from 11 (oxycodone ER) to 31 days (fentanyl transdermal and methadone). The mean treatment episode duration ranged from 26 (oxycodone ER) to 77 days (methadone). Of note, in general the mean duration of therapy for the ER/LA products were higher than the medians. These data indicate that the majority of pediatric patients on ER/LA opioid analgesics had shorter durations of therapy (i.e., for less than 31 days), a small subset of patients had longer duration of therapy.

Table 4 in Appendix A show pediatric patient counts by minimum and maximum days of therapy for the IR and ER/LA opioid analgesics. In the study sample, over 90% of pediatric patients (950,290 total pediatric patients) with prescriptions dispensed for hydrocodone/acetaminophen had duration of therapy of less than 2 weeks. Over 90% of pediatric patients with prescriptions claim for codeine/acetaminophen...
(679,447 total pediatric patients), and oxycodone IR (79,117 total pediatric patients) prescription claim had duration of therapy of less than 2 weeks.

In the study sample, for ER/LA opioid analgesics, approximately 80% of pediatric patients with prescription claim for oxycodone ER (1,412 total pediatric patients), morphine ER (1,325 total pediatric patients) had duration of therapy of less than 31 days. Approximately 50% of pediatric patients with prescription claim for fentanyl transdermal patches (529 total pediatric patients) and oral methadone (1,130 total pediatric patients) had duration of therapy of less than 31 days.

3.4 PRESCRIBER SPECIALTIES

Table 5 in Appendix A provides the national estimates of prescriptions dispensed for opioid analgesics, stratified by patient age and the top five prescriber specialties, from U.S. outpatient retail pharmacies during year 2015.

Among pediatric patients ages 0-1 years, pediatricians were the top prescriber specialty, accounting for 32% and 52% of prescriptions dispensed for IR and ER/LA opioid analgesics, respectively.

Among pediatric patients ages 2-6 years and 7-16 years, dentists were the top prescriber specialty for IR opioid analgesics at 19% of prescriptions dispensed to patients ages 2-6 years, and 29% of prescriptions dispensed to patients ages 7-16 years. Meanwhile, pediatricians were the top prescriber specialty for ER/LA opioid analgesics at 33% of prescriptions dispensed to patients ages 2-6 years, and 35% of prescriptions dispensed to patients ages 7-16 years.

3.5 INDICATIONS FOR USE

Table 6 in Appendix A provides the diagnoses (ICD-10) in terms of drug use mentions\(^b\) associated with the use of opioid analgesics, stratified by patient age, as reported by U.S. office-based physician surveys in 2015.

Among the IR opioid analgesics, hernia (ICD-10 K40.9 and K43.9) was the top diagnosis (52.5% of drug use mentions) in pediatric patients ages 0-1 years. In the older pediatric population, injuries and burns (ICD-10 S00.x-T30.0) were the top diagnoses associated with the use of IR opioid analgesics at 39% of drug use mentions in pediatric patients ages 2-6 years, and 53% of drug use mentions in pediatric patients ages 7-16 years. Although the drug use mentions were low, IR opioid analgesics appear to be used for conditions associated with chronic pain in patients ages 2-6 years and 7-16 years, such as cancer, osteoarthritis, abdominal pain, and sickle-cell disease.

Of note, there were no diagnoses captured in the pediatric population in association with the use of ER/LA opioid analgesics most likely due to the low pediatric utilization of these products.

4 DISCUSSION

Analyses of utilization trends in the outpatient retail setting show that opioid analgesics are prescribed and dispensed to pediatric patients. In 2015, pediatric patients 16 years of age and younger accounted for 4% (2.5 million patients) of the total 66.5 million patients of any age who received dispensed prescriptions for

\(^b\) Encuity Research, LLC uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.
opioid analgesics; the majority of patients were ages 7-16 years. There was a 34% decrease in the number of pediatric patients from 2011 to 2015; although the reason for this decrease is unknown, a similar decline in use was seen among adult patients during the study period. Of note, the utilization of oxycodone ER in pediatric patients was low and decreased over the study time period. However, because pediatric labeling for OxyContin was approved in August 2015, our findings may not reflect the effect of this labeling on the pediatric utilization trends of oxycodone ER.

Among all the pediatric age groups, the vast majority of opioid analgesic utilization was for the IR products. Of these, combination hydrocodone-acetaminophen IR and codeine-acetaminophen IR were the most commonly dispensed IR products to pediatric patients. Although pediatric ER/LA opioid analgesic utilization was low, methadone, fentanyl transdermal, oxycodone ER, and morphine ER were the most commonly dispensed products.

Based on the duration of use analyses of these products, IR opioid analgesics appear to be utilized for shorter duration compared to ER/LA opioid analgesics in pediatric patients. This finding is consistent with dispensing of IR opioid analgesics for the management of acute or breakthrough pain associated with an acute injury or a dental procedure. Conversely, ER/LA opioid analgesics appear to be utilized for longer duration, consistent with utilization in patients with medical illnesses which cause chronic pain. The majority of pediatric patients on ER/LA opioid analgesics had durations of therapy for less than 31 days; a small subset of patients had longer duration of therapy.

According to survey data, office-based physicians reported utilization of IR opioid analgesics primarily in association with acute conditions such as treatment of hernia in infants and injuries and/or burns in children. No indication data was captured for ER/LA opioid analgesics in the physician survey database most likely due to the low pediatric utilization of these products. Diagnosis data are not directly linked to dispensed prescriptions; the diagnoses data were obtained from surveys of a sample of 3,200 office-based physicians with 115 pain specialists reporting on patient activity during one day per month. Because of the small sample sizes captured with correspondingly large confidence intervals, these data should be interpreted with caution and may not represent national trends.

Research has found that poorly treated or untreated childhood pain can cause negative long-term impacts on the psychological development in adulthood. Appropriate pain management is important in improving the quality of life of children. Management of pain usually involves a multimodal approach; because of their analgesic and antipyretic properties, acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen are combined with opioid analgesics to reduce opioid dose and side effects. However, pain management in children may be inadequate due to the lack of knowledge on pain assessment and management, especially for chronic pain, in addition to the communication barriers unique to children. Treatment guidelines such as the World Health Organization (WHO) guideline for the management of persisting pain in children states there is no other class of medicines than strong opioids that is effective in the management of moderate and severe pain. Strong opioids are an essential element in pain management.

Immediate-Release opioid analgesics are commonly used for acute and breakthrough pain where immediate pain relief is needed for causes such as an injury, post-surgical procedures, and dental restorative treatment and extractions, consistent with the utilization data by prescriber specialty and the physician survey data. Extended-Release/Long-Acting (ER/LA) opioid analgesics are more appropriate for chronic persistent pain in children previously treated with IR opioids for medical illnesses such as cancer, which might cause long-term pain and require prolonged release of analgesics to relief pain for better compliance and dose scheduling. Pediatric utilization of methadone is often used to treat newborns.
and infants born to mothers on opioids. Our findings based on dispensed prescriptions claims data and physician survey data are consistent with utilization for these indications.

The prescriptions claims data should be interpreted with caution due to the following limitations: 1) some pediatric utilization findings may be a result of errors such as wrong date of birth on prescriptions; however, medical charts were not available for validation; 2) the prescription and patient estimates are nationally projected data based on a robust sample of the U.S. retail pharmacies, these data should be interpreted with caution for the low patient or prescription numbers which are based on very small sample sizes; and 3) because the prescription and patient estimates are obtained from two different databases, which capture different samples of prescription claims and have different projection methodologies, the patient and prescription data trends may be slightly different, especially for products with low utilization (See Appendix B for full database descriptions).

The duration-of-use analysis should be interpreted with the following limitations in mind: 1) because we used dispensing data obtained from outpatient pharmacies, our results are not generalizable to the inpatient setting; 2) our analysis may underestimate the duration of therapy of opioid analgesics in pediatric patients because it was restricted to 2015; 3) all analyses were conducted at the active moiety and formulation level (e.g. oxycodone ER), effects due to product-level variations is unknown; 4) our analysis assessed exposure to each selected opioid analgesic independently of other products; therefore, patients may be counted more than once for respective opioids; 5) the analyses did not assess patients who may have switched opioid analgesic or were on multiple opioid analgesics during the study period.

To date, the safety and efficacy of most opioid analgesics in patients aged 16 years and younger have not been established or labeled. Furthermore, there are few clinical guidelines for managing chronic pain in children. Additional research and clinical studies of opioid analgesics in children are necessary to inform health care providers of the safe use and proper dosing of opioid analgesics in the management of pain in children.

As a final note, a brief search of the literature identified one study evaluating opioid analgesics use in a non-random sample of 626 hospitals. This study found two million out of five million (40%) of pediatric hospitalizations from 2007 to 2012 were exposed to opioids. The most commonly used opioids in the inpatient setting were morphine, fentanyl, and hydromorphone. Similar to our results which examined outpatient pharmacy data, pediatric utilization of opioid analgesics increased with age. Of the patients treated with these products, the overall mean length of opioid analgesic therapy was 4.6 days (median 2.9 days). However, there was a wide variation across hospitals in the type of opioid used and the length of therapy used, even after adjusting for several patient and hospital characteristics.

5 CONCLUSIONS

A nationally estimated number of 2.5 million pediatric patients ages 16 years and younger received dispensed prescriptions for opioid analgesics in the outpatient setting in 2015. Our findings show that pediatric utilization accounted for 4% of total patients treated with opioid analgesics. Although the appropriateness of prescribing cannot be determined from our analyses, these data are consistent with utilization following pain management principles. However, patient outcomes related to the pediatric utilization of opioid analgesics were not available and is an area in need of further research. Furthermore, the majority of opioid analgesics are not labeled for use in children 16 years of age and younger. These reasons highlight the need to study opioid analgesics in pediatric patients to inform health care providers of the safe use and the proper dosing of these drug products in the management of pain in pediatric patients.

Reference ID: 3988377
6 REFERENCES


Table 1. National estimates of total *prescriptions* dispensed for opioid analgesics, stratified by patient age, from U.S. outpatient retail pharmacies, years 2011-2015

<table>
<thead>
<tr>
<th>Patient Age</th>
<th>Year 2011</th>
<th>Year 2012</th>
<th>Year 2013</th>
<th>Year 2014</th>
<th>Year 2015</th>
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<tr>
<td></td>
<td>TRxs</td>
<td>%</td>
<td>TRxs</td>
<td>%</td>
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<td>Total Prescriptions Dispensed for Opioid Analgesics</td>
<td>256,320,289</td>
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<td>258,891,737</td>
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<td>0-16 years</td>
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<td>4,234,286</td>
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<td>0-1 years</td>
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<td>7-16 years</td>
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### Table 1a. National estimates of *prescriptions* dispensed for opioid analgesics to the *pediatric patients ages 0-1 years*, stratified by active ingredient, from U.S. outpatient retail pharmacies, years 2011-2015

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<td><strong>Total Prescriptions Dispensed to Pediatric Patients</strong></td>
<td>4,607,090 100.0%</td>
<td>4,234,286 100.0%</td>
<td>3,689,373 100.0%</td>
<td>3,281,145 100.0%</td>
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<tr>
<td>Hydrocodone/Acetaminophen</td>
<td>35,051 27.9%</td>
<td>37,454 33.6%</td>
<td>39,433 43.0%</td>
<td>38,182 46.0%</td>
<td>33,112 47.5%</td>
</tr>
<tr>
<td>Codeine/Acetaminophen</td>
<td>75,364 60.0%</td>
<td>58,523 52.5%</td>
<td>38,405 41.9%</td>
<td>29,873 36.0%</td>
<td>22,499 32.3%</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>3,155 2.5%</td>
<td>3,598 3.2%</td>
<td>4,470 4.9%</td>
<td>6,663 8.0%</td>
<td>8,408 12.1%</td>
</tr>
<tr>
<td>Tramadol</td>
<td>6,215 4.9%</td>
<td>7,099 6.4%</td>
<td>4,969 5.4%</td>
<td>4,972 6.0%</td>
<td>4,038 5.8%</td>
</tr>
<tr>
<td>Morphine</td>
<td>1,203 1.0%</td>
<td>1,091 1.0%</td>
<td>946 1.0%</td>
<td>812 1.0%</td>
<td>783 1.1%</td>
</tr>
<tr>
<td>Oxycodone/Acetaminophen</td>
<td>3,688 2.9%</td>
<td>3,154 2.8%</td>
<td>3,093 3.4%</td>
<td>2,208 2.7%</td>
<td>571 0.8%</td>
</tr>
<tr>
<td>Meperidine</td>
<td>233 0.2%</td>
<td>164 0.1%</td>
<td>125 0.1%</td>
<td>72 0.1%</td>
<td>98 0.1%</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>109 0.1%</td>
<td>108 0.1%</td>
<td>78 0.1%</td>
<td>74 0.1%</td>
<td>60 0.1%</td>
</tr>
<tr>
<td>Tramadol/Acetaminophen</td>
<td>94 0.1%</td>
<td>60 0.1%</td>
<td>51 0.1%</td>
<td>36 &lt;0.1%</td>
<td>40 0.1%</td>
</tr>
<tr>
<td>Codeine</td>
<td>35 &lt;0.1%</td>
<td>30 &lt;0.1%</td>
<td>7 &lt;0.1%</td>
<td>21 &lt;0.1%</td>
<td>29 &lt;0.1%</td>
</tr>
<tr>
<td>Hydromorphone/Tbuprofen</td>
<td>98 0.1%</td>
<td>49 &lt;0.1%</td>
<td>34 &lt;0.1%</td>
<td>41 &lt;0.1%</td>
<td>23 &lt;0.1%</td>
</tr>
<tr>
<td>Opium</td>
<td>384 0.3%</td>
<td>148 0.1%</td>
<td>103 0.1%</td>
<td>66 0.1%</td>
<td>18 &lt;0.1%</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>7 &lt;0.1%</td>
<td>1 &lt;0.1%</td>
<td>5 &lt;0.1%</td>
<td>1 &lt;0.1%</td>
<td>18 &lt;0.1%</td>
</tr>
<tr>
<td>Pentazocine/Naloxone</td>
<td>36 &lt;0.1%</td>
<td>8 &lt;0.1%</td>
<td>4 &lt;0.1%</td>
<td>3 &lt;0.1%</td>
<td>6 &lt;0.1%</td>
</tr>
<tr>
<td>Transmucosal Immediate-Release Fentanyl (TIRF)</td>
<td>-- --</td>
<td>-- --</td>
<td>-- --</td>
<td>-- --</td>
<td>-- --</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>14 &lt;0.1%</td>
<td>6 &lt;0.1%</td>
<td>-- --</td>
<td>4 &lt;0.1%</td>
<td>-- --</td>
</tr>
<tr>
<td>Hydromorphone/Propoxyphene</td>
<td>-- --</td>
<td>1 &lt;0.1%</td>
<td>-- --</td>
<td>-- --</td>
<td>-- --</td>
</tr>
<tr>
<td>Pentazocine/Transdermal</td>
<td>-- --</td>
<td>1 &lt;0.1%</td>
<td>-- --</td>
<td>-- --</td>
<td>-- --</td>
</tr>
<tr>
<td><strong>Extended-Release/Long-Acting (ER/LA) Opioids</strong></td>
<td>3,289 2.6%</td>
<td>2,753 2.4%</td>
<td>2,441 2.6%</td>
<td>2,352 2.8%</td>
<td>1,909 2.7%</td>
</tr>
<tr>
<td>Methadone</td>
<td>2,408 73.2%</td>
<td>1,979 71.9%</td>
<td>1,862 76.3%</td>
<td>1,999 85.0%</td>
<td>1,583 82.9%</td>
</tr>
<tr>
<td>Fentanyl Transdermal</td>
<td>561 17.0%</td>
<td>506 18.4%</td>
<td>365 15.0%</td>
<td>195 8.3%</td>
<td>199 10.4%</td>
</tr>
<tr>
<td>Morphine</td>
<td>115 3.5%</td>
<td>130 4.7%</td>
<td>141 5.8%</td>
<td>84 3.6%</td>
<td>63 3.3%</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>129 3.9%</td>
<td>79 2.9%</td>
<td>45 1.8%</td>
<td>36 1.5%</td>
<td>33 1.7%</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>39 1.2%</td>
<td>36 1.3%</td>
<td>11 0.5%</td>
<td>17 0.7%</td>
<td>15 0.8%</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>-- --</td>
<td>-- --</td>
<td>-- --</td>
<td>-- 2.0%</td>
<td>8 0.4%</td>
</tr>
<tr>
<td>Tramadol</td>
<td>29 0.9%</td>
<td>14 0.5%</td>
<td>6 0.2%</td>
<td>7 0.3%</td>
<td>6 0.3%</td>
</tr>
<tr>
<td>Buprenorphine Transdermal</td>
<td>7 0.2%</td>
<td>7 0.3%</td>
<td>3 0.1%</td>
<td>4 0.2%</td>
<td>1 0.1%</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>-- --</td>
<td>-- --</td>
<td>6 0.2%</td>
<td>3 0.1%</td>
<td>-- --</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>4 0.1%</td>
<td>-- --</td>
<td>-- --</td>
<td>-- --</td>
<td>-- --</td>
</tr>
<tr>
<td>Oxycodone/Acetaminophen</td>
<td>-- --</td>
<td>-- --</td>
<td>-- --</td>
<td>2 0.1%</td>
<td>-- --</td>
</tr>
</tbody>
</table>

## National estimates of prescriptions dispensed for opioid analgesics to the pediatric patients ages 2-6 years, stratified by active ingredient, from U.S. outpatient retail pharmacies, years 2011-2015

<table>
<thead>
<tr>
<th>Year</th>
<th>Immediate-Release (IR) Opioids</th>
<th>Extended-Release/Long-Acting (ER/LA) Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TRxs</td>
<td>%</td>
</tr>
<tr>
<td>Total Prescriptions Dispensed to Pediatric Patients</td>
<td>4,607,090</td>
<td>100.0%</td>
</tr>
<tr>
<td>2-6 years</td>
<td>998,273</td>
<td>21.7%</td>
</tr>
<tr>
<td>Codeine/Acetaminophen</td>
<td>996,391</td>
<td>99.8%</td>
</tr>
<tr>
<td>Hydrocodone/Acetaminophen</td>
<td>620,174</td>
<td>62.2%</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>321,864</td>
<td>32.3%</td>
</tr>
<tr>
<td>Meperidine</td>
<td>9,052</td>
<td>0.9%</td>
</tr>
<tr>
<td>Tramadol</td>
<td>2,204</td>
<td>2.2%</td>
</tr>
<tr>
<td>Morphine</td>
<td>9,445</td>
<td>0.2%</td>
</tr>
<tr>
<td>Oxycodone/Acetaminophen</td>
<td>11,342</td>
<td>1.1%</td>
</tr>
<tr>
<td>Codeine</td>
<td>271</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Opium</td>
<td>219</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Tramadol/Acetaminophen</td>
<td>166</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Hydrocodone/Ibuprofen</td>
<td>63</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>35</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>1</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Pentazocine/Naloxone</td>
<td>11</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Transmucosal Immediate-Release Fentanyl (TIRF)</td>
<td>9</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>10</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Oxycodone/Acetaminophen</td>
<td>1</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Oxycodone/Ibuprofen</td>
<td>2</td>
<td>&lt;0.1%</td>
</tr>
</tbody>
</table>

Reference ID: 3988377
### Table 1c. National estimates of prescriptions dispensed for opioid analgesics to the pediatric patients ages 7-16 years, stratified by active ingredient, from U.S. outpatient retail pharmacies, years 2011-2015

<table>
<thead>
<tr>
<th>Year</th>
<th>TRxs</th>
<th>%</th>
<th>TRxs</th>
<th>%</th>
<th>TRxs</th>
<th>%</th>
<th>TRxs</th>
<th>%</th>
<th>TRxs</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Prescriptions Dispensed to Pediatric Patients</strong></td>
<td>4,607,090</td>
<td>100.0%</td>
<td>4,234,286</td>
<td>100.0%</td>
<td>3,689,373</td>
<td>100.0%</td>
<td>3,281,145</td>
<td>100.0%</td>
<td>2,988,067</td>
<td>100.0%</td>
</tr>
<tr>
<td><strong>7-16 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Immediate-Release (IR) Opioids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocodone/Acetaminophen</td>
<td>1,650,215</td>
<td>47.6%</td>
<td>1,557,447</td>
<td>48.4%</td>
<td>1,453,002</td>
<td>50.5%</td>
<td>1,303,855</td>
<td>50.0%</td>
<td>1,106,876</td>
<td>45.8%</td>
</tr>
<tr>
<td>Codeine/Acetaminophen</td>
<td>1,335,877</td>
<td>38.6%</td>
<td>1,168,981</td>
<td>36.3%</td>
<td>941,612</td>
<td>32.8%</td>
<td>808,954</td>
<td>31.0%</td>
<td>813,172</td>
<td>33.7%</td>
</tr>
<tr>
<td>Oxycodone/Acetaminophen</td>
<td>218,615</td>
<td>6.3%</td>
<td>202,222</td>
<td>6.3%</td>
<td>187,347</td>
<td>6.5%</td>
<td>184,586</td>
<td>7.1%</td>
<td>179,176</td>
<td>7.4%</td>
</tr>
<tr>
<td>Tramadol</td>
<td>149,218</td>
<td>4.3%</td>
<td>179,182</td>
<td>5.6%</td>
<td>173,992</td>
<td>6.1%</td>
<td>181,620</td>
<td>7.0%</td>
<td>166,871</td>
<td>6.9%</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>46,063</td>
<td>1.3%</td>
<td>54,114</td>
<td>1.7%</td>
<td>66,605</td>
<td>2.3%</td>
<td>84,201</td>
<td>3.2%</td>
<td>108,000</td>
<td>4.5%</td>
</tr>
<tr>
<td>Meperidine</td>
<td>21,030</td>
<td>0.6%</td>
<td>19,315</td>
<td>0.6%</td>
<td>17,583</td>
<td>0.6%</td>
<td>15,580</td>
<td>0.6%</td>
<td>13,744</td>
<td>0.6%</td>
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<tr>
<td>Hydrocodone/Ibuprofen</td>
<td>19,076</td>
<td>0.6%</td>
<td>16,994</td>
<td>0.5%</td>
<td>14,782</td>
<td>0.5%</td>
<td>12,042</td>
<td>0.5%</td>
<td>8,206</td>
<td>0.3%</td>
</tr>
<tr>
<td>Tramadol/Acetaminophen</td>
<td>9,235</td>
<td>0.3%</td>
<td>8,074</td>
<td>0.3%</td>
<td>7,080</td>
<td>0.2%</td>
<td>6,844</td>
<td>0.3%</td>
<td>7,927</td>
<td>0.3%</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>5,914</td>
<td>0.2%</td>
<td>5,854</td>
<td>0.2%</td>
<td>5,550</td>
<td>0.2%</td>
<td>5,587</td>
<td>0.2%</td>
<td>5,476</td>
<td>0.2%</td>
</tr>
<tr>
<td>Morphine</td>
<td>4,537</td>
<td>0.1%</td>
<td>4,391</td>
<td>0.1%</td>
<td>4,568</td>
<td>0.2%</td>
<td>4,658</td>
<td>0.2%</td>
<td>4,361</td>
<td>0.2%</td>
</tr>
<tr>
<td>Codeine</td>
<td>1,473</td>
<td>&lt;0.1%</td>
<td>1,370</td>
<td>&lt;0.1%</td>
<td>898</td>
<td>&lt;0.1%</td>
<td>707</td>
<td>&lt;0.1%</td>
<td>807</td>
<td>&lt;0.1%</td>
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<tr>
<td>Tapentadol</td>
<td>1,195</td>
<td>&lt;0.1%</td>
<td>874</td>
<td>&lt;0.1%</td>
<td>503</td>
<td>&lt;0.1%</td>
<td>382</td>
<td>&lt;0.1%</td>
<td>328</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>419</td>
<td>&lt;0.1%</td>
<td>486</td>
<td>&lt;0.1%</td>
<td>342</td>
<td>&lt;0.1%</td>
<td>244</td>
<td>&lt;0.1%</td>
<td>215</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Pentazocine/Naloxone</td>
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<td>&lt;0.1%</td>
<td>319</td>
<td>&lt;0.1%</td>
<td>290</td>
<td>&lt;0.1%</td>
<td>280</td>
<td>&lt;0.1%</td>
<td>182</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Transmucosal Immediate-Release Fentanyl (TIRF)</td>
<td>110</td>
<td>&lt;0.1%</td>
<td>43</td>
<td>&lt;0.1%</td>
<td>35</td>
<td>&lt;0.1%</td>
<td>16</td>
<td>&lt;0.1%</td>
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<td>&lt;0.1%</td>
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<td>Opioid</td>
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<td>34</td>
<td>&lt;0.1%</td>
<td>32</td>
<td>&lt;0.1%</td>
<td>34</td>
<td>&lt;0.1%</td>
<td>35</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>96</td>
<td>&lt;0.1%</td>
<td>81</td>
<td>&lt;0.1%</td>
<td>34</td>
<td>&lt;0.1%</td>
<td>17</td>
<td>&lt;0.1%</td>
<td>19</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Oxycodone/Ibuprofen</td>
<td>216</td>
<td>&lt;0.1%</td>
<td>157</td>
<td>&lt;0.1%</td>
<td>84</td>
<td>&lt;0.1%</td>
<td>38</td>
<td>&lt;0.1%</td>
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<td>&lt;0.1%</td>
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<td>&lt;0.1%</td>
<td>--</td>
<td>--</td>
<td>2</td>
<td>&lt;0.1%</td>
<td>2</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Pentazocine/Acetaminophen</td>
<td>113</td>
<td>&lt;0.1%</td>
<td>81</td>
<td>&lt;0.1%</td>
<td>63</td>
<td>&lt;0.1%</td>
<td>12</td>
<td>&lt;0.1%</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Meperidine/Promethazine</td>
<td>9</td>
<td>&lt;0.1%</td>
<td>1</td>
<td>&lt;0.1%</td>
<td>--</td>
<td>--</td>
<td>1</td>
<td>&lt;0.1%</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Propoxyphene/Acetaminophen</td>
<td>6</td>
<td>&lt;0.1%</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td><strong>Extended-Release/Long-Acting (ER/LA) Opioids</strong></td>
<td>15,781</td>
<td>0.5%</td>
<td>15,028</td>
<td>0.5%</td>
<td>14,025</td>
<td>0.5%</td>
<td>13,112</td>
<td>0.5%</td>
<td>11,806</td>
<td>0.5%</td>
</tr>
<tr>
<td>Morphine</td>
<td>3,499</td>
<td>22.2%</td>
<td>3,548</td>
<td>23.6%</td>
<td>3,264</td>
<td>23.3%</td>
<td>3,198</td>
<td>24.4%</td>
<td>3,133</td>
<td>26.5%</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>4,723</td>
<td>29.9%</td>
<td>4,313</td>
<td>28.7%</td>
<td>4,042</td>
<td>28.8%</td>
<td>3,549</td>
<td>27.1%</td>
<td>3,025</td>
<td>25.6%</td>
</tr>
<tr>
<td>Methadone</td>
<td>2,889</td>
<td>18.3%</td>
<td>2,658</td>
<td>17.7%</td>
<td>2,749</td>
<td>19.6%</td>
<td>2,516</td>
<td>19.2%</td>
<td>2,410</td>
<td>20.4%</td>
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<tr>
<td>Fentanyl Transdermal</td>
<td>3,293</td>
<td>20.9%</td>
<td>3,161</td>
<td>21.0%</td>
<td>2,524</td>
<td>18.0%</td>
<td>2,476</td>
<td>18.9%</td>
<td>2,192</td>
<td>18.6%</td>
</tr>
<tr>
<td>Tramadol</td>
<td>886</td>
<td>5.6%</td>
<td>838</td>
<td>5.6%</td>
<td>858</td>
<td>6.1%</td>
<td>727</td>
<td>5.5%</td>
<td>570</td>
<td>4.8%</td>
</tr>
<tr>
<td>Buprenorphine Transdermal</td>
<td>142</td>
<td>0.9%</td>
<td>137</td>
<td>0.9%</td>
<td>212</td>
<td>1.5%</td>
<td>193</td>
<td>1.5%</td>
<td>218</td>
<td>1.9%</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>284</td>
<td>1.8%</td>
<td>212</td>
<td>1.4%</td>
<td>164</td>
<td>1.2%</td>
<td>133</td>
<td>1.0%</td>
<td>94</td>
<td>0.8%</td>
</tr>
<tr>
<td>Oxycodone/Acetaminophen</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>165</td>
<td>1.3%</td>
<td>66</td>
<td>0.6%</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>8</td>
<td>0.0%</td>
<td>87</td>
<td>0.6%</td>
<td>125</td>
<td>0.9%</td>
<td>107</td>
<td>0.8%</td>
<td>41</td>
<td>0.3%</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>41</td>
<td>0.3%</td>
<td>73</td>
<td>0.5%</td>
<td>87</td>
<td>0.6%</td>
<td>44</td>
<td>0.3%</td>
<td>35</td>
<td>0.3%</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>5</td>
<td>&lt;0.1%</td>
<td>18</td>
<td>0.2%</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Morphine/Naltrexone</td>
<td>17</td>
<td>0.1%</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>2</td>
<td>&lt;0.1%</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>


Reference ID: 3988377
Table 2. National estimates of total patients who received prescriptions dispensed for opioid analgesics, stratified by patient age*, from U.S. outpatient retail pharmacies, years 2011-2015

<table>
<thead>
<tr>
<th>Year 2011</th>
<th>Year 2012</th>
<th>Year 2013</th>
<th>Year 2014</th>
<th>Year 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (N)</td>
<td>%</td>
<td>Patients (N)</td>
<td>%</td>
<td>Patients (N)</td>
</tr>
<tr>
<td><strong>Total Patients on Opioid Analgesics</strong></td>
<td>74,354,914</td>
<td>100.0%</td>
<td>74,170,663</td>
<td>100.0%</td>
</tr>
<tr>
<td>0-16 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 years</td>
<td>3,696,469</td>
<td>5.0%</td>
<td>3,512,496</td>
<td>4.7%</td>
</tr>
<tr>
<td>2-6 years</td>
<td>111,168</td>
<td>3.0%</td>
<td>105,326</td>
<td>3.0%</td>
</tr>
<tr>
<td>7-16 years</td>
<td>2,730,648</td>
<td>73.9%</td>
<td>2,611,444</td>
<td>74.3%</td>
</tr>
<tr>
<td>17+ years</td>
<td>70,656,695</td>
<td>95.0%</td>
<td>70,656,395</td>
<td>95.3%</td>
</tr>
<tr>
<td>Unknown Age</td>
<td>1,750</td>
<td>&lt;0.1%</td>
<td>1,772</td>
<td>&lt;0.1%</td>
</tr>
</tbody>
</table>


*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).

**Patient age subtotals may not sum exactly due to patients aging during the study period, and may be counted more than once in the individual age categories or time periods. For this reason, summing patients across patient age bands and time periods is not advisable and will result in overestimates of patient counts.

Reference ID: 3988377
Table 2a. National estimates of pediatric patients ages 0-1 years* who received prescriptions dispensed for opioid analgesics, stratified by active ingredient, from U.S. outpatient retail pharmacies, years 2011-2015

<table>
<thead>
<tr>
<th></th>
<th>Year 2011</th>
<th>Year 2012</th>
<th>Year 2013</th>
<th>Year 2014</th>
<th>Year 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Pediatric Patients on Opioid Analgesics</strong></td>
<td><strong>Members (N)</strong></td>
<td>%</td>
<td><strong>Members (N)</strong></td>
<td>%</td>
<td><strong>Members (N)</strong></td>
</tr>
<tr>
<td>0-1 years</td>
<td>3,696,469</td>
<td>100.0%</td>
<td>3,512,496</td>
<td>100.0%</td>
<td>3,020,392</td>
</tr>
<tr>
<td>Immediate-Release (IR) Opioids</td>
<td>109,885</td>
<td>98.8%</td>
<td>104,075</td>
<td>98.8%</td>
<td>81,720</td>
</tr>
<tr>
<td>Hydrocodone/Acetaminophen</td>
<td>30,998</td>
<td>28.2%</td>
<td>35,592</td>
<td>34.2%</td>
<td>36,930</td>
</tr>
<tr>
<td>Codeine/Acetaminophen</td>
<td>70,737</td>
<td>64.4%</td>
<td>58,983</td>
<td>56.7%</td>
<td>42,290</td>
</tr>
<tr>
<td>Tramadol</td>
<td>4,175</td>
<td>3.8%</td>
<td>4,694</td>
<td>4.5%</td>
<td>4,729</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>1,503</td>
<td>0.4%</td>
<td>476</td>
<td>0.5%</td>
<td>409</td>
</tr>
<tr>
<td>Morphine</td>
<td>111,168</td>
<td>3.0%</td>
<td>105,326</td>
<td>3.0%</td>
<td>82,839</td>
</tr>
<tr>
<td>Meperidine</td>
<td>142</td>
<td>0.1%</td>
<td>95</td>
<td>0.1%</td>
<td>82</td>
</tr>
<tr>
<td>Codeine</td>
<td>26</td>
<td>&lt;0.1%</td>
<td>23</td>
<td>&lt;0.1%</td>
<td>26</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>59</td>
<td>0.1%</td>
<td>68</td>
<td>0.1%</td>
<td>53</td>
</tr>
<tr>
<td>Hydrocodone/ibuprofen</td>
<td>80</td>
<td>0.1%</td>
<td>75</td>
<td>0.1%</td>
<td>41</td>
</tr>
<tr>
<td>Tramadol/acetaminophen</td>
<td>59</td>
<td>0.1%</td>
<td>69</td>
<td>0.1%</td>
<td>62</td>
</tr>
<tr>
<td>Opipl</td>
<td>6</td>
<td>&lt;0.1%</td>
<td>4</td>
<td>&lt;0.1%</td>
<td>4</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>17</td>
<td>&lt;0.1%</td>
<td>14</td>
<td>&lt;0.1%</td>
<td>--</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>1</td>
<td>&lt;0.1%</td>
<td>3</td>
<td>&lt;0.1%</td>
<td>--</td>
</tr>
<tr>
<td>Pentazocine/Naloxone</td>
<td>3</td>
<td>&lt;0.1%</td>
<td>3</td>
<td>&lt;0.1%</td>
<td>1</td>
</tr>
<tr>
<td>Transmucosal Immediate-Release Fentanyl (TIRF)</td>
<td>1</td>
<td>&lt;0.1%</td>
<td>3</td>
<td>&lt;0.1%</td>
<td>--</td>
</tr>
<tr>
<td>Oxycodone/ibuprofen</td>
<td>--</td>
<td>--</td>
<td>1</td>
<td>&lt;0.1%</td>
<td>--</td>
</tr>
<tr>
<td>Pentazocine/acetaminophen</td>
<td>--</td>
<td>--</td>
<td>1</td>
<td>&lt;0.1%</td>
<td>--</td>
</tr>
<tr>
<td><strong>Extended-Release/Long-Acting (ER/LA) Opioids</strong></td>
<td>1,377</td>
<td>1.2%</td>
<td>1,341</td>
<td>1.3%</td>
<td>1,185</td>
</tr>
<tr>
<td>Methadone</td>
<td>972</td>
<td>70.6%</td>
<td>905</td>
<td>67.5%</td>
<td>855</td>
</tr>
<tr>
<td>Fentanyl Transdermal</td>
<td>312</td>
<td>22.7%</td>
<td>326</td>
<td>24.3%</td>
<td>257</td>
</tr>
<tr>
<td>Morphine</td>
<td>43</td>
<td>3.1%</td>
<td>55</td>
<td>4.1%</td>
<td>32</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>26</td>
<td>1.9%</td>
<td>33</td>
<td>2.5%</td>
<td>25</td>
</tr>
<tr>
<td>Tramadol</td>
<td>12</td>
<td>0.9%</td>
<td>7</td>
<td>0.5%</td>
<td>3</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>7</td>
<td>0.5%</td>
<td>11</td>
<td>0.8%</td>
<td>9</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>--</td>
<td>--</td>
<td>3</td>
<td>0.2%</td>
<td>--</td>
</tr>
<tr>
<td>Buprenorphine Transdermal</td>
<td>6</td>
<td>0.4%</td>
<td>3</td>
<td>0.2%</td>
<td>5</td>
</tr>
<tr>
<td>Oxycodone/acetaminophen</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>


*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).

**Patient age subtotals may not sum exactly due to patients aging during the study period, and may be counted more than once in the individual age categories or time periods. For this reason, summing patients across patient age bands and time periods is not advisable and will result in overestimates of patient counts.

Reference ID: 3988377
Table 2b. National estimates of pediatric patients ages 2-6 years* who received prescriptions dispensed for opioid analgesics, stratified by active ingredient, from U.S. outpatient retail pharmacies, years 2011-2015

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Year 2011</th>
<th>Year 2012</th>
<th>Year 2013</th>
<th>Year 2014</th>
<th>Year 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients (N)</td>
<td>%</td>
<td>Patients (N)</td>
<td>%</td>
<td>Patients (N)</td>
</tr>
<tr>
<td>Total Pediatric Patients on Opioid Analgesics</td>
<td>3,696,469</td>
<td>100.0%</td>
<td>3,512,496</td>
<td>100.0%</td>
<td>3,020,392</td>
</tr>
<tr>
<td>Immediate-Release (IR) Opioids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Codeine/Acetaminophen</td>
<td>565,216</td>
<td>15.5%</td>
<td>509,105</td>
<td>14.5%</td>
<td>345,148</td>
</tr>
<tr>
<td>Hydrocodone/Acetaminophen</td>
<td>273,444</td>
<td>7.3%</td>
<td>230,757</td>
<td>6.6%</td>
<td>169,115</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>7,266</td>
<td>0.2%</td>
<td>7,266</td>
<td>0.2%</td>
<td>7,266</td>
</tr>
<tr>
<td>Tramadol</td>
<td>6,242</td>
<td>0.2%</td>
<td>6,242</td>
<td>0.2%</td>
<td>6,242</td>
</tr>
<tr>
<td>Meperidine</td>
<td>13,710</td>
<td>0.4%</td>
<td>13,710</td>
<td>0.4%</td>
<td>13,710</td>
</tr>
<tr>
<td>Morphine</td>
<td>702</td>
<td>0.0%</td>
<td>702</td>
<td>0.0%</td>
<td>702</td>
</tr>
<tr>
<td>Oxycodone/Acetaminophen</td>
<td>10,526</td>
<td>0.3%</td>
<td>10,526</td>
<td>0.3%</td>
<td>10,526</td>
</tr>
<tr>
<td>Codeine</td>
<td>162</td>
<td>0.0%</td>
<td>162</td>
<td>0.0%</td>
<td>162</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>156</td>
<td>0.0%</td>
<td>156</td>
<td>0.0%</td>
<td>156</td>
</tr>
<tr>
<td>Tramadol/Acetaminophen</td>
<td>67</td>
<td>0.0%</td>
<td>67</td>
<td>0.0%</td>
<td>67</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>3</td>
<td>0.0%</td>
<td>3</td>
<td>0.0%</td>
<td>3</td>
</tr>
<tr>
<td>Oxydorphone</td>
<td>3</td>
<td>0.0%</td>
<td>3</td>
<td>0.0%</td>
<td>3</td>
</tr>
<tr>
<td>Opiate</td>
<td>1</td>
<td>0.0%</td>
<td>1</td>
<td>0.0%</td>
<td>1</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>1</td>
<td>0.0%</td>
<td>1</td>
<td>0.0%</td>
<td>1</td>
</tr>
<tr>
<td>Pentazocine/Naloxone</td>
<td>3</td>
<td>0.0%</td>
<td>3</td>
<td>0.0%</td>
<td>3</td>
</tr>
<tr>
<td>Extended-Release/Long-Acting (ER/LA) Opioids</td>
<td>952</td>
<td>0.1%</td>
<td>1,007</td>
<td>0.1%</td>
<td>929</td>
</tr>
<tr>
<td>Fentanyl Transdermal</td>
<td>538</td>
<td>56.3%</td>
<td>499</td>
<td>49.9%</td>
<td>620</td>
</tr>
<tr>
<td>Methadone</td>
<td>291</td>
<td>30.6%</td>
<td>279</td>
<td>27.5%</td>
<td>208</td>
</tr>
<tr>
<td>Morphine</td>
<td>68</td>
<td>7.1%</td>
<td>70</td>
<td>6.8%</td>
<td>62</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>35</td>
<td>3.7%</td>
<td>35</td>
<td>3.4%</td>
<td>35</td>
</tr>
<tr>
<td>Tramadol</td>
<td>14</td>
<td>1.5%</td>
<td>15</td>
<td>1.4%</td>
<td>15</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>10</td>
<td>1.1%</td>
<td>11</td>
<td>1.0%</td>
<td>11</td>
</tr>
<tr>
<td>Butanorphine Transdermal</td>
<td>7</td>
<td>0.8%</td>
<td>7</td>
<td>0.7%</td>
<td>8</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>12</td>
<td>1.3%</td>
<td>12</td>
<td>1.2%</td>
<td>12</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>1</td>
<td>0.1%</td>
<td>1</td>
<td>0.1%</td>
<td>1</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1</td>
<td>0.1%</td>
<td>1</td>
<td>0.1%</td>
<td>1</td>
</tr>
</tbody>
</table>


*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).

**Patient age subtotals may not sum exactly due to patients aging during the study period, and may be counted more than once in the individual age categories or time periods. For this reason, summing patients across patient age bands and time periods is not advisable and will result in overestimates of patient counts.

Reference ID: 3988377
patients across patient age bands and time periods is not advisable and will result in overestimates of patient counts. **Patient age subtotals may not sum exactly due to patients aging during the study period, and may be counted more than once in the individual age categories or time periods. For this reason, summing patients across patient age bands and time periods is not advisable and will result in overestimates of patient counts.**

**Table 2c. National estimates of pediatric patients ages 7-16 years* who received prescriptions dispensed for opioid analgesics, stratified by active ingredient, from U.S. outpatient retail pharmacies, years 2011-2015**

<table>
<thead>
<tr>
<th></th>
<th>Year 2011</th>
<th>Year 2012</th>
<th>Year 2013</th>
<th>Year 2014</th>
<th>Year 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Pediatric Patients on Opioid Analgesics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients (N)</td>
<td>3,696,469</td>
<td>3,512,888</td>
<td>3,020,392</td>
<td>2,660,016</td>
<td>2,455,960</td>
</tr>
<tr>
<td>Patients (%)</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

**Immediate-Release (IR) Opioids**

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Year 2011</th>
<th>Year 2012</th>
<th>Year 2013</th>
<th>Year 2014</th>
<th>Year 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone/Acetaminophen</td>
<td>1,327,421</td>
<td>1,291,460</td>
<td>1,194,727</td>
<td>1,060,895</td>
<td>934,918</td>
</tr>
<tr>
<td>Codeine/Acetaminophen</td>
<td>1,212,133</td>
<td>1,099,363</td>
<td>883,374</td>
<td>748,098</td>
<td>721,016</td>
</tr>
<tr>
<td>Tramadol</td>
<td>112,428</td>
<td>135,812</td>
<td>143,319</td>
<td>169,933</td>
<td>172,905</td>
</tr>
<tr>
<td>Oxycodone/Acetaminophen</td>
<td>199,341</td>
<td>189,674</td>
<td>172,154</td>
<td>161,550</td>
<td>152,589</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>30,551</td>
<td>37,243</td>
<td>42,931</td>
<td>53,430</td>
<td>74,668</td>
</tr>
<tr>
<td>Meperidine</td>
<td>16,691</td>
<td>15,341</td>
<td>13,807</td>
<td>12,928</td>
<td>12,241</td>
</tr>
<tr>
<td>Hydrocodone/Ibuprofen</td>
<td>16,558</td>
<td>15,245</td>
<td>12,703</td>
<td>10,145</td>
<td>7,140</td>
</tr>
<tr>
<td>Tramadol/Acetaminophen</td>
<td>8,929</td>
<td>8,126</td>
<td>7,090</td>
<td>6,506</td>
<td>6,888</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>3,728</td>
<td>3,808</td>
<td>3,259</td>
<td>3,139</td>
<td>3,059</td>
</tr>
<tr>
<td>Morphine</td>
<td>2,183</td>
<td>2,222</td>
<td>2,302</td>
<td>2,379</td>
<td>2,291</td>
</tr>
<tr>
<td>Codeine</td>
<td>1,139</td>
<td>1,249</td>
<td>950</td>
<td>956</td>
<td>1,064</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>986</td>
<td>694</td>
<td>327</td>
<td>240</td>
<td>185</td>
</tr>
<tr>
<td>Pentazocine/Naloxone</td>
<td>391</td>
<td>290</td>
<td>106</td>
<td>81</td>
<td>74</td>
</tr>
<tr>
<td>Butorphan</td>
<td>166</td>
<td>163</td>
<td>106</td>
<td>81</td>
<td>74</td>
</tr>
<tr>
<td>Oxycodone/Ibuprofen</td>
<td>227</td>
<td>180</td>
<td>86</td>
<td>37</td>
<td>14</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>30</td>
<td>25</td>
<td>9</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Transmucosal Immediate-Release Fentanyl (TIRF)</td>
<td>41</td>
<td>18</td>
<td>9</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Opium</td>
<td>3</td>
<td>1</td>
<td>7</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Levorphan</td>
<td>1</td>
<td>1</td>
<td>--</td>
<td>--</td>
<td>3</td>
</tr>
<tr>
<td>Pentazocine/Acetaminophen</td>
<td>87</td>
<td>61</td>
<td>48</td>
<td>5</td>
<td>--</td>
</tr>
<tr>
<td>Meperidine/Promethazine</td>
<td>4</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Propoxyphene/Acetaminophen</td>
<td>1</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td><strong>Extended-Release/Long-Acting (ER/LA) Opioids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients (N)</td>
<td>7,613</td>
<td>7,673</td>
<td>6,763</td>
<td>6,554</td>
<td>5,853</td>
</tr>
<tr>
<td>Patients (%)</td>
<td>0.3%</td>
<td>0.3%</td>
<td>0.3%</td>
<td>0.3%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

**Oxycodone**

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Year 2011</th>
<th>Year 2012</th>
<th>Year 2013</th>
<th>Year 2014</th>
<th>Year 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone/Acetaminophen</td>
<td>2,100</td>
<td>2,863</td>
<td>2,579</td>
<td>2,096</td>
<td>1,765</td>
</tr>
<tr>
<td>Methadone</td>
<td>830</td>
<td>794</td>
<td>708</td>
<td>615</td>
<td>613</td>
</tr>
<tr>
<td>Tramadol</td>
<td>430</td>
<td>487</td>
<td>437</td>
<td>426</td>
<td>319</td>
</tr>
<tr>
<td>Fentanyl Transdermal</td>
<td>1,648</td>
<td>1,746</td>
<td>1,503</td>
<td>1,771</td>
<td>1,628</td>
</tr>
<tr>
<td>Morphine</td>
<td>1,782</td>
<td>1,875</td>
<td>1,610</td>
<td>1,543</td>
<td>1,537</td>
</tr>
<tr>
<td>Methadone</td>
<td>830</td>
<td>794</td>
<td>708</td>
<td>615</td>
<td>613</td>
</tr>
<tr>
<td>Tramadol</td>
<td>430</td>
<td>487</td>
<td>437</td>
<td>426</td>
<td>319</td>
</tr>
<tr>
<td>Buprenorphine Transdermal</td>
<td>59</td>
<td>55</td>
<td>86</td>
<td>92</td>
<td>75</td>
</tr>
<tr>
<td>Oxycodone/Acetaminophen</td>
<td>90</td>
<td>67</td>
<td>58</td>
<td>65</td>
<td>29</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>4</td>
<td>51</td>
<td>45</td>
<td>27</td>
<td>14</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>--</td>
<td>--</td>
<td>3</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7</td>
<td>16</td>
<td>15</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Morphine/Naltrexone</td>
<td>6</td>
<td>1</td>
<td>--</td>
<td>--</td>
<td>1</td>
</tr>
</tbody>
</table>


*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-15 years include patients less than 17 years old (16 years and 11 months).

**Patient age subtotals may not sum exactly due to patients aging during the study per od, and may be counted more than once in the individual age categories or time periods. For this reason, summing patients across patient age bands and time periods is not advisable and will result in overestimates of patient counts.*

Reference ID: 3988377
Table 3. Duration of therapy for selected immediate release (IR) and extended release (ER) opioids dispensed from US outpatient pharmacy settings to a sample* of pediatric patients ages 0-16 years, in 2015

<table>
<thead>
<tr>
<th>Products</th>
<th>Number of Patients</th>
<th>Days of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Median</td>
</tr>
<tr>
<td>Hydrocodone/acetaminophen</td>
<td>950,290</td>
<td>6.0</td>
</tr>
<tr>
<td>Codeine/acetaminophen</td>
<td>679,447</td>
<td>5.0</td>
</tr>
<tr>
<td>Oxycodone IR</td>
<td>79,117</td>
<td>6.0</td>
</tr>
<tr>
<td>Oxycodone ER</td>
<td>1,412</td>
<td>11.0</td>
</tr>
<tr>
<td>Morphine ER</td>
<td>1,325</td>
<td>13.0</td>
</tr>
<tr>
<td>Methadone oral</td>
<td>1,130</td>
<td>31.0</td>
</tr>
<tr>
<td>Fentanyl transdermal patches</td>
<td>529</td>
<td>31.0</td>
</tr>
</tbody>
</table>

* excludes patients with cash or unspecified prescriber specialty prescriptions.

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

Table 4. Estimated duration of therapy by deciles for a sample* of pediatric patients ages 0-16 years dispensed selected immediate release (IR) and extended release (ER) opioids, in the outpatient pharmacy setting, in 2015

<table>
<thead>
<tr>
<th>Products</th>
<th>Number of patients</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone/acetaminophen</td>
<td>950,290</td>
<td>1-3</td>
<td>3-4</td>
<td>4-4</td>
<td>4-5</td>
<td>5-6</td>
<td>6-6</td>
<td>6-7</td>
<td>7-9</td>
<td>9-12</td>
<td>12-365</td>
</tr>
<tr>
<td>Codeine/acetaminophen</td>
<td>679,447</td>
<td>1-3</td>
<td>3-4</td>
<td>4-4</td>
<td>4-4</td>
<td>4-5</td>
<td>5-6</td>
<td>6-6</td>
<td>6-8</td>
<td>8-11</td>
<td>11-365</td>
</tr>
<tr>
<td>Oxycodone IR</td>
<td>79,117</td>
<td>1-3</td>
<td>3-4</td>
<td>4-4</td>
<td>4-6</td>
<td>6-6</td>
<td>6-7</td>
<td>7-9</td>
<td>9-11</td>
<td>11-16</td>
<td>16-365</td>
</tr>
<tr>
<td>Oxycodone ER</td>
<td>1,412</td>
<td>1-4</td>
<td>4-5</td>
<td>5-6</td>
<td>6-7</td>
<td>8-11</td>
<td>11-11</td>
<td>12-16</td>
<td>16-31</td>
<td>31-49</td>
<td>49-365</td>
</tr>
<tr>
<td>Morphine ER</td>
<td>1,325</td>
<td>1-5</td>
<td>5-6</td>
<td>6-8</td>
<td>8-11</td>
<td>11-13</td>
<td>13-16</td>
<td>16-31</td>
<td>31-32</td>
<td>32-84</td>
<td>85-365</td>
</tr>
<tr>
<td>Methadone oral</td>
<td>1,130</td>
<td>1-6</td>
<td>6-10</td>
<td>11-16</td>
<td>16-28</td>
<td>29-31</td>
<td>31-46</td>
<td>46-67</td>
<td>68-120</td>
<td>121-259</td>
<td>263-365</td>
</tr>
<tr>
<td>Fentanyl transdermal patches</td>
<td>529</td>
<td>1-6</td>
<td>6-13</td>
<td>13-16</td>
<td>16-30</td>
<td>30-31</td>
<td>31-32</td>
<td>32-58</td>
<td>58-93</td>
<td>93-238</td>
<td>238-365</td>
</tr>
</tbody>
</table>

* excludes patients with cash or unspecified prescriber specialty prescriptions

<table>
<thead>
<tr>
<th>Total Prescriptions Dispensed for Opioid Analgesics</th>
<th>Year 2015</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0-1 years</strong></td>
<td><strong>226,176,312</strong></td>
<td><strong>100.0%</strong></td>
</tr>
<tr>
<td>Immediate-Release (IR) Opioids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatrician</td>
<td>69,707</td>
<td>97.3%</td>
</tr>
<tr>
<td>Hospitalist</td>
<td>7,198</td>
<td>10.3%</td>
</tr>
<tr>
<td>Urology</td>
<td>7,885</td>
<td>11.3%</td>
</tr>
<tr>
<td>Emergency Medicine</td>
<td>4,155</td>
<td>6.0%</td>
</tr>
<tr>
<td>Nurse Practitioner</td>
<td>3,855</td>
<td>5.5%</td>
</tr>
<tr>
<td>All Others</td>
<td>24,181</td>
<td>34.7%</td>
</tr>
<tr>
<td>Extended-Release/Long-Acting (ER/LA) Opioids</td>
<td>1,909</td>
<td>2.7%</td>
</tr>
<tr>
<td>Pediatrician</td>
<td>989</td>
<td>51.8%</td>
</tr>
<tr>
<td>Unspecified</td>
<td>200</td>
<td>10.5%</td>
</tr>
<tr>
<td>Neonatal-Perinatal Medicine</td>
<td>168</td>
<td>8.8%</td>
</tr>
<tr>
<td>Hospitalist</td>
<td>164</td>
<td>8.6%</td>
</tr>
<tr>
<td>Primary Care Practitioners</td>
<td>125</td>
<td>6.5%</td>
</tr>
<tr>
<td>All Others</td>
<td>263</td>
<td>13.8%</td>
</tr>
<tr>
<td><strong>2-6 years</strong></td>
<td><strong>489,190</strong></td>
<td><strong>0.2%</strong></td>
</tr>
<tr>
<td>Immediate-Release (IR) Opioids</td>
<td>487,710</td>
<td>99.7%</td>
</tr>
<tr>
<td>Dentist</td>
<td>94,666</td>
<td>19.4%</td>
</tr>
<tr>
<td>Otolaryngology</td>
<td>90,256</td>
<td>18.5%</td>
</tr>
<tr>
<td>Pediatrician</td>
<td>87,345</td>
<td>17.9%</td>
</tr>
<tr>
<td>Emergency Medicine</td>
<td>42,422</td>
<td>8.7%</td>
</tr>
<tr>
<td>Physician Assistant</td>
<td>25,613</td>
<td>5.3%</td>
</tr>
<tr>
<td>All Others</td>
<td>147,408</td>
<td>30.2%</td>
</tr>
<tr>
<td>Extended-Release/Long-Acting (ER/LA) Opioids</td>
<td>1,480</td>
<td>0.3%</td>
</tr>
<tr>
<td>Pediatrician</td>
<td>484</td>
<td>32.7%</td>
</tr>
<tr>
<td>Primary Care Practitioners</td>
<td>264</td>
<td>17.8%</td>
</tr>
<tr>
<td>Unspecified</td>
<td>211</td>
<td>14.3%</td>
</tr>
<tr>
<td>Nurse Practitioner</td>
<td>161</td>
<td>10.9%</td>
</tr>
<tr>
<td>Internal Medicine</td>
<td>102</td>
<td>6.9%</td>
</tr>
<tr>
<td>All Others</td>
<td>258</td>
<td>17.4%</td>
</tr>
<tr>
<td><strong>7-16 years</strong></td>
<td><strong>2,427,261</strong></td>
<td><strong>1.1%</strong></td>
</tr>
<tr>
<td>Immediate-Release (IR) Opioids</td>
<td>2,415,455</td>
<td>99.5%</td>
</tr>
<tr>
<td>Dentist</td>
<td>709,806</td>
<td>29.4%</td>
</tr>
<tr>
<td>Emergency Medicine</td>
<td>253,681</td>
<td>10.5%</td>
</tr>
<tr>
<td>Pediatrician</td>
<td>244,256</td>
<td>10.1%</td>
</tr>
<tr>
<td>Orthopedic Surgery</td>
<td>188,833</td>
<td>7.8%</td>
</tr>
<tr>
<td>Physician Assistant</td>
<td>178,385</td>
<td>7.4%</td>
</tr>
<tr>
<td>All Others</td>
<td>840,494</td>
<td>34.8%</td>
</tr>
<tr>
<td>Extended-Release/Long-Acting (ER/LA) Opioids</td>
<td>11,806</td>
<td>0.5%</td>
</tr>
<tr>
<td>Pediatrician</td>
<td>4,102</td>
<td>34.7%</td>
</tr>
<tr>
<td>Orthopedic Surgery</td>
<td>1,402</td>
<td>11.9%</td>
</tr>
<tr>
<td>Nurse Practitioner</td>
<td>1,290</td>
<td>10.9%</td>
</tr>
<tr>
<td>Hospitalist</td>
<td>923</td>
<td>7.8%</td>
</tr>
<tr>
<td>Physician Assistant</td>
<td>766</td>
<td>6.5%</td>
</tr>
<tr>
<td>All Others</td>
<td>3,323</td>
<td>28.1%</td>
</tr>
<tr>
<td><strong>17+ years</strong></td>
<td><strong>221,887,696</strong></td>
<td><strong>98.1%</strong></td>
</tr>
<tr>
<td>Unknown Age</td>
<td>1,300,549</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

Table 6. Diagnoses associated with the use of opioid analgesics as reported by U.S. office-based physician surveys, stratified by patient age, year 2015

<table>
<thead>
<tr>
<th>Age</th>
<th>Year 2015</th>
<th>Uses</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-16 years</td>
<td></td>
<td>78,337,000</td>
<td>100.0%</td>
</tr>
<tr>
<td>0-1 years</td>
<td></td>
<td>2,550,000</td>
<td>3.3%</td>
</tr>
<tr>
<td>0-1 years</td>
<td>Immediate-Release (IR) Opioids</td>
<td>99,000</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>Hernia (K40.9 and K43.9)</td>
<td>52,000</td>
<td>52.5%</td>
</tr>
<tr>
<td></td>
<td>Hypospadias, unspecified (Q54.9)</td>
<td>30,000</td>
<td>30.3%</td>
</tr>
<tr>
<td></td>
<td>Burn of unspecified degree of wrist and hand (T23.0)</td>
<td>9,000</td>
<td>9.2%</td>
</tr>
<tr>
<td></td>
<td>Neonatal withdrawal symptoms from maternal use of drugs of addiction (P96.1)</td>
<td>8,000</td>
<td>7.6%</td>
</tr>
<tr>
<td>2-6 years</td>
<td></td>
<td>495,000</td>
<td>19.4%</td>
</tr>
<tr>
<td>2-6 years</td>
<td>Immediate-Release (IR) Opioids</td>
<td>495,000</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>Injuries and burns (S42.x-T30.0)</td>
<td>191,000</td>
<td>38.6%</td>
</tr>
<tr>
<td></td>
<td>Hernia (K40.9, K42.0, and K42.9)</td>
<td>93,000</td>
<td>18.8%</td>
</tr>
<tr>
<td></td>
<td>Encounter for follow-up examination after completed treatment for conditions other than malignant neoplasm (Z09)</td>
<td>92,000</td>
<td>18.6%</td>
</tr>
<tr>
<td></td>
<td>Osteoarthritis, join disorders, and dorsoapthies (M19.9, M25.5, and M54.9)</td>
<td>44,000</td>
<td>8.9%</td>
</tr>
<tr>
<td></td>
<td>Unspecified abdominal pain (R10.9)</td>
<td>19,000</td>
<td>3.8%</td>
</tr>
<tr>
<td></td>
<td>Acute embolism and thrombosis of deep veins of lower extremity (I82.4)</td>
<td>17,000</td>
<td>3.4%</td>
</tr>
<tr>
<td></td>
<td>Ptosis of eyelid (H02.4)</td>
<td>14,000</td>
<td>2.8%</td>
</tr>
<tr>
<td></td>
<td>Presence of otological and audiological implants (Z96.2)</td>
<td>13,000</td>
<td>2.6%</td>
</tr>
<tr>
<td></td>
<td>Chronic tonsillitis and adenoiditis (J35.0)</td>
<td>11,000</td>
<td>2.2%</td>
</tr>
<tr>
<td></td>
<td>Chronic pain, not elsewhere classified (G89.2)</td>
<td>2,000</td>
<td>0.4%</td>
</tr>
<tr>
<td>7-16 years</td>
<td></td>
<td>1,956,000</td>
<td>76.7%</td>
</tr>
<tr>
<td>7-16 years</td>
<td>Immediate-Release (IR) Opioids</td>
<td>1,956,000</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>Injuries and burns (S00.x-T25.0)</td>
<td>1,032,000</td>
<td>52.8%</td>
</tr>
<tr>
<td></td>
<td>Encounter for follow-up examination after completed treatment for conditions other than malignant neoplasm (Z09)</td>
<td>404,000</td>
<td>20.7%</td>
</tr>
<tr>
<td></td>
<td>Diseases of the musculoskeletal system and connective tissue (M19.9-M79.6)</td>
<td>104,000</td>
<td>5.3%</td>
</tr>
<tr>
<td></td>
<td>Diseases of the skin and subcutaneous tissue (L03.0, L60.0, and L72.3)</td>
<td>83,000</td>
<td>4.2%</td>
</tr>
<tr>
<td></td>
<td>Congenital malformations and deformations of the musculoskeletal system (Q65.8, Q67.6, Q78.0)</td>
<td>66,000</td>
<td>3.4%</td>
</tr>
<tr>
<td></td>
<td>Diseases of the genitourinary system (N47, N62, and N63)</td>
<td>63,000</td>
<td>3.2%</td>
</tr>
<tr>
<td></td>
<td>Neoplasms (C72.3 and D23.9)</td>
<td>50,000</td>
<td>2.6%</td>
</tr>
<tr>
<td></td>
<td>Sickle-cell disease without crisis (D57.1)</td>
<td>46,000</td>
<td>2.4%</td>
</tr>
<tr>
<td></td>
<td>Diseases of the ear and mastoid process (H66.9 and H92.0)</td>
<td>32,000</td>
<td>1.6%</td>
</tr>
<tr>
<td></td>
<td>Thyrotoxicosis with diffuse goiter (E05.0)</td>
<td>28,000</td>
<td>1.4%</td>
</tr>
<tr>
<td></td>
<td>Unilateral inguinal hernia, without obstruction or gangrene (K40.9)</td>
<td>24,000</td>
<td>1.2%</td>
</tr>
<tr>
<td></td>
<td>All other diagnoses</td>
<td>24,000</td>
<td>1.2%</td>
</tr>
<tr>
<td>17+ years</td>
<td></td>
<td>74,091,000</td>
<td>94.6%</td>
</tr>
<tr>
<td>Unknown Age</td>
<td></td>
<td>1,696,000</td>
<td>2.2%</td>
</tr>
</tbody>
</table>


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APPENDIX B: DATABASE DESCRIPTIONS

**IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail**

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

**IMS Health, National Prescription Audit**

The National Prescription Audit (NPA™) measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures both what is prescribed by the physician and what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies.

NPA receives over 3.5 billion prescription claims per year, captured from a sample of the universe of approximately 59,400 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 88% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 45 - 75% (varies by class and geography) of mail service pharmacies and approximately 70-85% of long-term care pharmacies. Data are available on-line for 72- rolling months with a lag of 1 month.

**Symphony Health Solutions’ Integrated Dataverse® (IDV)**

Symphony Health Solutions’ Integrated Dataverse® (IDV) contains longitudinal patient data sources that capture adjudicated prescription, medical, and hospital claims across the United States for all payment types, including commercial plans, Medicare Part D, cash, assistance programs, and Medicaid. The IDV contains over 10 billion prescriptions claims linked to over 220 million unique prescription patients of with an average of 4.2 years of prescription drug history. Claims from hospital and physician practices include over 190 million patients with CPT/HCPCS medical procedure history as well as ICD-9 diagnosis history of which nearly 140 million prescription drug patients are linked to a diagnosis. The overall sample represents over 54,000 pharmacies, 1,500 hospitals, 800 outpatient facilities, and 80,000 physician practices.

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

Encuity Research, LLC., TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products

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mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.
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/s/

TRACY M PHAM  
09/20/2016  

JENNIE Z WONG  
09/21/2016  

MOHAMED A MOHAMOUD  
09/21/2016  

RAJDEEP K GILL  
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drug use data cleared by the data vendors  

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