FDA Briefing Document

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

September 15-16, 2016

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 the issue of how to best study opioid analgesics in pediatric populations 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.

FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

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

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DIVISION DIRECTOR MEMO

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

M E M O R A N D U M

DATE: August 22, 2016

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)
Pediatric Advisory Committee (PAC)

RE: Joint advisory committee meeting to discuss the appropriate development plans for establishing the safety and efficacy of prescription opioid analgesics for pediatric patients.

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 joint meeting of AADPAC, DSaRM, and PAC we will be discussing the development of opioid analgesics for pediatric patients. This is a broad topic and encompasses a number of important areas for consideration. We will ask for your advice about the appropriate use of opioid analgesics in children with pain and which patients are appropriate for study. We will ask you to comment on our current study requirements for immediate-release and extended-release opioids and our use of extrapolation of efficacy from adults to children over the age of 2. And we will also ask for your advice on managing the risks associated with the use of opioids in pediatric patients. There will be a number of presentations to help set the background for the

discussion. Presentations from FDA staff will include the regulations under which pediatric clinical trials are conducted, ethical considerations with pediatric clinical trials, and the current extent of opioid use in pediatric patients using available prescription data. We will also present a review of the labeling available to help clinicians manage pediatric patients, as well as a list of the pending studies required under the Pediatric Research Equity Act (PREA). We will then present the types of pediatric studies required of sponsors, the rationale for the use of extrapolation, and some of the associated challenges.

We have invited a number of experts to present information on the clinical management of pain in children including the use of immediate-release and extended-release opioids in clinical practice. We will hear about the types of risk management considered appropriate for the safety issues associated with the management of pain in children using opioids, and some of the data on the consequences of untreated pain. There will be a presentation about what is known about the risk for misuse, abuse and addiction in children who have been prescribed opioids for the management of pain. The challenges associates with the study of analgesics in pediatric clinical trials will also be presented.

Draft Discussion Points

1. Discuss the use of opioid analgesics in pediatric patients and the factors that impact decisions to prescribe these drugs in this population, noting the types of patients that are appropriate, medical conditions, safety, and other factors you believe are important for proper patient selection.

2. Discuss the appropriate pediatric populations (types of pain, age groups) for the study of immediate-release opioid analgesics and extended/long-acting opioid analgesics. If you do not agree that such studies should be conducted, discuss the reasons for that conclusion.

3. Discuss the current approach required by FDA for studying opioid analgesics in pediatric patients, including the use of extrapolation of efficacy from adults to pediatric patients ages 2 to <17 years based on expected similar systemic exposures between adults and pediatric patients.

4. Discuss the Division's current approach to pediatric opioid analgesic study designs and whether you agree, or recommend other designs that may be likely to result in successful studies and discuss ways to address the challenges of finding qualified study sites and investigators and low patient enrollment.

5. Discuss safety concerns associated with the use and study of opioids in pediatric patients and whether patient selection or management of these risks should differ from adults.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs – ODE IV
Division of Pediatric and Maternal Health

M E M O R A N D U M

DATE: August 24, 2016

FROM: Lynne Yao, MD
Director, Division of Pediatric and Maternal Health, CDER

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

RE: Background Document: Pediatric Drug Development Legislation

Historically, many drugs approved for use in adults were not studied in children. Because of the lack of adequate safety, efficacy and dosing information in children, medications were often administered "off label" to children. Safety and efficacy were also simply assumed to be the same in the pediatric and the adult population and did not take into account both known and potential safety and efficacy differences that may be present in a growing and developing pediatric patient.

Over the last two decades, FDA has worked to address the problem of inadequate testing of drugs in pediatric populations and inadequate pediatric use information in drug and biological product labeling. These efforts include offering incentives and requiring sponsors to conduct pediatric clinical studies. In 1994, FDA required manufacturers of marketed drugs to determine whether existing data were sufficient to support additional pediatric labeling, and to submit such information to FDA to seek approval of additional pediatric labeling. Although the 1994 rule addressed submission of data already existing to support pediatric labeling, this rule did not directly address the lack of adequate pediatric use information for the majority marketed drugs and biological products. In 1997, the Food and Drug Administration Modernization Act (FDAMA) allowed sponsors to receive an additional 6 months of marketing exclusivity for voluntary completion of pediatric clinical studies outlined in a Written Request (WR) issued by FDA. The Written Request includes details of study design, number of patients needed, and

important safety and efficacy endpoints to be measured. The Written Request also includes a due date for submission of the study data to the FDA. In 2002, this program was reauthorized under the Best Pharmaceuticals for Children Act (BPCA).

In addition, a requirement for pediatric clinical studies was first established as the Pediatric Rule in 1998 and later codified under the Pediatric Research Equity Act (PREA) in 2003. Under PREA, drug developers are required to provide FDA with a pediatric assessment of new drug applications submitted for new active ingredients, indications, dosage forms, dosing regimens, and routes of administration. A pediatric assessment must include data adequate to assess the dosing, safety, and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations. Unlike BPCA, PREA applies only to those drugs developed for diseases and/or conditions that occur in both the adult and pediatric populations. Drugs that have been granted Orphan Designation (i.e., intended to treat rare diseases) are exempt from PREA. BPCA and PREA are designed to work together to increase the inclusion of pediatric information in product labeling. Both BPCA and PREA were substantially revised in 2007 under the Food and Drug Administration Amendments Act (FDAAA) as FDA and industry gained experience in the implementation of the laws and in pediatric product development in general. In 2010, the Biologics Price Competition and Innovation Act (BPCIA) extended the provisions of BPCA to biological products, allowing an additional 6 months of exclusivity for voluntary completion of pediatric clinical studies outlined in a Written Request (WR) issued by FDA. In addition, FDA is required to establish an internal committee to carry out the activities under BPCA and PREA. This internal committee, known as the Pediatric Review Committee includes FDA experts in clinical pharmacology, statistics, chemistry, ethics, legal issues, and other pediatric expertise pertaining to the pediatric products under review. This process for review of pediatric studies submitted under BPCA and PREA, greatly decreases the need to convene an advisory committee meeting. For example, in 2014, FDA approved pediatric labeling changes under BPCA and/PREA in 36 different products, none of which were discussed at by an advisory committee. In 2015, FDA approved 53 labeling changes under BPCA and/or PREA and only 2 (fluticasone furoate /vilanterol inhalation powder; and mepolizumab) were discussed during the review of the original application in adults (including patients with 12 years of age and older), and not related to a pediatric-specific issue.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Office of the Commissioner
Office of Special Medical Programs (OSMP)
Office of Pediatric Therapeutics (OPT)

Date: August 26, 2016

Reviewer: Robert "Skip" Nelson, M.D., PhD.
Deputy Director and Senior Pediatric Ethicist, OPT

Subject: Additional Safeguards for Children in Research (21 CFR 50, Subpart D)

Historically, children were viewed as vulnerable subjects who should be protected from the risks of research. The result was a paucity of safety and effectiveness data that made the use of therapeutic agents a virtual uncontrolled experiment whenever they were prescribed for children. The lack of safety and efficacy data in children and neonates means that physicians frequently prescribe outside the terms of the product approval ("off-label") with regard to dose, age group, route of administration, indication, or using modified or extemporaneous formulations. The vulnerability of children stems from a number of factors. Children commonly lack mature decision-making capacity; they are subject to the authority of others; they may defer in ways that can mask underlying dissent; and their rights and interests may be socially undervalued. As with adults, children may have acute medical conditions requiring immediate decisions without adequate time for education and deliberation; they may have serious medical conditions that cannot be effectively treated; and they may lack important socially distributed goods that would be provided as a consequence of research participation. Parental permission and child assent procedures alone cannot mitigate these vulnerabilities. Rather, studies in the pediatric population must be designed to minimize risk and maximize the possibility of therapeutic benefit.

The additional protections for children to be enrolled in a clinical investigation can be ordered into three protective domains, with each protection building on an adequate response to the prior protection. First, the enrollment of children in a clinical investigation must be considered scientifically necessary before the evaluation of whether the research interventions or procedures present an appropriate balance of risk and potential benefit. Second, a clinical investigation must be found to have an appropriate balance of risk and potential benefit before invoking the third protection of parental permission and child assent. This document does not discuss parental permission or child assent.

The Ethical Principle of Scientific Necessity

The ethical principle of "scientific necessity" holds that children should not be enrolled in a clinical investigation unless it is necessary to achieve an important scientific and/or public health objective concerning the health and welfare of children. For example, answering an "important scientific question" may generate information that is necessary and timely for establishing the appropriate pediatric use of investigational therapeutics. A corollary is that children should not

be enrolled in studies that are duplicative or unlikely to yield important knowledge applicable to children about the product or condition under investigation. A major public health objective of FDA-regulated pediatric clinical trials is to establish the dosing, safety and efficacy of investigational products sufficiently to support concurrent licensure of products for both the pediatric and adult populations. Deviations from this default position may be warranted when safety or efficacy considerations prevent or delay pediatric investigations.

The ethical principle of "scientific necessity" is grounded in regulations and/or guidelines governing human subject protections worldwide. For example, FDA regulations require that risks to subjects are minimized by eliminating unnecessary procedures, and that the selection of subjects must be equitable (21 CFR 56.111). Consistent with the recommendations of the US National Commission, equitable selection requires that subjects who are capable of informed consent (i.e., competent adults) should be enrolled prior to subjects who cannot consent (e.g., children).[1] The principle of equitable selection is based on the ability of an adult to assess whether the risks of research are justified either by the possibility for direct clinical benefit or by the knowledge that may be obtained. The additional safeguards for children enrolled in research places limits on the research risks to which children may be exposed given the child's inability to make the same assessment.

Timing of Pediatric Studies

An unintended consequence of the rigid adherence to the principle of equitable selection was the exclusion of children from many clinical investigations that would have benefited this vulnerable population. Nevertheless, when appropriate, a sequential approach to a pediatric research program may be necessary to generate sufficient adult human data to support either 1) an acceptably low risk of the experimental intervention or procedure absent any prospect of direct benefit (the low risk pathway, using 21 CFR 50.51 and 50.53) or 2) a sufficient prospect of direct benefit (PDB) to justify the risks in the higher risk pathway (using 21 CFR 50.52).

The criteria for initiating a clinical trial in children under the higher risk pathway is that sufficient "proof of concept" for a prospect of direct benefit exists that justifies exposing children to the known (and perhaps unknown or theoretical) risks of the intervention. Adult data may be important in establishing the evidence in support of this justification. However, once there are sufficient adult data on which to make this judgment, pediatric development should proceed without further delay. In other words, when appropriate, adults should be enrolled prior to adolescents and younger children only to establish the data needed in support of the judgment that the risks of introducing the intervention in children are justified by the prospect of direct benefit (21 CFR 50.52). Once this threshold has been reached, pediatric product development should proceed, even if an appropriate adult disease population exists.

If the product is being developed for an indication that occurs in both children and adults, the goal should be concurrent licensure unless there are safety concerns that would delay or even preclude pediatric studies. Adult and pediatric development may proceed either sequentially or

[1] Department of Health Education and Welfare. Research Involving Children: Report and Recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Federal Register. 1978;43(9):2083-114.

concurrently, depending on the product and factors such as the severity of the disease, anticipated risks to children and availability of alternate treatments. However, concurrent development still requires sufficient information about PDB in children to support initiating pediatric trials. If safety or efficacy results of adult trials are necessary to inform pediatric development, sequential development may be necessary. Sequential development may be considered for certain products in which, for example, serious safety concerns exist. Frequently, opioid analgesic products are developed following a sequential approach because of the safety concerns with these products. However, off-label pediatric use of such products is likely to occur once they are marketed for the adult indication, and in the absence of pediatric studies prior to marketing, nothing will be known about dosing, safety or effectiveness of the drug for children who are exposed.

Importantly, sequential development does not necessarily mean that concurrent licensure cannot be achieved. For example, if a phase 2 study of an antiviral agent showed decreased viral burden in adult studies, this information may help to provide the proof of concept necessary to support PDB in children. Dosing and safety studies could then be performed in children while the pivotal efficacy trial was initiated in adults. Particularly if the efficacy of the agent were extrapolated to some or all subgroups of the pediatric population, sufficient pediatric data may be available at the conclusion of the adult phase III studies to support concurrent licensure.

Appropriate Balance of Risks and Potential Benefit

Title 21 CFR Part 50, subpart D (subpart D) provides additional safeguards to children enrolled in clinical investigations. Before a pediatric trial may proceed, subpart D requires both (1) an assessment of the level of risk that the interventions and/or procedures included in a clinical trial would pose to pediatric subjects (i.e., minimal risk, slightly more than minimal risk, or greater than minimal risk) and (2) of the anticipated outcome or consequence of the interventions and/or procedures (i.e., the prospect of direct clinical benefit to subjects, the development of generalizable knowledge about the subjects' disorder or condition, or the opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children).

The additional protections for children enrolled in research fall into two main categories: (1) absent any prospect of direct benefit to the enrolled child, the intervention or procedure must present either minimal risk (21 CFR 50.51) or a minor increase over minimal risk (21 CFR 50.53) under the "lower risk" pathway, or (2) the intervention or procedure must present a prospect of direct benefit that is sufficient to justify greater risks (i.e., the "higher" risk pathway under 21 CFR 50.52). A clinical investigation that is not approvable under either the lower or higher risk pathways may be referred by an institutional review board (IRB) for federal panel review under 21 CFR 50.54 for a determination as to whether the clinical investigation meets the requirements of subpart D regulations.

<u>Low Risk Pathway</u>

There is general consensus that a child's exposure to risk in pediatric research must be low in the absence of direct therapeutic benefit to that child. For example, for research on non-consenting subjects that does not offer direct therapeutic benefit, the International Conference on

Harmonisation (ICH) E6 Guidelines specify that "the foreseeable risks to the subjects are low" and that "the negative impact on the subjects' well-being is minimized and low."[2] We will review the two categories of research in subpart D that comprise the low risk pathway: "minimal risk" and "minor increase over minimal risk" in the context of no direct benefit for the individual pediatric participant.

Minimal Risk

21 CFR 50.51 uses the term "minimal risk" which is defined as "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" (21 CFR 50.3k).

The U.S. National Commission defined minimal risk as the risks normally encountered in the daily life or routine examination of healthy children.[3] The subsequent omission of "healthy children" from the definition may allow for a "relativistic interpretation" indexed to the research participants' own experiences. However, three national advisory committees (the Secretary's Advisory Committee on Human Research Protections [SACHRP], the Institute of Medicine [IOM], and the National Human Research Protections Advisory Committee [NHRPAC]) have agreed that the definition of 'minimal risk' should be interpreted as those risks of daily life encountered by normal, average, healthy children living in a safe environment.[4] This interpretation is intended to prevent children who may be exposed to greater risk in their daily lives (e.g. from living in an unsafe environment) from being exposed to greater risk in research than would be allowable for children living in safer environments.

Examples of minimal risk interventions may include "modest changes in diet or schedule, physical examination, obtaining blood and urine specimens …developmental assessments… most questionnaires, observational techniques, noninvasive physiological monitoring, [and] psychological tests and puzzles."[5] Other examples include "obtaining stool samples, administering electroencephalograms, … [and] a taste test of an excipient or tests of devices involving temperature readings orally or in the ear."[6] However, federal panels clearly indicate that risk may be cumulative. For example, the number of procedures included in a protocol or the number of times that an individual procedure is repeated in a given period of time may be a factor in assessing the risk. "Although a single blood draw by needle stick normally involves

[2] International Conference on Harmonisation (ICH). ICH Harmonised Tripartite Guideline - Guideline for Good Clinical Practice E6(R1) 1996 [February 27, 2015]. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf.
[3] Department of Health Education and Welfare. Research Involving Children: Report and Recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Federal Register. 1978;43(9):2083-114.
[4] Institute of Medicine. IOM Committee on Clinical Research Involving Children: Ethical Conduct of Clinical Research Involving Children. 2010/07/30 ed. Field MJ, Behrman RE, editors. Washington DC: National Academies Press (US); 2004.
[5] Department of Health Education and Welfare. Research Involving Children: Report and Recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Federal Register. 1978;43(9):2083-114.
[6] Food and Drug Administration. FDA Interim Rule, Code of Federal Regulations Title 21 CFR 50 Subpart D Federal Register Vol. 66, No. 79 April 24, 2001.

minimal harm or discomfort, multiple needle sticks for blood draws in a short period could, depending on the child's age and other circumstances, present more than minimal risk of harm or discomfort."[7]

Minor Increase over Minimal Risk

FDA regulations also include a category of "minor increase over minimal risk" (21 CFR 50.53). An intervention or procedure approved under this category must also involve "experiences to subjects that are reasonably commensurate with those inherent in their actual or expected… situations" and be "likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition." According to the National Commission, the increase in risk allowable under this category was intended to be "slight", and such risks should involve "no significant threat" to the child's health or wellbeing. "Given this conservative limit, the… promise of [substantial future benefits to children other than the subject] does justify research which goes beyond, but only slightly beyond, minimal risk."[8] The justification for this classification also includes: 1) the increased risk is warranted due to scientific necessity and 2) conscientious parents can be entrusted with the authority to evaluate this level of non-beneficial risk exposure.[9]

According to SACHRP, when evaluating risk an IRB should take into account the proposed procedure, population under study, and the qualifications of the research personal. Echoing the National Commission, SACHRP recommended that the increase in the probability and magnitude of harm should only be "slightly" more than minimal risk, any potential harms associated with the procedure should be "transient and reversible", and there should be no or an extremely small probability that participants will experience pain, discomfort, stress, or harm associated with the procedure that is severe.[10] Even if the average risk associated with an intervention or procedure is thought to be low, if the risk estimate is unknown, reflects a large degree of variability, or has not been adequately characterized, then the risks of an intervention or procedure cannot be considered only a minor increase over minimal risk. Both NHRPAC and the IOM concluded that what constitutes a minor increase in research involving children should not allow for a higher threshold for children with high-risk or high-burden conditions than for children with less serious conditions.[11,12] In addition, the application of this category of research

[7] Institute of Medicine. IOM Committee on Clinical Research Involving Children: Ethical Conduct of Clinical Research Involving Children. 2010/07/30 ed. Field MJ, Behrman RE, editors. Washington DC: National Academies Press (US); 2004.
[8] Department of Health Education and Welfare. Notice of Proposed Rule-Making: Subpart D--Additional Protections for Children. Federal Register 1978;43:31785.
[9] Institute of Medicine. IOM Committee on Clinical Research Involving Children: Ethical Conduct of Clinical Research Involving Children. 2010/07/30 ed. Field MJ, Behrman RE, editors. Washington DC: National Academies Press (US); 2004.
[10] Secretary's Advisory Committee on Human Research Protections. Meeting Minutes April 18, 2005 [December 1, 2014]. Available from: http://www hhs.gov/ohrp/archive/sachrp/mtgings/mtg04-05/min04-05.pdf.
[11] Institute of Medicine. IOM Committee on Clinical Research Involving Children: Ethical Conduct of Clinical Research Involving Children. 2010/07/30 ed. Field MJ, Behrman RE, editors. Washington DC: National Academies Press (US); 2004.
[12] National Human Research Protections Advisory Committee (NHRPAC) - Clarifying Specific Portion of 45 CFR 46 Subpart D that Governs Children's Research [cited 215 2/27/2015]. Available from: http://www.hhs.gov/ohrp/archive/nhrpac/documents/nhrpac16.pdf.

includes several key concepts: "disorder or condition," "vital importance," and "reasonably commensurate" as discussed in the following paragraphs.

"*Disorder or condition*" can be defined as a set of "specific physical, psychological, neuro-developmental, or social characteristics" that scientific evidence or clinical knowledge has shown to compromise the child's health or "to increase risk of developing a health problem in the future."[13] Therefore, a child could be healthy, but "at risk" for the condition that is the object of the research. Healthy (i.e., not-at-risk) children should be excluded from greater than minimal risk research without a prospect of direct benefit absent referral for review under 21 CFR 50.54.[14,15]

Consistent with this definition, the IOM report listed four examples of "at risk" conditions that may enable the enrollment of otherwise healthy children into research that posed a minor increase over minimal risk. Children who are obese may be considered "at risk" of type 2 diabetes, such that obese children may be allowed to participate in a nonbeneficial experiment to examine the time course and mechanism of insulin resistance. Being a neonate may be a sufficient "condition" to allow a microdosing study to better understand the ontogeny of drug metabolizing enzymes that could be considered a minor increase over minimal risk. The designation of a child as having behavioral problems by a teacher might allow psychological testing for research purposes that is considered to be a minor increase over minimal risk. Although children with acute lymphoblastic leukemia may have the condition of being at risk of relapse, serial nontherapeutic bone marrow aspirates was considered greater than a minor increase over minimal risk.[16]

The requirement for "*vital importance*" is consistent with the principle of scientific necessity and thus closely tied to the child's "disorder or condition."[17] Establishing that medical products are safe and effective in the pediatric population is a critical public health objective which protects children from risk and enhances their wellbeing. In this context, early phase and exploratory trials to better understand the natural history of a particular disease or to develop endpoints for later registrational trials may be crucial to pediatric product development. Nontherapeutic procedures in children that contribute to these important outcomes may meet the vital importance requirement, even if product development is at an early stage.

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[13] Institute of Medicine. IOM Committee on Clinical Research Involving Children: Ethical Conduct of Clinical Research Involving Children. 2010/07/30 ed. Field MJ, Behrman RE, editors. Washington DC: National Academies Press (US); 2004.

[14] International Conference on Harmonisation (ICH). ICH Harmonised Tripartite Guideline - Guideline for Good Clinical Practice E6(R1) 1996 [February 27, 2015]. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf.

[15] Food and Drug Administration. Guidance for Clinical Investigators, Institutional Review Boards and Sponsors: Process for Handling Referrals to FDA Under 21 CFR 50.54—Additional Safeguards for Children in Clinical Investigations 2006 [December 1, 2014]. Available from: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127605.pdf.

[16] Institute of Medicine. IOM Committee on Clinical Research Involving Children: Ethical Conduct of Clinical Research Involving Children. 2010/07/30 ed. Field MJ, Behrman RE, editors. Washington DC: National Academies Press (US); 2004.

[17] Institute of Medicine. IOM Committee on Clinical Research Involving Children: Ethical Conduct of Clinical Research Involving Children. 2010/07/30 ed. Field MJ, Behrman RE, editors. Washington DC: National Academies Press (US); 2004.

The National Commission used "*reasonably commensurate*" to describe research activities that are reasonably similar (but need not be identical) to procedures that prospective research participants may ordinarily experience. The Institute of Medicine noted that "although a child might not have experienced a particular research procedure...the procedure could still be described to the child as potentially presenting levels of pain, immobility, anxiety, time away from home, or other effects that would be similar to those produced by procedures that they have experienced."[18] The goal is to make the research procedures tangible for the child and parents, thereby improving child assent and parental permission.[19,20]

NHRPAC, SACHRP and IOM all provided examples of interventions or procedures that may be considered a minor increase over minimal risk. For example, NHRPAC produced the following table regarding common procedures and the level of risk each may pose.

Table I: Common procedures and category of risk

PROCEDURE*	CATEGORY OF RISK		
Venipuncture/fingerstick/heelstick	X		
Urine collection via bag	X		
Urine collection via catheter		X	
Urine collection via suprapubic tap			X
Chest xray	X		
Bone density test	X		
Wrist xray for bone age	X		
Lumbar puncture		X	
Collection of saliva	X		
Collection of small sample of hair	X		
Vision testing	X		
Hearing testing	X		
Complete neurological exam	X		
Oral glucose tolerance test	X		
Skin punch biopsy w/topical pain relief		X	
Bone marrow aspirate w/topical pain relief		X	
Organ biopsy			X
Standard psychological tests	X		
Classroom observation	X		

* The category of risk is for a single procedure. Multiple or repetitive procedures are likely to affect the level of risk.

If an intervention or procedure cannot be considered only a minor increase over minimal risk, it would need to be evaluated under the higher risk pathway described in the next section.

[18] Institute of Medicine. IOM Committee on Clinical Research Involving Children: Ethical Conduct of Clinical Research Involving Children. 2010/07/30 ed. Field MJ, Behrman RE, editors. Washington DC: National Academies Press (US); 2004.
[19] Department of Health Education and Welfare. Research Involving Children: Report and Recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Federal Register. 1978;43(9):2083-114.
[20] Council for International Organizations of Medical Sciences (CIOMS). International Ethical Guidelines for Biomedical Research Involving Human Subjects Geneva: Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO); 2002 [December 1, 2014]. Available from: http://www.cioms.ch/publications/layout_guide2002.pdf.

Higher Risk Pathway and Direct Benefit

The higher risk pathway (21 CFR 50.52) becomes necessary when existing data indicate that the risks of the intervention or procedure are greater than a minor increase over minimal risk, or when insufficient data are available to support a lower risk determination. Critical to this pathway is the requirement that interventions and procedures must "hold out the prospect of direct benefit to individual subjects," and that this prospect of direct benefit must be sufficient to justify the risks. In addition, this balance of risk and potential benefit must be comparable to the available alternatives, thus setting this judgment in the context of the natural history, prognosis and treatment alternatives for a specific disease. This pathway is the relevant pathway for pediatric clinical trials of opioid analgesics in patients with painful conditions.

FDA regulations do not define "direct" benefits, and the literature offers varying views on which benefits are direct. However, the majority view from a previous Pediatric Ethics Subcommittee discussion was that direct benefit must accrue to the individual research participant, and result from the specific research intervention or procedure and not from ancillary benefits such as health care that may be provided in the clinical trial. In addition, generalizable knowledge *per se* is not considered a direct benefit.[21]

Diagnostic or monitoring procedures (e.g., additional scans, blood draws, or biopsies) may be needed to answer the scientific questions posed by the clinical trial, or to evaluate the safety of other interventions. Diagnostic or monitoring procedures may not *per se* offer a prospect of direct benefit, yet may be critical in evaluating the safety of other interventions that do offer a prospect of direct benefit. If the monitoring procedure is made necessary by the administration of the investigational product, the risks of the monitoring procedure may be justified by the prospect of direct benefit of the experimental intervention. Using this approach, the administration of the investigational product and the monitoring made necessary by that administration could both be considered under the higher risk pathway (i.e., 21 CFR 50.52). In addition, monitoring procedures that may impact on the child's clinical care may offer a prospect of direct benefit. For example, if clinical monitoring of blood levels in order to adjust drug dosing were necessary, the risks of venipuncture may be justified under a prospect of direct benefit because the information obtained in this way may affect clinical management. Similarly, if safety monitoring of hepatic enzymes might result in the discontinuation of the investigational product for safety reasons, these laboratory tests may be considered to hold out the prospect of direct benefit under 21 CFR 50.52.

Interventions and procedures that would not be clinically indicated for diagnosing, monitoring or treating a child's disease (e.g. "nontherapeutic" blood or CSF studies for research biomarkers) are not approvable under this category of research. Hence, absent referral for a federal panel review under 21 CFR 50.54, nontherapeutic interventions and procedures judged to exceed a minor increase over minimal risk may not be approvable in children.

[21] Food and Drug Administration. FDA Final Rule, Code of Federal Regulations Title 21 CFR 50 Subpart D Federal Register Vol. 78, No. 38 February 26, 2013.

Federal Panel Review Under 21 CFR 50.54

If an IRB determines that a clinical investigation involving children as subjects does not meet the requirements of 21 CFR 50.51, 50.52 or 50.53, the clinical investigation may proceed only if the IRB finds and documents that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and refers the protocol to FDA for Federal panel review.[22] The Pediatric Ethics Subcommittee provides advice on the acceptability of the protocol through the Pediatric Advisory Committee to the FDA Commissioner. Based on this advice, the FDA Commissioner makes a final determination on whether the criteria for study acceptability are fulfilled:

- The clinical investigation in fact satisfies 21 CFR 50.51, 50.52 or 50.53, or
- The following three conditions described in 21 CFR 50.54 are met:
  - The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.
  - The clinical investigation will be conducted in accordance with sound ethical principles; and
  - Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in §50.55.

Component Analysis

As noted earlier, any given protocol may contain multiple interventions and/or procedures, and each must be evaluated under the categories of Subpart D. In 1978, the U.S. National Commission recommended that "to determine the overall acceptability of the research, the risk and anticipated benefit of activities described in a protocol must be evaluated individually as well as collectively."[23] For adult subjects, the risks of research participation can be justified either by the anticipated direct benefits to the subjects or by the importance of the anticipated knowledge. In other words, higher risk procedures may be justified in research involving adult subjects by the knowledge to be gained. This is not the case for research involving children. In pediatric studies, the allowable risk exposure for an intervention or procedure not offering a prospect of direct benefit must be restricted to low risk. Thus, the individual research interventions and procedures that are contained in an investigational protocol must be assessed according to whether they do (21 CFR 50.52) or do not (21 CFR 50.51 or 50.53) offer a prospect of direct benefit - an approach referred to as "component analysis." While component analysis has been debated in the literature, all parties agree on the importance of assessing interventions or procedures individually as to whether they do or do not hold out a prospect of direct benefit so

[22] Food and Drug Administration. Guidance for Clinical Investigators, Institutional Review Boards and Sponsors: Process for Handling Referrals to FDA Under 21 CFR 50.54—Additional Safeguards for Children in Clinical Investigations 2006 [December 1, 2014]. Available from: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127605.pdf.

[23] Department of Health Education and Welfare. Research Involving Children: Report and Recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Federal Register. 1978;43(9):2083-114.

that the risks of non-beneficial interventions or procedures are not justified through the inclusion of unrelated beneficial interventions or procedures in the same protocol.[24,25,26]

Component analysis may be approached by applying the following three steps.

1. Analyze the protocol to determine whether each research intervention and/or procedure contained in protocol does or does not offer the enrolled child a prospect of direct benefit.
2. Assess the risk level of those interventions and/or procedures that do not offer the child a prospect of direct benefit. This risk level must not exceed a minor increase over minimal risk (i.e., "low" risk) (21 CFR 50.53).
3. Assess whether the risks of those interventions and/or procedures that do offer a prospect of direct benefit are justified by those potential benefits, and that this balance of risks and potential direct benefits are comparable to any available alternatives (21 CFR 50.52).

Thus, component analysis would require that the risks of an experimental intervention or procedure must be justified by the prospect of direct benefit from that same intervention or procedure, and not by other interventions or procedures included in the protocol. For example, the risks of a lumbar puncture must be justified by the prospect of direct benefit from that same lumbar puncture. If the lumbar puncture is not being performed for the health benefit of the enrolled child, then the lumbar puncture would be considered nontherapeutic and would need to be evaluated under the lower risk pathway (21 CFR 50.51 or 21 CFR 50.53). The risks of a nontherapeutic lumbar puncture may not be balanced against other health benefits that the child might receive as a result of study participation (e.g. more intensive monitoring of their health condition or free health care.)

To determine whether a procedure may be considered therapeutic or nontherapeutic, both the reason for performing the procedure and timing of the procedure need to be considered. If the specified procedure would generally be performed as part of routine clinical management of children with the given disorder at the same or similar time points as would be required by the investigational protocol, these procedures may be approvable under 21 CFR 50.52 as presenting a prospect of direct clinical benefit. In addition, procedures that might change clinical management of a child's condition (e.g. therapeutic drug monitoring or follow-up diagnostic imaging) may be considered therapeutic. However, procedures that are performed, for example, solely for the purpose of evaluating research endpoints or measuring research biomarkers and would not routinely be performed in children with the given disorder at the specified time points outside of the study are considered "nontherapeutic", and thus must be evaluated under the lower risk pathway. The failure to carefully distinguish the different components of a clinical investigation may result in the risks of an intervention or procedure that does not hold out the prospect of direct benefit exceeding the allowable ceiling of a minor increase over minimal risk (absent referral under 21 CFR 50.54).

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[24] Department of Health Education and Welfare. Research Involving Children: Report and Recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Federal Register. 1978;43(9):2083-114.

[25] Institute of Medicine. IOM Committee on Clinical Research Involving Children: Ethical Conduct of Clinical Research Involving Children. 2010/07/30 ed. Field MJ, Behrman RE, editors. Washington DC: National Academies Press (US); 2004.

[26] Medical Research Council. Medical Research involving Children 2004 [February 27, 2015]. Available from: http://www.mrc.ac.uk/documents/pdf/medical-research-involving-children/.

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

Memorandum

DATE: August 26, 2016

FROM: Steven Galati, MD, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Pamela Horn, MD, DAAAP

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

RE: Opioid Analgesic Products with Pediatric Labeling

The following opioid analgesics have pediatric information in the package insert as reproduced below.

1. ACTIQ (fentanyl citrate) oral transmucosal lozenge

Warning Respiratory depression

- Death has been reported in children who have accidentally ingested ACTIQ. ACTIQ must be kept out of reach of children.

Pediatric Use

- Safety and effectiveness in pediatric patients below 16 years of age have not been established.
- In a clinical study, 15 opioid-tolerant pediatric patients with breakthrough pain, ranging in age from 5 to 15 years, were treated with ACTIQ. The study was too small to allow conclusions on safety and efficacy in this patient population. Twelve of the fifteen

opioid-tolerant children and adolescents aged 5 to 15 years in this study received ACTIQ at doses ranging from 200 mcg to 600 mcg. The mean (CV%; range) dose-normalized (to 200 mcg) Cmax and AUC0-8 values were 0.87 ng/mL (51%; 0.42-1.30) and 4.54 ng·h/mL (42%; 2.37-6.0), respectively, for children ages 5 to <11 years old (N = 3) and 0.68ng/mL (72%; 0.15-1.44) and 8.38 (192%; 0.84-50.78), respectively, for children ages ≥11 to <16 y (N = 9).

2. BUPRENORPHINE (buprenorphine hydrochloride) solution for injection

Dosage and Administration

- Buprenorphine hydrochloride injection has been used in children 2-12 years of age at doses between 2-6 micrograms/kg of body weight given every 4-6 hours. There is insufficient experience to recommend a dose in infants below the age of two years, single doses greater than 6 micrograms/kg of bodyweight, or the use of a repeat or second dose at 30-60 minutes (such as is used in adults). Since there is some evidence that not all children clear buprenorphine faster than adults, fixed interval or "round-the-clock" dosing should not be undertaken until the proper inter-dose interval has been established by clinical observation of the child. Physicians should recognize that, as with adults, some pediatric patients may not need to be remedicated for 6-8 hours.

Clinical Pharmacology

- A single, ten-patient, pharmacokinetic study of doses of 3 mcg/kg in children (age 5-7 years) showed a high inter-patient variability, but suggests that the clearance of the drug may be higher in children than in adults. This is supported by at least one repeat-dose study in postoperative pain that showed an optimal inter-dose interval of 4-5 hours in pediatric patients as opposed to the recommended 6-8 hours in adults.

Precautions

Pediatric Use

- The safety and effectiveness of buprenorphine hydrochloride have been established for children between 2 and 12 years of age. Use of buprenorphine hydrochloride in children is supported by evidence from adequate and well controlled trials of buprenorphine hydrochloride in adults, with additional data from studies of 960 children ranging in age from 9 months to 18 years of age. Data is available from a pharmacokinetic study, several controlled clinical trials, and several large postmarketing studies and case series. The available information provides reasonable evidence that buprenorphine hydrochloride may be used safely in children ranging from 2-12 years of age, and that it is of similar effectiveness in children as in adults.

3. CODEINE/ACETAMINOPHEN

Contraindications

- Codeine-containing products are contraindicated for post-operative pain management in children who have undergone tonsillectomy and/or adenoidectomy. This product should not be administered to patients who have previously exhibited hypersensitivity to codeine or acetaminophen.

Warnings and Precautions

- Children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Codeine-containing products are contraindicated for postoperative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy (see CONTRAINDICATIONS).
- ……. Children with this genetic variation who were prescribed codeine after tonsillectomy and/or adenoidectomy for obstructive sleep apnea may be at greatest risk based on reports of several deaths in this population due to respiratory depression. Codeine-containing products are contraindicated in all children who undergo tonsillectomy and/or adenoidectomy. Advise caregivers of children receiving codeine-containing products for other reasons to monitor for signs of respiratory depression.
- Respiratory depression and death have occurred in children with obstructive sleep apnea who received codeine in the post-operative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme CYP2D6 or high morphine concentrations). These children may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Codeine containing products are contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy (see CONTRAINDICATIONS and WARNINGS).

Dosage and Administration

- The usual dose of codeine phosphate in children is 0.5 mg/kg.
- Adult doses of codeine higher than 60 mg fail to give commensurate relief of pain but merely prolong analgesia and are associated with an appreciably increased incidence of undesirable side effects. Equivalently high doses in children would have similar effects.

4. OXYCONTIN (oxycodone hydrochloride) extended-release tablets

Indication

- Opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent

Dosage and Administration

- For use only in pediatric patients 11 years and older already receiving and tolerating opioids for at least 5 consecutive days with a minimum of 20 mg per day of oxycodone or its equivalent for at least two days immediately preceding dosing with OXYCONTIN. OXYCONTIN is not appropriate for use in pediatric patients requiring less than a 20 mg total daily dose. Table 1, based on clinical trial experience, displays the conversion factor when switching pediatric patients 11 years and older (under the conditions described above) from opioids to OXYCONTIN.

Consider the following when using the information in Table 1.

• This is not a table of equianalgesic doses.

• The conversion factors in this table are only for the conversion from one of the listed oral opioid analgesics to OXYCONTIN.

• The table cannot be used to convert from OXYCONTIN to another opioid. Doing so will result in an over-estimation of the dose of the new opioid and may result in fatal overdose.

• The formula for conversion from prior opioids, including oral oxycodone, to the daily dose of OXYCONTIN is mg per day of prior opioid x factor = mg per day of OXYCONTIN. Divide the calculated total daily dose by 2 to get the every-12-hour OXYCONTIN dose. If rounding is necessary, always round the dose down to the nearest OXYCONTIN tablet strength available.

Table 1: Conversion Factors When Switching Pediatric Patients 11 Years and Older to OXYCONTIN

Prior Opioid	Conversion Factor	
	Oral	Parenteral*
Oxycodone	1	--
Hydrocodone	0.9	--
Hydromorphone	4	20
Morphine	0.5	3
Tramadol	0.17	0.2

*For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for high-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor.

Titration and Maintenance of Therapy in Adults and Pediatric Patients 11 Years and Older

- There are no well-controlled clinical studies evaluating the safety and efficacy with dosing more frequently than every 12 hours. As a guideline for pediatric patients 11 years and older, the total daily oxycodone dosage usually can be increased by 25% of the current total daily dosage.

Clinical Trial Experience in Pediatric Patients 11Years and Older

- The safety of OXYCONTIN has been evaluated in one clinical trial with 140 patients 11 to 16 years of age. The median duration of treatment was approximately three weeks. The most frequently reported adverse events were vomiting, nausea, headache, pyrexia, and constipation. Table 3 includes a summary of the incidence of treatment emergent adverse events reported in ≥5% of patients.

Pediatric Use

- The safety and efficacy of OXYCONTIN have been established in pediatric patients ages 11 to 16 years. Use of OXYCONTIN is supported by evidence from adequate and well-controlled trials with OXYCONTIN in adults as well as an open-label study in pediatric patients ages 6 to 16 years. However, there were insufficient numbers of patients less than 11 years of age enrolled in this study to establish the safety of the product in this age group.
- The safety of OXYCONTIN in pediatric patients was evaluated in 155 patients previously receiving and tolerating opioids for at least 5 consecutive days with a minimum of 20 mg per day of oxycodone or its equivalent on the two days immediately preceding dosing with OXYCONTIN. Patients were started on a total daily dose ranging between 20 mg and 100 mg depending on prior opioid dose.
- The most frequent adverse events observed in pediatric patients were vomiting, nausea, headache, pyrexia, and constipation [see Dosage and Administration (2.1), Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Trials (14)].

Pharmacokinetics

- In the pediatric age group of 11 years of age and older, systemic exposure of oxycodone is expected to be similar to adults at any given dose of OXYCONTIN.

Clinical Studies

- OXYCONTIN has been evaluated in an open-label clinical trial of 155 opioid-tolerant pediatric patients with moderate to severe chronic pain. The mean duration of therapy was 20.7 days (range 1 to 43 days). The starting total daily doses ranged from 20 mg to 100 mg based on the patient's prior opioid dose. The mean daily dose was 33.30 mg (range 20 to 140 mg/day). In an extension study, 23 of the 155 patients were treated beyond four weeks, including 13 for 28 weeks. Too few patients less than 11 years were enrolled in the clinical trial to provide meaningful safety data in this age group.

5. DURAGESIC (Fentanyl Transdermal System)

Dosage and Administration

- No pediatric specific dosing language.

Clinical Trial Experience

- The safety of DURAGESIC was evaluated in three open-label trials in 289 pediatric patients with chronic pain, 2 years of age through 18 years of age. Adverse reactions reported by ≥1% of DURAGESIC-treated pediatric patients are shown in Table 5.

Table 5. Adverse Reactions Reported by ≥1% of DURAGESIC-treated Pediatric Patients in 3 Clinical Trials of DURAGESIC

System/Organ Class Adverse Reaction	DURAGESIC % (N=289)
Gastrointestinal disorders	
Vomiting	34
Nausea	24
Constipation	13
Diarrhea	13
Abdominal pain	9
Abdominal pain upper	4
Dry mouth	2
General disorders and administration site conditions	
Edema peripheral	5
Fatigue	2
Application site reaction	1
Asthenia	1
Immune system disorders	
Hypersensitivity	3
Metabolism and nutrition disorders	
Anorexia	4
Musculoskeletal and connective tissue disorders	
Muscle spasms	2
Nervous system disorders	
Headache	16
Somnolence	5
Dizziness	2
Tremor	2
Hypoesthesia	1
Psychiatric disorders	
Insomnia	6
Anxiety	4
Depression	2
Hallucination	2
Renal and urinary disorders	
Urinary retention	3
Respiratory, thoracic and mediastinal disorders	
Respiratory depression	1
Skin and subcutaneous tissue disorders	
Pruritus	13
Rash	6
Hyperhidrosis	3
Erythema	3

Specific Populations

Pediatric Use

- The safety of DURAGESIC was evaluated in three open-label trials in 289 pediatric patients with chronic pain, 2 years of age through 18 years of age. Starting doses of 25 mcg/h and higher were used by 181 patients who had been on prior daily opioid doses of at least 45 mg/day of oral morphine or an equianalgesic dose of another opioid. Initiation of DURAGESIC therapy in pediatric patients taking less than 60 mg/day of oral morphine or an equianalgesic dose of another opioid has not been evaluated in controlled clinical trials.
- The safety and effectiveness of DURAGESIC in children under 2 years of age have not been established.
- To guard against excessive exposure to DURAGESIC by young children, advise caregivers to strictly adhere to recommended DURAGESIC application and disposal instructions [see Dosage and Administration (2.4), (2.5) and Warnings and Precautions (5.3)].

Pharmacokinetics

Pediatric Use

- In 1.5 to 5 year old, non-opioid-tolerant pediatric patients, the fentanyl plasma concentrations were approximately twice as high as that of adult patients. In older pediatric patients, the pharmacokinetic parameters were similar to that of adults. However, these findings have been taken into consideration in determining the dosing recommendations for opioid-tolerant pediatric patients (2 years of age and older). For pediatric dosing information, refer to [see Dosing and Administration (2.1)].

Clinical Studies

- In the pediatric population, the safety of DURAGESIC has been evaluated in 289 patients with chronic pain 2–18 years of age. The duration of DURAGESIC use varied; 20% of pediatric patients were treated for ≤ 15 days; 46% for 16–30 days; 16% for 31–60 days; and 17% for at least 61 days. Twenty-five patients were treated with DURAGESIC for at least 4 months and 9 patients for more than 9 months.

6. LORTAB (hydrocodone bitartrate and acetaminophen) syrup

Dosage and Administration

- The usual dosages for children are given by the table below, and are to be given every 4 to 6 hours as needed for pain. These dosages correspond to an average individual dose of

0.20 mL/kg of LORTAB ELIXIR (providing 0.135 mg/kg of hydrocodone bitartrate and 4.0 mg/kg of acetaminophen). Dosing should be based on weight whenever possible.

BODY WEIGHT	APPROXIMATE AGE	DOSE every 4 to 6 hours	MAXIMUM TOTAL DAILY DOSE (6 doses per day)
12 to 15 kg (27 to 34 lbs.)	2 to 3 years	2.8 mL	16.8 mL
16 to 22 kg (35 to 50 lbs.)	4 to 6 years	3.75 mL	22.5 mL
23 to 31 kg (51 to 69 lbs.)	7 to 9 years	5.6 mL	33.6 mL
32 to 45 kg (70 to 100 lbs.)	10 to 13 years	7.5 mL	45 mL
46 kg and up (101 lbs. and up)	14 years to adult	11.25 mL	67.5 mL

- The total daily dosage for children should not exceed 6 doses per day.
- It is of utmost importance that the dose of LORTAB ELIXIR be administered accurately. It is strongly recommended that care givers obtain and use a calibrated measuring device. Health care providers should recommend a dropper that can measure and deliver the prescribed dose accurately, and instruct care givers to use extreme caution in measuring the dosage.

Precautions

Pediatric Use

- Safety and effectiveness in the pediatric population below the age of two years have not been established. Use of LORTAB ELIXIR in the pediatric population is supported by the evidence from adequate and well controlled studies of hydrocodone and acetaminophen combination products in adults with additional data which support the development of metabolic pathways in children two years of age and over (see DOSAGE AND ADMINISTRATION for pediatric dosage information).

7. MEPERIDINE (meperidine hydrochloride) tablet

Dosage and Administration

- The usual dosage is 1.1 mg/kg to 1.8 mg/kg orally, up to the adult dose, every 3 or 4 hours as necessary.

Precautions

Pediatric Use

- Literature reports indicate that meperidine has a slower elimination rate in neonates and young infants compared to older children and adults. Neonates and young infants may also be more susceptible to the effects, especially the respiratory depressant effects. Meperidine should therefore be used with caution in neonates and young infants, and any potential benefits of the drug weighed against the relative risk to a pediatric patient.

8. **SOMA COMPOUND WITH CODEINE (carisoprodol, apsirin and codeine phosphate) tablets**

Warnings

- Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to CYP2D6 polymorphism (see WARNINGS – Codeine Phosphate-Death Related to Ultra-Rapid Metabolism of Codeine to Morphine).

Contraindications

- Codeine sulphate is contraindicated for postoperative pain management in children who have undergone tonsillectomy and/or adenoidectomy (see WARNINGS – Codeine Phosphate – Death Related to Ultra-Rapid Metabolism of Codeine to Morphine).

Nonteratogenic effects

- For children exposed to meprobamate in utero, one study found no adverse effects on mental or motor development or IQ scores.

Precautions

Pediatric Use

- The efficacy, safety, and pharmacokinetics of Carisoprodol, Aspirin and Codeine Phosphate Tablets in pediatric patients less than 16 years of age have not been established.
- Respiratory depression and death have occurred in children with obstructive sleep apnea who received codeine in the post-operative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for CYP2D6 or high morphine concentrations). These children may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Codeine is contraindicated for postoperative pain management in these patients (see WARNINGS – Death Related to Ultra-Rapid Metabolis m of Codeine to MorphineandCONTRAINDICATIONS).

9. **SUBLIMAZE (fentanyl citrate) injection**

Precautions

- Pediatric Use: The safety and efficacy of fentanyl citrate in children under two years of age have not been established.

- Rare cases of unexplained clinically significant methemoglobinemia have been reported in premature neonates undergoing emergency anesthesia and surgery which included the combined use of fentanyl, pancuronium and atropine. A direct cause and effect relationship between the combined use of these drugs and the reported cases of methemoglobinemia has not been established.

Dosage and Administration

- Usage in Children: For induction and maintenance in children 2 to 12 years of age, a reduced dose as low as 2 to 3 mcg/kg is recommended.

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

Memorandum

DATE: August 24, 2016

FROM: Steven Galati, MD, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Pamela Horn, MD, DAAAP

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

RE: Current Approach to Studying Opioid Analgesics in Pediatric Patients

Introduction

"The performance of research studies to evaluate drugs in children is critical for determining the safety and efficacy of medications in children. …Without proper drug studies in children, children may not benefit from and may even be harmed by drugs that are available to adults. Also, certain disorders affect children primarily, necessitating drug testing on appropriately aged subjects. It is morally imperative, therefore, to formally study drugs in children so that they can enjoy appropriate access to existing and new therapeutic agents."[1]

There are few analgesic products labeled for use in pediatric patients aside from the nonsteroidal anti-inflammatory drugs indicated for juvenile rheumatoid arthritis. As a result, there is an unmet need for pediatric-specific labeling of analgesics to assist clinicians in proper patient selection and in determining the appropriate dosing for their patients. For many years, DAAAP had required pediatric opioid analgesic development include pharmacokinetic studies, followed by adequate and well-controlled efficacy trials and safety studies. However, few sponsors completed pediatric analgesic studies for a number of reasons. DAAAP began to re-evaluate the approach to pediatric analgesic studies and considered the use of extrapolation of pediatric

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

efficacy from findings in adults. The regulatory definition of extrapolation of pediatric efficacy can be found in the Code of Federal Regulations at 21CFR §355c:

> "If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, [FDA] may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies."

To explore whether there was a scientific basis for using extrapolation of pediatric efficacy from adult data, in December 2009, FDA convened a scientific workshop of thought leaders in pediatric pain, pediatric clinical studies, pediatric ethics and pediatric drug development. Participants discussed the available science to support extrapolation for analgesic drug classes including opioid analgesics. Additionally, when efficacy trials were going to be required, approaches to study designs that would lessen the burden on patients and families were considered. A summary of the scientific discussion was later published.[2]

DAAAP integrated the scientific data into an updated following approach for pediatric opioid analgesic clinical development into the existing regulations for pediatric drug development.

Pediatric population

For drug development, the pediatric patient population is defined as 0 to less than 17 years of age. Age cohorts are not established in regulation and should be based on a scientific rationale (e.g., metabolism of a critical enzyme, clinical endpoints, and ability to swallow the formulation). For ethical reasons, healthy children cannot be enrolled in pediatric analgesic studies. Pediatric study participants must be patients with the potential to benefit from participation in the study. For immediate-release (IR) opioid analgesic products, pediatric patients must have acute pain that is severe enough to require treatment with an opioid. For extended-release (ER) opioid analgesic products, pediatric patients must have pain that is severe enough to require treatment with an around-the-clock opioid for at least two to four weeks. In general, because the lowest doses available with extended-release products are often larger than an acceptable starting dose for pediatric patients, patients already must be taking and tolerant to opioid analgesic equivalent to no less than the lowest dose of the ER study drug prior to study enrollment.

Required Pediatric Assessment for Opioid Analgesic Products

For the efficacy assessment of opioid analgesics, the age cohorts have been delineated based on whether extrapolation of efficacy from adults is acceptable or efficacy trials will be required, taking into consideration the scientific discussion from the December 2009 scientific workshop.

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

Another factor is the feasibility of conducting studies for the proposed indication based on the prevalence of the condition in pediatric patients.

For immediate-release (IR) opioid products, which are generally indicated for the treatment of acute painful conditions, the requirements for pediatric studies typically include the entire 0 to less than 17 age range because acute pain is prevalent enough in the entire age range to make studies potentially feasible. For extended-release (ER) opioid products, which are generally indicated for chronic painful conditions, the requirements for pediatric studies are typically waived for the 0 to less than 7 age group because estimates of prevalence of chronic painful conditions in this age range are too low to make studies feasible.

Extrapolating efficacy when possible in the pediatric pain population is important because there are a limited number of pediatric patients available to enroll in trials, children are vulnerable and require additional safeguards in pediatric studies (e.g., inability to consent or communicate symptoms as well as adults, developing organ systems), and extrapolating efficacy allows studies to be smaller and enroll fewer patients because more patients are needed to study efficacy than to study safety and pharmacokinetics. Extrapolating efficacy cannot always be employed, such as when the product has a novel mechanism. Another barrier to extrapolating efficacy is when the drug exposures observed in the pediatric pharmacokinetic study do not match exposures in adults. In this case, the assumption that the exposures between the two populations will match is incorrect and if exposures are lower in the pediatric population than in the adult population, the doses studied cannot be concluded to have been efficacious without additional data. For this reason FDA recommends that sponsors collect pain assessments and rescue medication use in pharmacokinetic studies to provide context for interpreting the pharmacokinetic data in the event that the data between adults and the pediatric study population do not match.

In summary, the pediatric study requirements for opioid analgesics are as follows:

Immediate-release (IR) opioid analgesic products

- Ages 0 to less than 2 years of age: Efficacy, safety and pharmacokinetics
- Ages 2 to less than 17 years of age: Safety and pharmacokinetics with extrapolation of efficacy from adult studies

Extended-release (ER) opioid analgesic products

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

Enrollment Challenges

There are numerous enrollment challenges when designing and carrying out a clinical study in the pediatric population. Parents may be reluctant to enroll their child into a clinical study for concern that they will be harmed, receive less effective treatment or need to undergo extensive blood sampling that is needed for pharmacokinetic and safety analyses. The preferred randomized parallel-group, placebo-controlled analgesic clinical trial utilized in adults poses ethical concerns when enrolling children. For example, the use of a placebo in children is

problematic because there is no potential benefit to the child in participating in the study and the child may have difficulty expressing discomfort or reporting inadequate pain relief. Additionally, for painful conditions, there are many alternative effective treatments available. A practical challenge is enrolling a sufficient number of patients to provide adequate statistical power. There are relatively few patients in some pain populations especially for the youngest patients and for chronic pain. Additional concerns exist regarding studying neonates. These concerns include painful procedures such as blood sampling.

Pediatric Study Design Elements

Another topic discussed at the December 2009 scientific workshop was alternatives to the traditional placebo-controlled study designs used in analgesic studies of adult patients. Once a product is determined to be an analgesic in an adult, the question for pediatric studies is not whether the product is an analgesic, but whether it works in pediatric patients and what are the appropriate doses for a balance of efficacy and safety.

Because efficacy studies of immediate-release opioid analgesic products are only required for pediatric patients under the age of 2 years, to avoid exposing children to unnecessary pain, an "add on" study design was discussed. In this type of study, patients receive the standard of care, and the study drug or placebo are added on to the existing treatment. If the study drug is effective in the setting, there would be less use of the standard of care, often either patient-controlled analgesia (PCA) or nurse-controlled analgesia (NCA), and the primary efficacy endpoint is the difference in the amount of standard of care used between the two treatment groups. For patients over the age of 2 years, open-label pharmacokinetic and safety studies can be conducted.

When determining how to evaluate extended-release opioid analgesics in pediatric patients 7 to less than 17 years of age, a review of prescribing practices has shown that these products are used in settings of pain were enough to require an opioid in patients following painful procedures such as extensive orthopedic surgeries, or other surgeries expected to require management with an opioid around-the-clock for at least two to four weeks. Other patients that may be suitable are children with chronic pain due to sickle cell disease crises or cancers. Because efficacy is extrapolated from adults in the 7 to less than17 age range, these studies are open-label and the primary objective of these studies is assessing safety and pharmacokinetics. To collect adequate data, the design must be a multiple-dose study (e.g., weeks in duration) because the target pediatric population is expected to require treatment with the product beyond a typical acute phase of pain.

Limitations in Pediatric Studies/Drug Development

As described above, Sponsors may have difficulty with enrollment in pediatric studies. This can be attributed to the relatively small number of eligible pediatric patients as well as parental reluctance to enroll their child in a clinical study. Study sites are often difficult to identify and gaining approval by institutional review boards (IRBs) may be challenging. Additionally, there are numerous challenges with assessments of pain in children, especially in children too young to self-report. There exists wide developmental differences across the pediatric age range, thus

more than one scale may be necessary to capture verbal and nonverbal children often necessitating separate studies.

Current and Prior Pediatric Opioid Analgesic Development Programs

Using the regulatory authorities available to FDA, the current and prior pediatric development programs for opioid analgesics are listed below.

Written Requests

1. Buprenorphine (Butrans) – 2011
2. Fentanyl
    a. Actiq – 2006
    b. Duragesic – 2001
3. Oxycodone (OxyContin) – 2011
4. Tapentadol (Nucynta) – 2015
5. Tramadol (Ultram)– 1999

Pediatric Assessment Post-marketing requirements

1. Morphine/naltrexone (Embeda)
2. Tapentadol (Nucynta and Nucynta ER)
3. Hydrocodone (Zohydro ER)
4. Buprenorphine (Belbuca)
5. Oxycodone/acetaminophen (Xartemis XR)
6. Buprenorphine (Butrans)
7. Hydrocodone (Hysingla)
8. Oxycodone/naloxone (Targiniq)
9. Hydromorphone (Dilaudid HP Injection)
10. Morphine immediate release tablets
11. Oxycodone oral solution
12. Oxymorphone (Opana and Opana ER)
13. Hydromorphone (Exalgo)
14. Codeine tablets and solution
15. Fentanyl (Ionsys)
16. Hydromorphone (Palladone)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
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Clinical Pharmacology Considerations for Pediatric Studies of Opioid Analgesics

FDA issued a Draft Guidance "General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products Guidance for Industry" in 2014 (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm425885.pdf). 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 that are planning to conduct clinical studies in pediatric populations. 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. Pediatric studies described below are based on the draft guidance's PK-only Approach (i.e., full extrapolation).

It is important to recognize the availability of published clinical experience, in adults and pediatrics, for several of the drugs in the opioid analgesic class (for example, morphine, oxycodone, hydrocodone/acetaminophen, hydromorphone, fentanyl, etc.) which have been in use for the past several decades. It is also important to recognize several hospitals and professional societies have established guidelines for use of opioid analgesics in adults and pediatric patients experiencing pain due to different causes. Because of the variability in the clinical practice and due to lack of unanimous recommendations across the pain societies/hospital systems across different conditions of pain, the clinical pharmacology approach is to assume, as recommended by the guidance, the following:

> 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.

General Clinical Pharmacology considerations for a study in pediatric patients Birth – 17 years of age:

The Agency's guidance emphasizes understanding the important developmental changes in absorption, distribution, metabolism and excretion combined with all possible disease processes that might interfere with the developmental changes (See excerpt from the Agency's draft guidance below). The guidance also notes the potential utility of understanding liver maturation at the enzyme level, in order to utilize the relationship between drug clearance and body size, especially in older children. As indicated above, extrapolation of safety and efficacy is not assumed for any opioid drug from adults to pediatric patients <2 years of age.

Precise estimation of PK parameters, sample size calculation, and number of blood samples play a critical role in pediatric PK studies. FDA's draft guidance recommends that the distinct age groups to be studied should be chosen based on known information about development of drug-metabolizing enzymes and excretory mechanisms, and safety considerations. For all age groups, 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. The specific criteria is discussed in a publication by Wang and Jadhav (2012) titled "Clarification on Precision Criteria to Derive Sample Size When Designing Pediatric Pharmacokinetic Studies" (J Clin Pharmacol 52: 1601-1606). EMA's pediatric guidance also addresses specific considerations for preterm and term newborn infants, infants and toddlers.

Pediatric Clinical Pharmacology Plan for Immediate-Release (IR) Opioid Analgesic Products (Pediatric patients 2 – 17 years of age) and Extended-Release and Long-Acting (ERLA) Opioid Analgesic Products (Pediatric patients 7 – 17 years of age).

A full or "traditional" PK approach with rich blood sampling or a population PK approach with sparse PK sampling may be used to characterize PK parameters in pediatric patients. The goal of the clinical pharmacology program should be to identify a dosing regimen in children that will achieve plasma opioid exposure that is comparable to adults (See below about importance of simulations and specific measures for comparison prior to conduct of pediatric studies). This may be accomplished by leveraging data from adult bioavailability and population PK studies to precisely plan blood sampling in an adequate number of pediatric patients in the following age groups for IR and ERLA products:

1. Age groups to be studied for opioid IR products: Ages 2-<7, ≥7 – 12 years, and ≥12-<17 years.

2. Age groups to be studied for opioid ERLA products: Ages 7 -<12 years and ≥12-<17 years.

The age groups above do not cover the entire pediatric age range and are defined based on clinical considerations (See the clinical section of the document).

- As described above, precise estimation of PK parameters, sample size calculation, and number of blood samples play a critical role in pediatric PK studies.

- The sponsor should justify blood sampling using a sparse sampling strategy. The sampling strategy should adequately identify a blood sampling scheme that will capture absorption characteristics

(important for ERLA opioids), in addition to clearance and volume of distribution. The sponsor has to justify with simulations that a given dose selected for use in a specific age group (For example, 7-<12 yrs and ≥12-<17 years) has a reasonable chance to "achieve plasma opioid exposure (For example: AUCss, Cminss and Cmax, etc.) that is comparable to adults". PK data from a completed pediatric PK study with sparse sampling should be merged with PK data from adults and a population PK analysis must be conducted to investigate the impact of relevant covariates. Simulations must be conducted, using final PK parameters for children, to identify doses required in pediatric patients that would yield plasma exposures comparable to adults. The matching exposure is calculated to inform initial dose selection such that pediatric patients will receive an "initial dose" that would produce similar exposure with respect to an "initial dose" that is utilized in adults prior to any dose increase for pain management. The safety study should utilize age-appropriate formulations and doses derived from the aforementioned predictions.

  - Single-dose study: PK evaluation of a single dose of an IR or ERLA product may be used if the IR or ERLA PK is known to be linear and dose-proportional in adults and therefore single-dose PK can be predictive of multiple-dose PK. The single-dose PK data must be used, by nonparametric superposition or compartmental methods, to predict doses required in pediatric patients to achieve plasma exposure comparable to adult subjects. The safety study should utilize doses derived from the aforementioned predictions.

  - Multiple-dose study: Pediatric patients that will require opioid ERLA use for more than two weeks may be dosed up to steady-state (as known in adults). Justification of timing of blood samples during absorption phase, peak plasma (Cmax) levels, and in the elimination phase (to calculate AUC0-tau/AUCss) should be based on adult PK data. The goal of such a multiple-dose PK study is to confirm that the dose selected in pediatric patients will achieve plasma opioid exposure that is comparable to adults. The safety study should utilize doses derived from the aforementioned predictions. Sponsors are required to submit the information described above to justify dose-selection.

- ERLA products formulated in combination with an antagonist, such as naltrexone or naloxone, used for abuse deterrence: In addition to the above considerations for opioid ERLA PK, the pediatric PK studies should determine if the antagonist levels in pediatrics will exceed those noted in adult PK studies. Sponsors should justify blood sampling (preferably around known Tmax) based on single-dose and steady-state observations for the ERLA formulation in adult bioavailability studies.

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

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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[1]

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.[2]

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.[3] Congress subsequently passed the Best Pharmaceuticals for Children Act (BPCA)[4] in 2002 and the Pediatric Research Equity Act (PREA) in 2003.[5] Both BCPA and PREA were reauthorized in 2007.[6] In 2012, BPCA and PREA were made permanent under Title V of the Food and Drug Administration Safety and Innovation Act (FDASIA).[7]

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.[8] 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.[9] 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

[3] Public Law No. 105-115, 111 Stat. 2296 (Nov. 21, 1997).
[4] Public Law No. 107-109, 115 Stat. 1408 (Jan. 4, 2002).
[5] Public Law No. 108-155, 117 Stat. 1936 (Dec. 3, 2003).
[6] Food and Drug Administration Amendments Act of 2007 (FDAAA), Public Law No. 110-85, 121 Stat. 823 (Sept. 27, 2007).
[7] Public Law No. 112-144, 126 Stat. 993 (July 9, 2012).
[8] Section 505A of the FD&C Act; 21 U.S.C. 355a.
[9] Section 505B of the FD&C Act; 21 U.S.C. 355c.

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.[10] 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.[11] 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.[12]

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.[13] 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

[10] Section 505A of the FD&C Act; 21 U.S.C. 355a; Section 505B of the FD&C Act; 21 U.S.C. 355c.
[11] Section 505B(a)(1) of the FD&C Act; 21 U.S.C. 355c(e)(1).
[12] Section 505B(a)(4)(D) of the FD&C Act; 21 U.S.C. 355c(A)(4)(D).
[13] See *Guidance for Industry*: *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, May 1998, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078749.pdf.

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_{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

[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.[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.

[16] See the draft *Guidance for Industry*: *Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*, Feb. 2012, available at http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm292362.pdf.

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,[17] 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),[18] 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

[17] Food and Drug Administration: Table of Pharmacogenomic Biomarkers in Drug Labeling (2008), available at http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm.

[18] See *Guidance for Industry*: *Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations* (Footnote 16).

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.[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.[20]

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

[19] See 21 CFR 56.109(h) and 21 CFR 56.111(c).

[20] See *Guidance for Clinical investigators, Institutional Review Boards, and Sponsors Process for Handling Referrals to FDA Under 21 CFR 50.54*, December 2006, available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127605.pdf.

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.

Case 2: IRB review of a clinical pharmacology study using pediatric human subjects under 21 CFR 50.52.

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 Administration-Regulated Products, 78 FR12937, 12937-12950 (Feb. 26, 2013).

[22] See section 4.8.14., ICH *Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance*, Apr. 1996, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf. See also the ICH *Guidance for Industry: E11 Clinical Investigation of Medicinal Products in the Pediatric Population*, Dec. 2000, available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129477.pdf.

[23] See section 505B(e)(2)(B) of the FD&C Act; 21 U.S.C. 355c(e)(2)(B) and the draft *Guidance for Industry-Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*, available at http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf.

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.[24,25] 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[26] in the Appendix of this guidance illustrates the different approaches in conducting pediatric clinical studies.

PK Only Approach (i.e., full extrapolation[27]): 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

[24] Section 505B(e)(2)(B) of the FD&C Act; 21 U.S.C. 355c(e)(2)(B).

[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).

[26] This algorithm is an updated version of the Pediatric Study Decision Tree that was appended to the *Guidance for Industry: Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications*, Apr. 2003, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf.

[27] For a discussion of the different approaches to extrapolation, see Dunne J, Rodriguez WJ, Murphy MD, et al., "Extrapolation of adult data and other data in pediatric drug-development programs." Pediatrics. 2011 Nov;128(5):e1242-1249.

population, and experience with the drug, or other drugs in its therapeutic class, in the disease or condition or related diseases or conditions.[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.

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.

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

[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.[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.[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.

[29] See *Guidance for Industry*: *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (Footnote 13).

[30] See the *Guidance for Industry: Population Pharmacokinetics*, Feb. 1999, available at http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM133184.pdf.

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/m^2).

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., 5^{th} to 95^{th} 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.[31] 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/m^2) 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.[32] If there is a pediatric indication, an age-appropriate dosage formulation must be made available for pediatric patients.[33] 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.[34] If the sponsor conducts the pediatric studies using such a formulation,

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[31] Centers for Disease Control and Prevention, National Center for Health Statistics, 2000 CDC Growth Charts for the United States: Methods and Development (May 2002), available at http://www.cdc.gov/nchs/data/series/sr_11/sr11_246.pdf.

[32] See also the ICH *Guidance for Industry: E11 Clinical Investigation of Medicinal Products in the Pediatric Population* (Footnote 22).

[33] See section 505B(a)(2) of the FD&C Act; 21 U.S.C. 355c(a)(2).

[34] Pediatric Written Request Template. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM207644.pdf.

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.

Example of age groups to be studied for the drug or biologic product
≥1 month to <6 months
6 months to <24 months
2 years to <6 years
6 years to <12 years
12 years to <17 years

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

[35] See also the draft *Guidance for Industry*: *Clinical Pharmacogenomics: Premarketing Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling*, Jan. 2013, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM337169.pdf.

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):

CrCl (ml/min/1.73 m^2) = (K * Ht) / Scr

height (Ht) in cm; serum creatinine (Scr) in mg/dl

K (proportionality constant):

Infant (LBW < 1year): K=0.33

Infant (Term <1year): K=0.45

Female Child (<12 years): K=0.55

Male Child (<12 years): K=0.70

b. Cockcroft-Gault equation (pediatric patients $\geq$ 12 years of age):

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.[36] 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.[37] 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_{max}, 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.

[37] See the *Guidance for Industry: Bioanalytical Method Validation*, May 2001, available at http://www.fda.gov/downloads/Drugs/Guidances/ucm070107.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 Guidance[40] 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).

738 Standards Council [42] and the CDER Study Data Standards web sites for more information.[43] The
739 sponsor should also submit PK and exposure-response data used for modeling and simulation in
740 an SAS.XPT-compatible format.

[42] FDA Resources for Data Standards, available at http://www fda.gov/ForIndustry/DataStandards/default.htm.
[43] Study Data Standards for Submission to CDER, available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635 htm.

741 **APPENDIX**[44]

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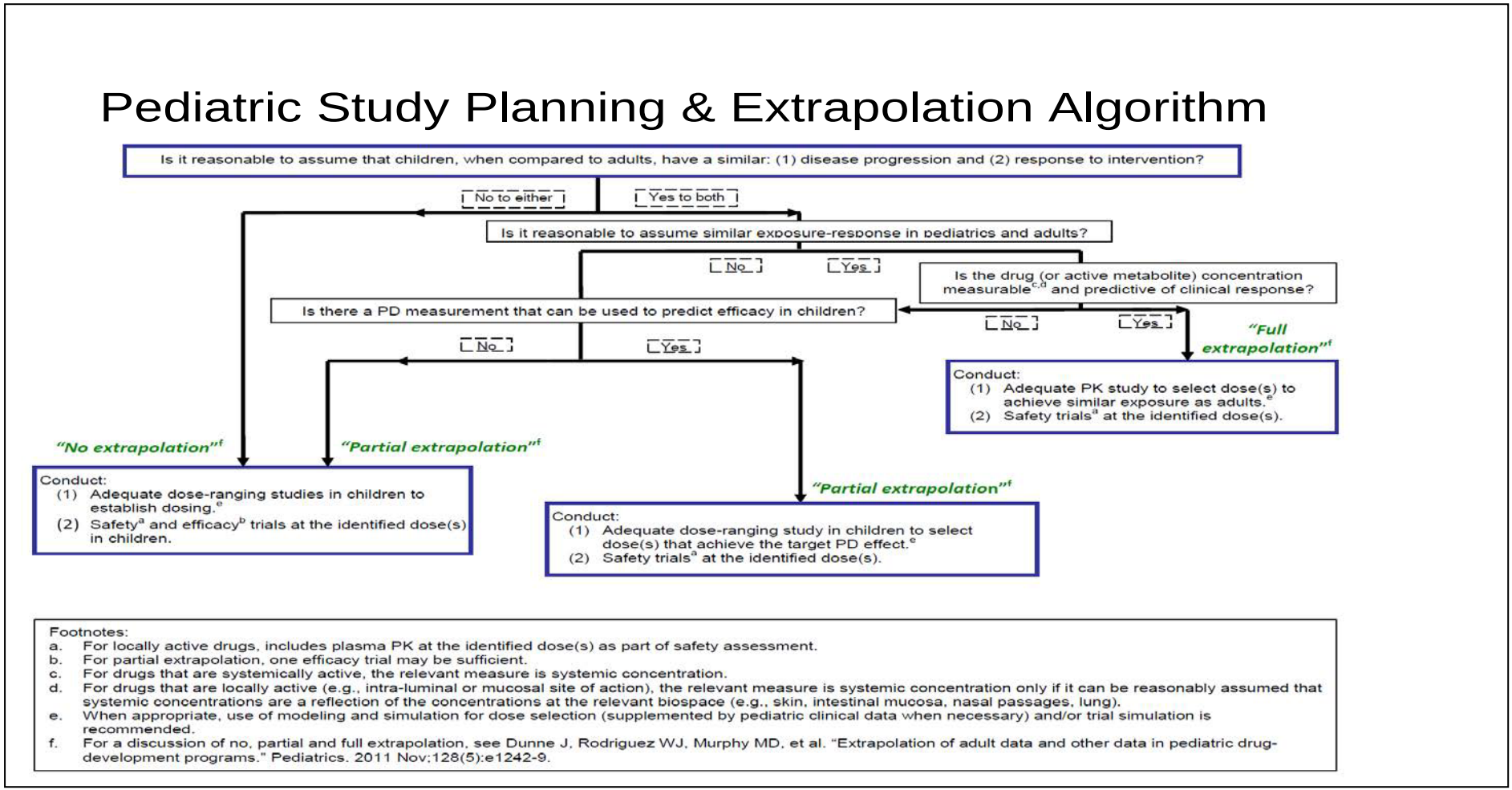

[44] See the Guidance for Industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (Footnote 13).

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Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Review of Adverse Opioid Analgesic-Related Outcomes in the Pediatric Population

Date:	August 22, 2016
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Drug Name(s):	Opioid analgesics
Subject:	Opioid analgesics in the pediatric population: a review of the epidemiologic literature examining the outcomes of misuse, abuse, addiction, overdose, and death
TSI #:	466
RCM #:	2016-1725

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EXECUTIVE SUMMARY

On August 13th 2015, the Food and Drug Administration (FDA) approved labeling for the use of Oxycontin® in select patients aged 11-17 years. This regulatory action highlighted the public health need for a better understanding of the risk of serious adverse outcomes associated with therapeutic medical opioid analgesic use in pediatric populations (≤21 years old). FDA scheduled an advisory committee (AC) to discuss appropriate development plans for establishing the safety and efficacy of prescription opioid analgesics for pediatric patients, including obtaining pharmacokinetic data and the use of extrapolation (docket number FDA-2016-N-0584). To inform this discussion, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted the Division of Epidemiology (DEPI) to review the epidemiologic literature for studies examining adverse opioid analgesic-related outcomes related to misuse, abuse, addiction, overdose, and death in pediatric populations.

A question of particular interest is if legitimate medical use of opioid analgesics in pediatric patients increases these patients' risk of subsequently experiencing serious adverse opioid-related outcomes. The only longitudinal study to examine this question observed an increased risk of short-term future misuse of opioids among high school seniors previously exposed to opioids for legitimate medical purposes.[1] Additional prospective longitudinal studies are needed to confirm this study's results.

Much of the literature examines data drawn from large, nationally-representative surveys such as Monitoring the Future (MTF) and the National Survey on Drug Use and Health (NSDUH), which survey youths about non-medical use of prescription opioids (NMUPO). Both MTF and NSDUH data show that past-month and past-year NMUPO prevalence rates among persons aged ≤18 years have declined in the last five years compared to the mid-late 2000's. As of 2014, NSDUH data indicate that the prevalence of past-month NMUPO in persons aged 12-17 years and 18-25 years was 1.9% and 2.8%, respectively.[2]

Data from these surveys indicate that females aged 12-17 years are more likely to engage in NMUPO than males in this age group,[3] and whites and Native Americans have higher prevalence rates of past-year NMUPO than other racial/ethnic groups.[4] Depressive symptoms,[5] poor academic performance,[6] living in a single-parent home,[6] and annual family income <$20,000[5] are associated with increased odds of NMUPO in persons aged 12-17 years. Past-year alcohol, cigarette, marijuana, or cocaine/inhalant use is associated with increased odds of NMUPO in this age group as well.[6] Many youths reporting NMUPO obtain drugs from their own leftover prescriptions,[7] or for free from family and friends.[8]

1 INTRODUCTION

Opioid analgesic abuse and dependence have become increasingly common in the United States over the past two decades for several reasons, and represent major public health concerns due to the risk of death associated with opioid analgesic-associated respiratory depression.[9]

On August 13th 2015, the Food and Drug Administration (FDA) approved labeling for the use of long-acting opioid analgesic OxyContin® (oxycodone hydrochloride) in select patients aged 11 to 17 years.[a] It was the first approval of a long-acting oral opioid analgesic for pediatric patients. Because physicians can generally prescribe any approved drug to any patient for any condition as they see fit ("off-label use"), the approval aimed to provide prescribers with data-driven opioid analgesic dosing considerations for select pediatric patients.

This regulatory action underscored the need for a better understanding of the risk of serious adverse outcomes associated with opioid analgesic use in pediatric populations. The FDA scheduled an advisory committee (AC) to discuss appropriate development plans for establishing the safety and efficacy of prescription opioid analgesics for pediatric patients, including obtaining pharmacokinetic data and the use of extrapolation (docket number FDA-2016-N-0584).[b]

To provide context for this discussion, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted the Division of Epidemiology (DEPI) to search the epidemiologic literature for studies examining opioid analgesic-related outcomes related to misuse, abuse, addiction, overdose, and death in pediatric populations. We sought to answer the following questions:

- Do pediatric patients who experience adverse opioid analgesic-related outcomes have a history of legitimate use of prescription opioid analgesics? Is there a differential risk of abuse between those patients who have a legitimate prescription and those who do not?
- What is known about the risk of misuse, abuse, addiction, overdose, and death in pediatric populations who are prescribed opioid analgesics? What is not known? What should FDA know in order to make sound regulatory decisions in this space?
- What data sources are available to research this topic? What types of study designs would be useful to better understand this issue in the future?

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[a] Approval letter located at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/022272Orig1s027ltr.pdf, accessed 6/21/2016.

[b] Federal Register notice at https://www.federalregister.gov/articles/2016/02/19/2016-03468/anesthetic-and-analgesic-drug-products-advisory-committee-the-drug-safety-and-risk-management, accessed 8/8/2016.

The goal of this document is to provide an assessment of the available epidemiologic literature examining the adverse outcomes of misuse, abuse, addiction, overdose, and death in pediatric populations who are prescribed opioid analgesics.

2 REVIEW METHODS AND MATERIALS

DEPI worked with the FDA Library to search PubMed for peer-reviewed epidemiologic studies in the biomedical literature published from January 2000 to March 2016 that examined adverse opioid analgesic-related outcomes in persons aged <21 years. Our primary outcomes of interest were misuse, abuse, addiction, overdose, and death. The search string used in PubMed is shown in Appendix 1. We excluded case studies, case series, reviews, letters, editorials, animal studies, pharmacokinetic/pharmacodynamic studies, and commentaries. Article abstracts were reviewed for possible inclusion, with more detailed text analysis guiding final study selection.

Terminology in this area of study varies. FDA defines "pediatric patients" as persons aged 21 years or younger at the time of their diagnosis or treatment.[c] However, data sources used by researchers may define this term differently. This document typically includes the age range of interest for each study examined to provide as much specificity as possible. Additionally, for the purposes of this document, we assumed that the majority of opioid analgesic-related toxicities occurring in persons aged <12 years were due to unintentional poisonings associated with naivety (e.g., a toddler getting into a medicine cabinet) rather than with patterns of aberrant drug-related behaviors. Consequently this document focuses primarily on populations aged 12 to 21 years.

Adverse outcome definitions vary as well. FDA defines "abuse" as the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect, and defines "misuse" as the intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse.[10] Terms such as medical misuse, non-medical use, and extramedical use are also commonplace in this body of literature, each with its own specific definition depending on the data source. This document preserves the language used within each study in the study's analysis, and provides definitions as needed.

3 REVIEW RESULTS

DEPI identified 55 studies examining the adverse opioid-related outcomes of misuse, abuse, addiction, overdose, and death in pediatric populations using the methods described above.

Of the 55 studies, there were:

- 3 cohort studies;
- 1 randomized controlled trial;

[c] See final rule at 21 CFR 814.3(s) (79 FR 1740, January 10, 2014).

- 45 cross-sectional studies; and
- 6 ecologic[d] studies.

The following sections examine many of these studies in greater detail. Appendix 4 summarizes all the reviewed studies.

3.1 COHORT STUDIES

Three cohort studies examining adverse opioid analgesic-related outcomes in the pediatric population are reviewed below.

Miech et al. (2015)[1]

Authors analyzed data from 6,220 respondents who completed baseline Monitoring the Future (MTF; discussed in greater detail in Section 3.3.2) assessments between 1990 and 2012 as 12th graders and who responded to at least one of three follow-up surveys in the panel studies (a response rate of 71% for the follow-up surveys) to evaluate past-year opioid misuse as a function of therapeutic medical opioid use before 12th grade.[e] The analysis pool had 13,542 observations, and respondents, in general, contributed a mode of two follow-up survey observations.

The primary outcome measure was past-year opioid misuse, defined as "taking a narcotic other than heroin without a doctor telling you to on one or more occasions." Frequency of misuse and misuse to "get high or relax" were also assessed as independent outcome measures.

Results showed that 502 of the 6220 participants (8.1% cumulative incidence) reported any past-year opioid misuse in one of three follow-up intervals.

Adjusting for sex, race, parental education level, 12th grade academic performance, past-two week binge drinking, and pre-12th grade marijuana, cigarette, barbiturate/sedative, and opioid misuse, the legitimate medical use of opioids by the 12th grade was associated with a 33% (95% CI: 4%-70%) increased risk of future opioid misuse after the 12th grade. Twelfth graders reporting current opioid misuse, cigarette smoking, marijuana use, and sedative misuse also had a significantly increased risk of future opioid misuse in the multivariate models. Certain variables – such as racial minority status and high academic achievement – were protective against future opioid misuse.

Although the MTF panel study sample is a nationally representative probability sample, the sample used for this specific study may not be, as it only includes students who completed at least one follow-up assessment. Additionally, details of the initial (legitimate) opioid medical exposure are limited: data were not collected on duration of exposure, dose/strength, indication for use, or when the legitimate drug exposure occurred relative to 12th grade. Many of these factors could be residual confounders or

[d] Ecologic studies are observational epidemiologic studies in which at least one variable is measured at the population, rather than the individual, level.

[e] For additional information please see document authored by Alex Secora entitled *Review of Miech et al. 2015 article published in Pediatrics: "Prescription opioids in adolescence and future opioid misuse."* TSI #466.

effect modifiers in the association between prior opioid exposure and future misuse. Only risk for one to five years after graduation was assessed, leaving risk patterns beyond this timeframe unknown.

In sum, this study suggests an increased risk of future NMUPO among 12th graders previously exposed to opioids for legitimate medical purposes compared to 12th graders with no opioid exposure. Additional prospective studies are needed to confirm these findings and to characterize relevant adolescent risk factors for short-term and longer-term opioid misuse.

McCabe et al. (2013)[11]

The authors examined the prevalence and patterns associated with past-year medical use of opioids (using as prescribed), medical misuse of opioids (using more than prescribed), and non-medical use of prescription opioids (NMUPO; using drugs prescribed for someone else) among 7th-12th graders over a two year timeframe. The investigators administered the web-based Secondary Student Life Survey (SSLS) to 2,050 7th-12th graders in two southeastern Michigan school districts multiple times over two years, and analyzed data only from students who responded to the survey in both years. This survey assessed demographic characteristics and problem behaviors (e.g., bullying, gambling), and included questions drawn from the National Survey on Drug Use and Health (NSDUH) and Monitoring the Future (MTF) about alcohol and drug use. It also featured content from the Youth Self Report (YSR) questionnaire to collect data on sleeping and physical pain problems. The survey featured instruments called the Drug Abuse Screening Test, Short Form (DAST-10; sensitivity 0.70, specificity 0.80) and the adolescent-focused CRAFFT[f] survey (sensitivity 0.80, specificity 0.86) to screen for probable drug abuse or dependence.[g]

The authors observed that approximately 80% of 7th-12th graders prescribed opioids reported using their medications as prescribed. Of those respondents reporting past-year NMUPO in year 1, 25% continued this behavior in year 2. Appropriate medical use and NMUPO for pain relief were more prevalent among females than males.

Importantly, medical users of opioids in year 1 did not have statistically significantly increased odds of abnormal results on either the DAST-10 or CRAFFT instruments upon subsequent measurement. Adolescents who reported only medical misuse of opioids in year 1 had higher odds of abnormal screening results on CRAFFT (odds ratio [OR]=5.1,

[f] CRAFFT is a mnemonic acronym of first letters of key words in six screening questions that follow the first section of the screen, which asks about any drug use: Have you ever ridden in a CAR driven by someone (including yourself) who was "high" or had been using alcohol or drugs; do you ever use alcohol or drugs to RELAX, feel better about yourself, or fit in; do you ever use alcohol or drugs while you are by yourself, ALONE; do you ever FORGET things you did while using alcohol or drugs; do your FAMILY or FRIENDS ever tell you that you should cut down on your drinking or drug use; have you gotten into TROUBLE while you were using alcohol or drugs?

[g] The DAST-10 has been validated in adult psychiatric outpatients (Cocco et al. 1998), and a modified version of the DAST-10 has been validated by the author in college students (McCabe et al. 2006). DEPI is unable to identify a validation study for the DAST instrument in adolescents. The CRAFFT instrument has been validated in adolescent outpatients (Knight et al. 2002).

95% confidence interval [CI]:2.4-10.6) or DAST-10 (OR=4.7, CI:2.1-10.8) in year 2. Adolescents who reported NMUPO for non-pain relief in year 1 had higher odds of abnormal screening results on CRAFFT (OR=9.6, CI:3.9-23.6) or DAST-10 (OR=6.4, CI:2.4-16.9) in year 2 as well.

There are limitations that should be considered in interpreting these study results. The sample of adolescents was not nationally representative, and the follow-up assessment only assessed short-term risk (1-2 years after baseline). There was no assessment of longer-term risk or whether risk patterns were maintained over time. The screening instruments abstracted into the survey are not diagnostic, and DAST-10 may need further validation in the adolescent population; additional professional evaluation would be required to confirm the presence or absence of substance use disorders in respondents with abnormal screening results.

Despite these limitations, this cohort study provides evidence of an association between NMUPO and an increased risk of an abnormal screen for drug abuse or dependence in the near future. Importantly, it also suggests that medical use of opioid analgesics is not associated with subsequent (1-2 years after baseline) abnormal drug abuse screening results.

McCabe et al. (2014)[12]

The investigators used data from MTF's panel studies from 1976 to 2005 to examine NMUPO (use of a prescription opioid without a doctor's orders to do so) patterns during the transition from adolescence to adulthood. Each year, MTF selects approximately 2,400 high school seniors from the cross-sectional component of its data collection to follow in two year intervals as panel studies, effectively creating an annual cohort. This group is examined at a minimum of four time points (called "waves"): wave 1 is the initial survey in 12th grade, and data from waves 2, 3, and 4 are collected at roughly age 19/20, 21/22, and 23/24, respectively, through a mailed survey. MTF over-samples from 12th graders who report drug-related behaviors for inclusion in the panel studies.

The longitudinal sample examined consisted of over 27,000 individuals in 30 cohorts who participated in all four waves of data collection. Approximately 11.6% (CI:11.2-12.0%) of the sample reported past-year NMUPO in at least one of the four waves. Among those who reported past-year NMUPO in at least one wave, 69% (CI:67.6-70.4%), 20.5% (CI: 19.3-21.7%), 7.8% (CI:7.1-8.6%), and 2.7% (CI:2.3-3.1%) reported NMUPO in one, two, three, and four waves, respectively. The authors observed that participants who reported past-year marijuana use, past-two week binge drinking behavior, or graduated from 1992-2005 had greater odds of multiple waves of NMUPO compared to other panels.

Data were not available regarding quantity of opioid used on each occasion, or whether NMUPO was preceded by a legitimate prescription for opioids. Additionally, attrition analyses showed that those who reported NMUPO and other problem behaviors were less likely to participate in the study over time, potentially resulting in underestimation of the prevalence of health risk behaviors in the population of interest. This study assessed

short-term risk (one to five years after graduation). There was no assessment of longer-term risk or whether risk patterns are maintained over time.

These results indicate that most NMUPO among American high school seniors is self-limiting. However, approximately one third of those reporting NMUPO as 12th graders continue nonmedical use beyond age 18. This study does not suggest an association between legitimate use of opioids and future NMUPO; instead, its results indicate that 12th graders reporting NMUPO are more likely to engage in other drug-related behaviors in young adulthood.

3.2 RANDOMIZED CONTROLLED TRIAL STUDIES

One cluster randomized controlled study examined the effects of brief universal preventive interventions conducted in adolescents on long-term prescription drug misuse outcomes.

Spoth et al. (2013)[13]

In this group of three cluster randomized controlled studies, the investigators evaluated the effect of various interventions on Iowa and Pennsylvania middle school students' self-reported prescription opioid misuse (use of a prescription opioid not under a doctor's orders) in young adulthood .

In study 1 (1993), investigators randomized 6th graders in 33 Iowa schools in small (<8,500 residents) communities to one of three interventions (11 schools per intervention): Iowa Strengthening Families Program (ISFP), a control intervention, or a Preparing for the Drug-Free Years (PDFY) program.[h] The ISFP program is a 14-session parenting skills, children's social skills, and family life skills training program.[i] Parents and children participate in the program, both separately and together. In addition to a baseline survey in 6th grade, investigators evaluated responses to drug-related surveys in 7th, 8th, 10th, and 12th grades, as well as at ages 21 and 25. The authors observed that 13.5% of those assigned the control intervention reported lifetime prescription opioid misuse at age 25, while only 4.7% of those who received the ISFP intervention reported lifetime prescription opioid misuse at age 25 – a relative reduction of 65%.

In study 2 (1998), investigators randomized Iowa 7th graders in 36 schools in districts with enrollments of <1,200 students to one of three interventions (12 schools per intervention): Strengthening Families Program: For Parents and Youth 10-14 (SFP 10-14) with life skills training (LST), a control intervention, or solely LST. SFP 10-14 is a revised version of ISFP, and LST is a middle school substance abuse prevention program that teaches students social and self-management skills regarding peer- and media-pressure to use drugs, educating participants on the immediate consequences of substance

[h] The PDFY program is a skill-based, parent-oriented workshop that helps parents address risks that can contribute to drug abuse while strengthening family bonding by building protective factors. Findings from the PDFY cluster were not reported in the publication. For more information on PDFY, please visit http://www.strengtheningfamilies.org/html/programs_1999/05_PDFY.html.

[i] For more information on ISFP, please visit http://www.extension.iastate.edu/sfp10-14/.

abuse.[j] In addition to pre- and post-tests in the 7th grade, investigators followed participants with drug-related survey questions yearly in 8th through 12th grades, yearly from ages 19-22, and again at age 25. The authors observed that prescription opioid misuse rates were higher for the control condition across all time points: 8.8% of persons aged 25 years who received the control intervention reported lifetime prescription opioid misuse, while 6.0% of persons aged 25 years who received the SFP 10-14+LST intervention reported lifetime prescription opioid misuse – a relative reduction of approximately 32%.

In study 3 (2002), investigators randomized two consecutive cohorts of Iowa and Pennsylvania 6th graders and their families in 28 schools in districts with enrollments of 1,300-5,200 students to one of two interventions (14 schools per intervention): SFP 10-14 plus one of three school-based curricula,[k] or a control intervention. The three school-based curricula focused on fostering better understanding of the norms and behaviors regarding substance misuse, peer-resistance skills, and self-management. Investigators followed participants with surveys about drug-related questions yearly in 8th through 12th grades. The authors observed that 27.8% of 12th graders who received the control intervention reported lifetime prescription opioid misuse, while 22.1% of 12th graders who received the SFP 10-14 plus any school-based curricula reported lifetime prescription opioid misuse – a relative reduction of approximately 21%.

Overall this publication indicates that brief school- and family-based interventions during adolescence were associated with reductions in the likelihood of misusing opioids in early adulthood. However, combining three trials into a single publication resulted in a lack of granularity for any single trial; details such as the number of participants within each study are not easily identified. Similarly, it is unclear how many participants completed the entire curriculum for each intervention across all the studies, or whether partial curriculum completion was associated with meaningful risk reduction. School selection and cohort identification within the schools are not described in detail. is also unclear whether these results from predominantly small, non-urban settings would be generalizable to other communities; limited demographic detail is provided. Perhaps most importantly, this study provides no insight into the risk of future opioid misuse among pediatric patients prescribed opioid analgesics for legitimate medical purposes.

While this study suggests that brief school- and family-based interventions during adolescence were associated with reductions in the likelihood of misusing opioids in early adulthood, the lack of granularity in the publication makes it difficult to interpret the study's methodology. Further research confirming these results and better characterizing the relative effectiveness of the various interventions is warranted.

3.3 CROSS-SECTIONAL STUDIES

[j] Findings from the LST-only cluster were not reported in the publication.

[k] Curricula selected from the PROmoting School community-university Partnerships to Enhance Resilience (PROSPER) delivery model for evidence-based programs. For a description of the available school-based curricula, visit http://www.ppsi.iastate.edu/publicationsupplements/PF217/programs.pdf.

The majority of studies reviewed were cross-sectional studies, such as anonymous surveys and questionnaires. Cross-sectional studies are informative for describing prevalence trends.

DEPI reviewed 42 cross-sectional studies for this document; these studies are summarized in Appendix 4. Rather than describe each study's results, this document will summarize the findings of studies that may help answer the questions posed in the introduction that are relevant to this Advisory Committee meeting.

Additionally, this section describes of the major data sources used by these publications. Over half of these cross-sectional studies drew data from the same two sources: the National Survey on Drug Use and Health (NSDUH), and Monitoring the Future (MTF). These are two of the largest, most comprehensive, and longest-running nationally-representative surveys examining young populations' drug use patterns. An understanding of these data sources' methodologies and designs may allow for a better appreciation of the strengths and limitations of this body of research.

3.3.1 National Survey on Drug Use and Health (NSDUH)

NSDUH is an annual, nationally representative survey of the civilian, non-institutionalized population of individuals aged 12 and older (N=~70,000) supported by the Substance Abuse and Mental Health Administration (SAMHSA). Formerly called the National Household Survey on Drug Abuse (1971-2001), NSDUH is the largest and longest-running survey of its kind in the country, and its data provide details on drug use patterns in America. Data are collected through computer-assisted, in-person interviews conducted in English or Spanish with residents of households and non-institutional group quarters (e.g., shelters, rooming houses, dormitories, boarding houses, halfway houses), as well as civilians living on military bases. The survey excludes homeless, incarcerated, and institutionalized individuals, as well as individuals who are in nursing homes or are active duty military personnel. Respondents are paid $30 for their time and participation.[2]

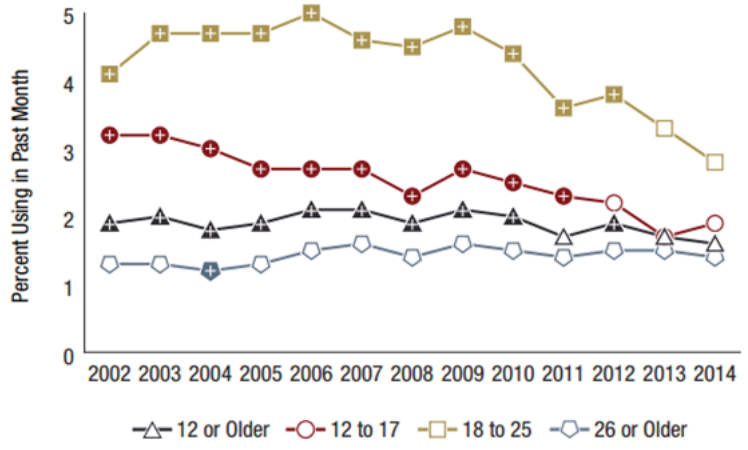
NSDUH uses a state-based, independent, multistage area probability sample to identify respondents. Each state is stratified into approximately equally populated state sampling regions (SSRs), from which census tracts are selected. Census block groups are then identified within census tracts, and area segments (i.e., a collection of census blocks) are selected within census block groups. Finally, dwelling units are selected within the area segments, and within each dwelling unit, up to two residents aged 12 or older are selected for interview. As of 2014, NSDUH allocates more interviews to more populous states, which improves the precision of the national estimates.

In addition to information about tobacco and alcohol use, NSDUH asks participants about use patterns for a variety of drugs, including non-medical use (NMU) of prescription pain relievers. The survey shows pictures of a variety of pills to help respondents respond accurately. NMU is defined as 1) use of the drug without a prescription belonging to the respondent, or 2) taking the drug for the experience or feeling the drug caused. NSDUH's definition of NMU thus incorporates elements from FDA's definitions of misuse (use of a drug not as prescribed) and abuse (use of the drug for its psychologically pleasurable

effects). NSDUH also asks questions that are components of diagnostic criteria for abuse based on the DSM-IV definition for substance use disorder.

A summary of the questions asked about prescription pain reliever NMU is included in Appendix 2, and results from the 2015 annual report describing pain reliever NMU are below.[2]

Figure 1. Past month nonmedical use of pain relievers among people aged 12 or older, by age group: Percentages, 2002-2014[2]



+ Difference between this estimate and the 2014 estimate is statistically significant at the .05 level.

Table 1. Past month nonmedical use of pain relievers among people aged 12 or older, by age group: Percentages, 2002-2014[2]

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
12 or Older	1.9+	2.0+	1.8+	1.9+	2.1+	2.1+	1.9+	2.1+	2.0+	1.7	1.9+	1.7	1.6
12 to 17	3.2+	3.2+	3.0+	2.7+	2.7+	2.7+	2.3+	2.7+	2.5+	2.3+	2.2	1.7	1.9
18 to 25	4.1+	4.7+	4.7+	4.7+	5.0+	4.6+	4.5+	4.8+	4.4+	3.6+	3.8+	3.3	2.8
26 or Older	1.3	1.3	1.2+	1.3	1.5	1.6	1.4	1.6	1.5	1.4	1.5	1.5	1.4

+ Difference between this estimate and the 2014 estimate is statistically significant at the .05 level.

In 2014, approximately 1.9% of Americans aged 12-17 reported past-month NMU of pain relievers, corresponding to approximately 467,000 adolescents. This represents a decline of 41% from 2002, when 3.2% of adolescents reported past-month NMU. The 2014 level (1.9%) of past-month NMU in this age group was similar to levels seen in 2012 (2.2%) and 2013 (1.7%).

In 2014, approximately 2.8% of Americans aged 18-25 reported past-month NMU of pain relievers, corresponding to approximately 978,000 adolescents. This represents a decline of 32% from 2002, when 4.1% of adolescents reported past-month NMU. The 2014 level (2.8%) of past-month NMU in this age group is lower than levels seen in 2012 (3.8%) and 2013 (3.3%).

3.3.2 Monitoring the Future (MTF)

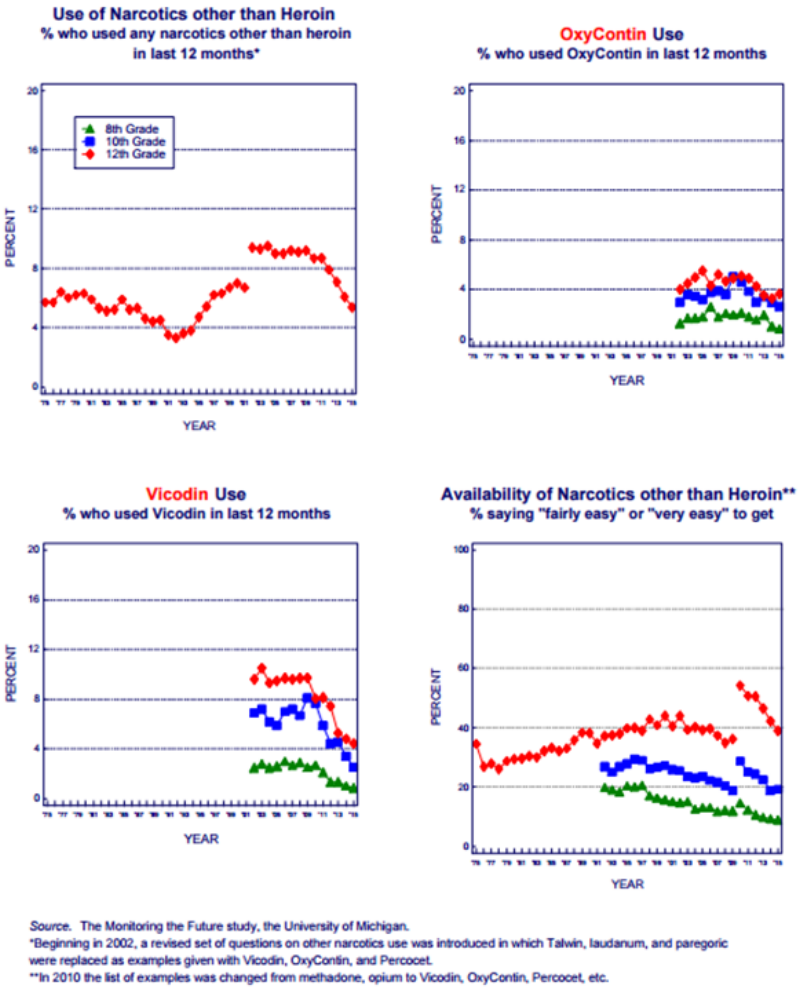
Monitoring the Future (MTF) is an annual survey examining drug use trends and related attitudes among America's secondary school students, college students, and adults through age 50. MTF is composed of three substudies: (a) an annual survey of high school seniors that was initiated in 1975; (b) ongoing panel studies of representative samples from each graduating class (i.e., 12th graders) that have been conducted by mail since 1976; and (c) annual surveys of 8th and 10th graders that began in 1991. Each spring, students in the 8th, 10th, and 12th grades complete a self-administered, paper-based, machine-readable questionnaire in a class period during school hours. In 2014, approximately 41,600 students in 377 public and private secondary schools were surveyed.[14] In addition, approximately 2,400 respondents who participate in the survey of 12th graders are followed longitudinally in the panel studies on a biennial basis, effectively creating a cohort drawn from the cross-sectional results.

To secure a nationally representative sample of high school seniors, the survey uses a three-stage sampling procedure:

- Stage 1: Geographic Areas. The geographic areas used are the primary sampling units (PSUs) developed by the Sampling Section of the University of Michigan's Institute for Social Research's Survey Research Center for use in the center's nationwide interview studies. Local field representatives can be assigned to administer the data collections in practically all included schools.
- Stage 2: Schools. In the major metropolitan areas, more than one high school is often included in the sampling design; in most other sampling areas, a single high school is sampled. In all cases, the selections of high schools are made such that the probability of drawing a school is proportionate to the size of its senior class. The larger the senior class (according to recent records), the higher the selection probability assigned to the high school. When a sampled school is unwilling to participate, a replacement school as similar to it as possible is selected from the same geographic area.
- Stage 3: Students. Within each selected school, up to 350 seniors may be included in the data collection. In schools with fewer than 350 seniors, the usual procedure is to include all of them in the data collection. In larger schools, a subset of seniors is selected either by randomly sampling classrooms or by some other random method that is convenient for the school and judged to be unbiased. Sample weights are assigned to each respondent so as to take into account variations in the sizes of samples from one school to another, as well as (smaller) variations in selection probabilities occurring at the earlier stages of sampling.

MTF asks questions about non-medical use (NMU; using the drugs without a doctor's order to do so) of non-heroin narcotics, as well as perceived risk, disapproval, and perceived availability of many types of drugs. Appendix 3 contains a summary of the questions included in MTF regarding non-heroin narcotic NMU. Figure 2 is a graphic from the 2015 annual report summarizing the prevalence of past-year non-heroin narcotic NMU.[14]

Figure 2. Trends in the annual use and availability of non-heroin narcotics – as well as OxyContin and Vicodin specifically – among 8th, 10th, and 12th graders through 2015[14]



Source. The Monitoring the Future study, the University of Michigan.
*Beginning in 2002, a revised set of questions on other narcotics use was introduced in which Talwin, laudanum, and paregoric were replaced as examples given with Vicodin, OxyContin, and Percocet.
**In 2010 the list of examples was changed from methadone, opium to Vicodin, OxyContin, Percocet, etc.

MTF data indicate that approximately 5.4% of 12th graders reported past-year NMU of non-heroin narcotics in 2015, with 3.7% and 4.4% reporting past-year Oxycontin® or Vicodin® NMU, respectively. The percentage of 12th graders reporting past-year or past-month NMU of non-heroin narcotics has decreased steadily from 2009 to 2015 (Tables 2 and 3).

Table 2. Trends in the past-year prevalence of non-medical use of non-heroin narcotics among 12th graders through 2015.[14]

Year	2008	2009	2010	2011	2012	2013	2014	2015
Prevalence (%)	9.1	9.2	8.7	8.7	7.9	7.1	6.1	5.4

Table 3. Trends in the past-month prevalence of non-medical use of non-heroin narcotics among 12th graders through 2015.[14]

Year	2008	2009	2010	2011	2012	2013	2014	2015
Prevalence (%)	3.8	4.1	3.6	3.6	3.0	2.8	2.2	2.1

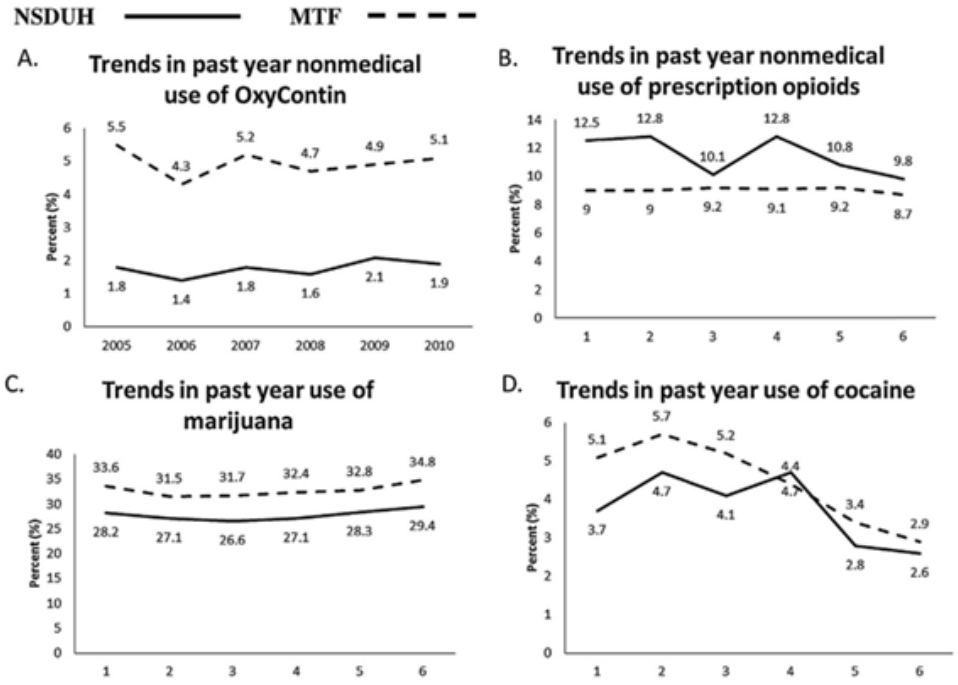
3.3.3 NSDUH vs. MTF

While often considered together, MTF and NSDUH have important differences. In contrast to MTF, NSDUH is household-based, uses a computer-assisted interview system, and shows respondents pill cards with pictures of specific drugs, which may increase identification accuracy of drugs used during the survey. MTF is school-based and uses paper-and-pencil surveys. One study suggests that school-based surveys tend to elicit higher prevalence rates of illicit behavior than household-based surveys, while computer-assisted methods tend to elicit higher prevalence rates of illicit behavior than paper-based methods.[15]

NSDUH's definition of NMU combines FDA's definitions of misuse and abuse (use not as prescribed or for the psychological effects), while MTF effectively captures misuse (use of a drug not as prescribed), but not abuse, of drugs in its questioning. NSDUH does not survey institutionalized individuals, and MTF does not survey high school dropouts. Dropouts tend to engage in riskier health behaviors than non-dropouts, so MTF may not capture data from a high-risk group, potentially underestimating health risk behavior prevalence.[16]

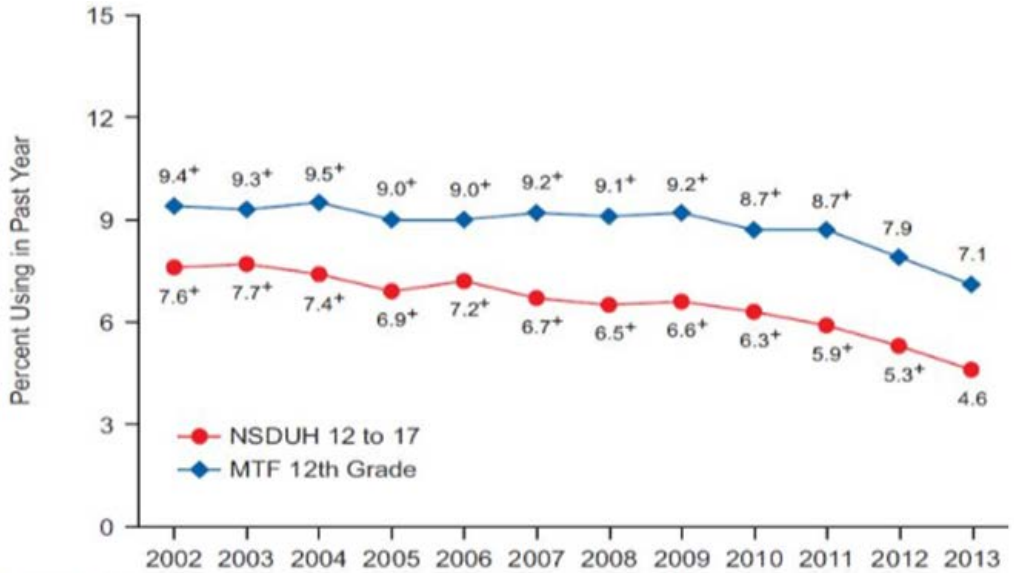
A study comparing 12th graders' MTF and NSDUH responses from 2005 to 2010 observed that prevalence estimates of past-year NMU of Oxycontin® were two-to-three times higher in MTF than in NSDUH. However, prevalence estimates of past-year NMU of any prescription opioids were consistently higher in NSDUH than in MTF (Figure 3).[17]

Figure 3. Trends in past-year prevalence of NMU of selected drugs among 12th graders in the 2005-2010: NSDUH and MTF estimates.[17]



An additional graphic confirms the variation in prevalence estimates for past-year NMUPO between the two surveys.[18] A possible explanation for some of the observed differences is a grouping effect: grouping 12 year olds with 17 year olds may lower NSDUH's observed prevalence of certain health risk behaviors compared to MTF's survey of solely high school seniors.

Figure 4. Past-year NMUPO among youths in NSDUH and MTF: 2002-2013.[18]



MTF = Monitoring the Future; NSDUH = National Survey on Drug Use and Health.

* Difference between this estimate and the 2013 estimate is statistically significant at the .05 level.

Note: Data for MTF are for "narcotics other than heroin."

Although NSDUH and MTF have inherent limitations, these limitations do not represent a significant threat to the validity of either survey's findings. NSDUH data are informative because the data are detailed, the dataset is large, and data files are readily available. Likewise, MTF is a valuable data source for drug abuse researchers because of the population studied, the scale of the dataset, and its longitudinal panel studies.

3.3.4 RELEVANT NSDUH AND MTF STUDY RESULTS

Dozens of studies have used these data sources to examine associations between young people and prescription pain reliever abuse, misuse, and non-medical use of prescription opioids (NMUPO). While every reviewed study is summarized in the Appendix 4 table, the results of the most relevant studies for answering the questions posed in this document's introduction are outlined below, and are grouped by genre of association.

Please note that the below studies may have used different years' data for their analyses; owing to temporal variations in drug use, these results may have shifted since the time of data gathering analyses.

3.3.4.1 DEMOGRAPHY

- Persons aged 16 years are more likely to initiate NMUPO than any other persons aged 12-21 years.[19] Persons aged 15-18 years have higher odds (OR=2.75, CI:2.32-3.27) of reporting NMUPO than those aged 12-15 years.[6]
- Females aged 12-17 years are more likely than males to report NMUPO (OR=1.36, CI:1.26-1.47) or symptoms of opioid abuse/dependence (OR=1.39, OR:1.13-1.70).[3]
- Persons aged 12-17 years reporting an annual family income of <$20,000 have greater odds (OR=1.7, CI:1.4-2.0) of reporting NMUPO than respondents reporting an annual family income of >$75,000.[5]
- By ethnicity and race, the percentage of respondents aged 12-17 years indicating past-year NMUPO varies in prevalence from a low of 4.3% (CI:3.3-5.4%) among Asian or Pacific Islander respondents to a high of 9.7% (CI: 7.4-12.6%) among Native American respondents (summary table below).*[4]

Table 4: One-year prevalence of analgesic opioid misuse among 72,561 adolescents aged 12 to 17 years by race/ethnicity (percentage and 95% confidence interval)*[4]

	White (n=43,778)	African American (n=10,109)	Native American (n=1122)	Asian or Pacific Islander (n=2481)	Multiple (n=2814)	Hispanic (n=12,257)
Analgesic opioid misuse	**7.5 (7.2-7.8)**	**5.5 (4.9-6.1)**	**9.7 (7.4-12.6)**	**4.3 (3.3-5.4)**	**8.8 (7.2-10.8)**	**5.6 (5.0-6.4)**

*Adapted from Wu et al. (2011)

3.3.4.2 ACTIVITIES & CONTEXT

- Persons aged 12-17 years reporting the following social, educational, and home contexts have increased odds of reporting NMUPO:[6]
    - No mother (OR=1.38, CI:1.09-1.74) or father (OR=1.36, CI:1.16-1.60) in home
    - Grades of D or worse (OR=2.84, CI:2.29-3.51)
    - Past jail/detention (OR=2.00, CI:1.60-2.49)
    - Past-year move (OR=1.46, CI:1.24-1.73)
- 12th graders who participate in high-injury sports have increased odds (e.g., wrestling [OR=1.49, CI:1.01-2.19], football [OR=1.50, CI:1.12-1.99]) of NMUPO than those who do not participate in these sports.[20]
- Among 12th graders reporting past-year NMUPO, 45% reported pain relief as a motivation.[21]
- Nearly 50% of persons aged 12-17 years reporting past-year NMUPO got these drugs for free from friends or family.[8]
- Over 36% of 12th graders reporting NMUPO obtained the drugs from their own previous prescriptions from which they had leftover pills.[7]

3.3.4.3 MENTAL HEALTH

- Females aged 12-17 years had higher odds (OR=3.7, CI:2.7-5.2) of reporting both NMUPO and a major depressive episode (MDE) in the past year than males of the same age group.[5]
- Persons aged 12-17 years reporting past-year NMUPO had more than twice the prevalence of a past-year MDE than those who reported no past-year NMUPO.[5]
- Persons aged 12-17 years who received past-year mental health treatment had higher odds (OR=2.08, CI:1.78-2.43) of NMUPO than those who did not receive mental health treatment.[6]

3.3.4.4 OTHER DRUG USE

- Persons aged 12-17 years have increased odds of reporting NMUPO if they also report past-year marijuana (OR=9.4, CI:8.0-11.0), cigarette (OR=7.8, CI:6.6-9.0), alcohol (OR=7.0, CI:5.8-8.4), or cocaine/inhalant (OR=10.1, CI:8.4-12.1) use.[6]
- Alcohol use disorder among persons aged 12-17 years is associated with higher odds (OR=3.4, CI:2.5-4.6) of reporting past-year NMUPO.[5]
- Prior NMUPO among persons aged 12-21 years is associated with an increased risk (HR=13.1, CI:10.7-16.0) of subsequent heroin initiation.[22]

3.4 ECOLOGIC STUDIES

Seven ecologic studies[1] examining adverse opioid analgesic-related outcomes in the pediatric population are reviewed below.

Gilchrist et al. (2012)[23]

Using data from the national vital statistics system (NVSS) from 2000 to 2009, CDC researchers analyzed causes of unintentional injury deaths among persons aged 0 to 19 years in the United States. During this time period, the death rate due to unintentional poisoning among persons aged 10-14 years remained largely unchanged (0.1 to 0.2 per 100,000 population; p=0.116), while the rate among persons aged 15-19 years nearly doubled (1.7 to 3.3 per 100,000; p<0.001). Additionally, the percentage of poisoning deaths in this latter age group with prescription drugs as a contributing cause increased from 30% in 2000 to 57% in 2009.

This study did not feature individual-level data to allow for control of potential confounders such as prescription indication or clinical comorbidity. NVSS is a death certificate-based data system, and death certificates vary greatly in specificity. Cause of death is a clinical determination by a medical examiner or coroner (ME/C), which has a subjective component. While these data doubtless include poisonings due to opioid analgesic overdose, other poisoning etiologies are included as well. Although this analysis included all fatal poisonings – not solely opioid-related ones – it is reasonable to suspect that opioids played a significant role in this increase over this timeframe. However, this study provides no insight into the source of the drug implicated in the poisoning or the sequence of events leading to the adverse outcome, which are central concerns of this particular review.

Calcaterra et al. (2013)[24]

Using CDC WONDER multiple cause-of-death (MCOD) data to identify pharmaceutical opioid-related overdose fatalities from 1999 to 2009 by age strata and sex, the authors observed crude overdose death rates per 100,000 persons among females aged 15-24 years was 1.32 (CI: 1.25-1.39), and 4.69 (CI: 4.56-4.82) for males in the same age category.

This study did not stratify opioid-related overdose death rates over time by age group, which would have been valuable for this document's purposes. The study could not account for additional causes of death related to substance abuse – e.g., motor vehicle crashes while intoxicated on a substance – and did not feature individual-level data to allow for control of potential confounders such as prescription indication or clinical comorbidity. CDC WONDER MCOD is a death certificate-based data system, and death certificates vary greatly by cause of death specificity. Cause of death is a clinical determination by a ME/C, which has a subjective component.

This study's results indicate that between 1999 and 2009, the opioid-related overdose fatality rate was approximately 3.5 times higher among men than women aged 15-24 years. The age-adjusted overdose death rate due to pharmaceutical opioids rose during

[1] Ecologic studies are observational epidemiologic studies in which at least one variable is measured at the population, rather than the individual, level.

this same time period. This gender disparity in opioid overdose death rates may enable more targeted methods of risk reduction on a public health level: the knowledge that young men have over thrice the opioid-related fatality rate compared to young women may give a provider pause in considering his or her prescribing practices for certain patients. However, this study provides no insight into the source of the drug implicated in the poisoning or the sequence of events leading to the adverse outcome, which are central concerns of this review.

Rudd et al. (2014)[25]

Using state health department mortality data from 28 states solicited by CDC in 2014, the authors examined heroin and opioid pain reliever (OPR) death rates from 2010 to 2012 in a variety of populations. The authors observed that the death rate from heroin overdose across all age strata doubled in this timeframe, rising from 1.0 (n=1,779) to 2.1 (n=3,635) per 100,000 population. In contrast, the OPR death rate declined from 6.0 (n=10,427) to 5.6 (n=9,869) per 100,000 population during this timeframe. Within the 15-24 year old age stratum, fatal heroin overdose rates increased over this timeframe, rising from 1.2 to 2.3 per 100,000 population – an 86.3% increase. Over this period, fatal OPR overdoses decreased in the 15-24 year old age stratum, falling from 4.3 to 3.1 per 100,000 population – a 28.1% decrease.

These analyses are limited in that over 20% of death certificates do not specify the drug involved in fatal overdoses, so these numbers are likely an underestimate. Additionally, although these data cover a majority of the states in the union, the data are not necessarily nationally representative.

Although OPRs still account for many more deaths in the overall population than heroin, the uptick in heroin-related deaths among young people is disturbing. These data, in concert with the study published by Cerda et al. showing an association between prior NMUPO and an increased risk of heroin initiation, highlight the complex and potentially fluid relationship between licit and illicit drug use. However, this publication does not suggest that there is an association between legitimate opioid use in pediatric populations and future licit or illicit opioid misuse.

Tormoehlen et al. (2011)[26]

In 2001, the Joint Committee on Accreditation of Healthcare Organizations (JCAHO) established standards for pain assessment and treatment. Using data from a single poison center in Indiana, the authors examined the number of calls reporting opioid exposures involving persons aged 12-18 years from 1994 to 2007, using the JCAHO pain control initiative as a midpoint. The main outcome measure was the number of adolescent opioid cases reported for 1994-2000 compared to 2001-2007; secondary outcomes included outcome severity, analysis of case counts by specific opioid, and correlation of the number of cases and the amount of opioids distributed within the state. The authors observed that the opioid exposure rate per 1,000 adolescent cases increased from 20.1 in 1994-2000 to 36.2 in 2001-2007, and the opioid complication rate per 1,000 adolescent cases increased from 1.6 in 1994-2000 to 4.9 in 2001-2007.

Poison control centers do not consistently capture fatal events and rely on voluntary reports by patients or providers, and likely underestimate the actual public health burden

of opioid toxicity. Adolescents may be less likely to contact poison control centers in the context of a problematic drug reaction or overdose for fear of repercussions. Misclassification is a concern as well: poison control centers accept calls from lay-people who may misreport the ingested drug. It is unclear to what extent these results from a single poison control center can be generalized to a broader population. It is also difficult to establish the JCAHO initiative as causing the increase in exposure in this age group using this type of study design and data source.

This study's results show that the count and proportion of opioid-related calls to an Indiana poison control center involving persons aged 12-18 years increased when comparing data from 1994-2000 to data from 2001-2007. However, this study provides no insight into the source of the drug implicated in the poisoning or the sequence of events leading to the adverse outcome, both of which are central concerns of this review.

Warner et al. (2011)[27]

Using data from the National Vital Statistics System (NVSS), the authors examined trends in drug poisoning deaths nationwide over the past several decades. The investigators observed that from 1999 to 2008, the drug poisoning death rate per 100,000 population for persons under age 15 remained largely unchanged (0.1 in 1999 vs. 0.2 in 2008), while the rate for persons aged 15-24 increased from 3.2 in 1999 to 8.2 in 2008.

NVSS is a robust data source, but has limitations, as it is based on death certificate data. Death certificates vary in terms of specificity of drug identified and rely on the clinical expertise of the ME/C, which carries a subjective component. The age-stratified analysis did not restrict to deaths caused solely by opioid analgesics, instead analyzing all drug poisonings. Nevertheless, these data highlight a troubling rise in fatal drug poisonings in the pediatric population, and opioid analgesics can reasonably be assumed to contribute significantly to this burden. However, this study provides no insight into the source of the drug implicated in the poisoning or the sequence of events leading to the adverse outcome, which are central concerns of this review.

Zosel et al. (2013)[28]

RADARS® is a proprietary data system that collects poison center call data to provide information on prescription opioid and stimulant abuse and misuse in the American population. The authors used RADARS® data to describe adolescent (13-19 years) exposures to prescription opioids (oxycodone, fentanyl, hydrocodone, hydromorphone, morphine, methadone, buprenorphine, and tramadol) from 2007 to 2009. There were 10,966 opioid-related adolescent cases over this time period, and the most frequently reported drugs involved were hydrocodone, oxycodone, and tramadol.

The use of poison control center data has limitations. Poison control centers do not reliably capture fatal events, making these numbers an underestimate of the true burden on the population. The data are created through voluntary reports by patients or providers, and are therefore likely an underestimate of the true burden on the population. Adolescents may be less likely to contact poison control centers in the context of a problematic drug reaction or overdose for fear of repercussions. Misclassification is a concern as well: poison control centers accept calls from lay-people who may misreport the ingested drug.This study provides no insight into the source of the drug implicated in

the poisoning or the sequence of events leading to the adverse outcome, which are central concerns of this review.

4 DISCUSSION

This review summarizes the epidemiologic data on the adverse outcomes of misuse, abuse, addiction, overdose, and death in pediatric populations prescribed and using opioid analgesics. The introduction posed several questions of interest:

- What is known about the risk of misuse, abuse, addiction, overdose, and death in pediatric populations who are prescribed opioid analgesics? What is not known? What should FDA know in order to make sound regulatory decisions in this space?
- Do pediatric patients who experience opioid analgesic-related adverse outcomes have a history of either legitimate or nonmedical use of prescription opioid analgesics?
- What data sources are available to research this topic? What types of study designs would be useful to better understand this issue in the future?

The majority of the reviewed studies were cross-sectional or ecologic in nature, and many relied on one of two data sources: NSDUH or MTF. There were three longitudinal studies and a single clinical trial that had the potential to directly address these questions.

Overall, the most recent NSDUH data (2014) indicates that well under 5% of persons aged 12 to 25 years engaged in past-month NMUPO.[2] Both MTF and NSDUH data show that past-month and past-year NMUPO prevalence have declined in recent years in the pediatric population compared to the mid-late 2000's.[14] McCabe et al.'s 2014 study concluded that most NMUPO among high school seniors is a self-limiting phenomenon, perhaps associated with the transitional period from adolescence to adulthood where drug experimentation is not uncommon.[12]

Researchers observed several notable associations in this body of pediatric drug abuse research:

- Females are more likely to engage in NMUPO than males
- Whites and Native Americans have higher prevalence rates of past-year NMU than other racial/ethnic groups
- A history of a major depressive episode, poor academic performance, single-parent homes, and low annual family income are associated with increased odds of NMUPO
- Many who report NMUPO obtain the drugs from their own leftover prescriptions, or for free from family and friends
- Past-year use of alcohol, cigarette, marijuana, or cocaine/inhalants is associated with increased odds of NMUPO among adolescents; additionally, one particularly troubling report indicated that NMUPO in adolescence was associated with an increased risk of initiating heroin in young adulthood

Ecologic data provide insights into broader trends. From 2000 to 2009, the rate of fatal drug poisonings in persons aged 15-19 years nearly doubled, and heroin death rates

nearly doubled in persons aged 15-24 years from 2010 to 2012. However, these ecologic studies do not address the central question of interest, which is whether prescribing opioids to youths for legitimate medical purposes increases these persons' risk for future opioid misuse.

A central concern is whether a legitimate opioid analgesic prescription for a young person increases that person's risk for subsequent misuse and abuse of opioids. In contrast to McCabe et al.'s 2013 study which observed no association between legitimate opioid use and subsequent (one to two years after baseline) abnormal drug screening results among 7th-12th graders,[11] Miech et al.'s 2015 study observed an increased risk of short-term (one to five years after graduation) future misuse of opioids in 12th graders previously exposed to opioids for legitimate medical purposes.[1] The results of the study by Miech et al. are particularly troubling, and warrant confirmation through additional research.

Longitudinal studies provide valuable information on the risk of adverse opioid-related outcomes in pediatric patients, and additional studies are needed to better characterize drug safety concerns in this population. A useful study design would be to follow a cohort of adolescents prescribed opioid analgesics for legitimate medical purposes over time to observe the incidence of opioid-related adverse outcomes.

Current research indicates that NMUPO prevalence rates in the pediatric population are declining. However, a particularly striking area of continuing concern is the potential importance of reducing available drug supply: a large proportion of adolescents engaging in NMUPO obtain the drugs for free from friends or family, and from leftover medications in a medicine cabinet. Reducing availability of powerful opioid analgesics is critical to prevent temptation. Prescribers are the gatekeepers to prescription opioid analgesics, and should grant access to these drugs only to patients who truly need them and in as small a supply as necessary.

Like many of the studies reviewed for this document, our methods and analysis have limitations. Every effort was made to identify and review each relevant study in the literature; however, it is possible that some studies were not captured in our search.

5 CONCLUSION

It is possible that legitimate use of an opioid analgesic in adolescence increases an individual's risk of subsequent aberrant drug-related behaviors. However, the association between adolescent use of an opioid for legitimate medical purposes and future NMUPO is based on results from a single study, and needs confirmation through additional studies. Due to the paucity of longitudinal studies in this research space, little is known about the risk of long-term adverse opioid analgesic-related outcomes – such as misuse, abuse, addiction, overdose, and death – in pediatric patients who use opioids for legitimate medical purposes. Prospective cohort studies would be especially informative for these purposes.

Many adolescents reporting NMUPO report obtaining the drugs from leftover prescriptions or from family and friends. Reducing drug availability should be a public health priority to mitigate unnecessary exposure risk in this vulnerable population.

6 RECOMMENDATIONS

FDA should consider encouraging investigators to conduct prospective cohort studies in pediatric patients prescribed opioid analgesics for medical purposes to evaluate the risk of long-term adverse outcomes associated with opioid use, and factors associated with those risks.

FDA should promote proper disposal of leftover prescription opioid analgesics by patients, particularly in households where children are present. Additionally, FDA should consider working with clinicians and pharmacists to explore ways to reduce potential excess drug availability.

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APPENDICES

Appendix 1: PubMed search string conducted on March 4, 2016 with FDA Library to identify epidemiologic studies examining adverse opioid-related outcomes in the pediatric population

Search **(#37 AND #38)** Filters: **Publication date from 2000/01/01 to 2016/12/31; Adolescent: 13-18 years; Young Adult: 19-24 years**	2580	15:03:
Search **(("Analgesics, Opioid"[Mesh]) OR opioid*[tiab] OR opioid analgesic*[tiab] OR opiate*[tiab])** Filters: **Publication date from 2000/01/01 to 2016/12/31; Adolescent: 13-18 years; Young Adult: 19-24 years**	5572	15:01:
Search **((((("Substance-Related Disorders"[Mesh]) OR substance abuse[tiab] OR abuse[tiab] OR "Prescription Drug Misuse"[Mesh]) OR misuse[tiab] OR aberrant[tiab] OR nonmedical[tiab] OR non-medical[tiab] OR "Opioid-Related Disorders"[Mesh]) OR "Drug Overdose"[Mesh]) OR overdos* [tiab] OR "Death"[Mesh] OR death*[tiab] OR morbid*[tiab] OR fatal*[tiab] OR mortal*[tiab])** Filters: **Publication date from 2000/01/01 to 2016/12/31; Adolescent: 13-18 years; Young Adult: 19-24 years**	143587	14:59:
Search **(#21 AND #32)** Filters: **Publication date from 2000/01/01 to 2016/12/31; Adolescent: 13-18 years; Young Adult: 19-24 years**	2164	14:54:
Search **(#21 AND #32)** Filters: **Publication date from 2000/01/01 to 2016/12/31; Child: birth-18 years; Adolescent: 13-18 years; Young Adult: 19-24 years**	2842	14:54:
Search **(#21 AND #32)** Filters: **Publication date from 2000/01/01 to 2016/12/31; Child: birth-18 years; Adolescent: 13-18 years**	2842	14:54:
Search **(#21 AND #32)** Filters: **Publication date from 2000/01/01 to 2016/12/31; Child: birth-18 years**	2842	14:53:
Search **((((("Substance-Related Disorders"[Mesh]) OR substance abuse OR abuse OR "Prescription Drug Misuse"[Mesh]) OR misuse OR aberrant OR nonmedical OR non-medical OR "Opioid-Related Disorders"[Mesh]) OR "Drug Overdose"[Mesh]) OR overdos* OR "Death"[Mesh] OR death* OR morbid* OR fatal* OR mortal*** Filters: **Publication date from 2000/01/01 to 2016/12/31; Child: birth-18 years**	221984	14:52:
Search **"Analgesics, Opioid"[Mesh]) OR opioid* OR opioid analgesic* OR opiate*** Filters: **Publication date from 2000/01/01 to 2016/12/31; Child: birth-18 years**	6586	14:43:
Search Filters: **Publication date from 2000/01/01 to 2016/12/31; Child: birth-18 years**	1339879	14:43:
Search **("Analgesics, Opioid"[Mesh]) OR opioid* OR opioid analgesic* OR opiate*)** Filters: **Publication date from 2000/01/01 to 2016/12/31**	59843	14:42:
Search **(("Analgesics, Opioid"[Mesh]) OR opioid* OR opioid analgesic* OR opiate*) AND ("Benzodiazepines"[Mesh] OR benzodiazepine*)) AND (co-prescription OR coprescription OR concomitant OR concurrent OR polypharmacy)** Filters: **Publication date from 2000/01/01 to 2016/12/31**	201	14:40:

Appendix 2: NSDUH Prescription Pain Reliever Question Summary

(abstracted by DEPI)[m]

Screening:
Have you ever used any prescription pain reliever? [Y/N]
Which of the following prescription pain relievers have you used in the last 12 months? [Pill cards shown here]

If yes to either screening question:
Have you ever used any prescription pain reliever in any way a doctor did not direct you to use it? [Y/N]
Examples include:

- Using it without a prescription of your own
- Using it in greater amounts, more often, or longer than you were told to take it

How old were you when you first used [DRUG]* in a way not directed by doctor? What month?

*[DRUG] includes every major opioid analgesic category, including methadone and buprenorphine.

Past year use: How have you used [DRUG] in a way other than prescribed?

- Greater amount than directed
- Without a prescription
- Other

Most recent use: What [DRUG] did you use most recently? Why did you use [DRUG]?

- Relieve pain
- Relieve tension / relax
- Experimentation
- To feel good or get high
- Sleep aid
- Help with feelings/emotions
- Increase/decrease effect of another drug
- Because I'm "hooked"
- Other reason

Information on past month use:

- Did you use [DRUG] in a manner other than prescribed? [Y/N] On how many days (estimate)?
- Did you mix with alcohol within a couple of hours of using [DRUG]? [Y/N]

[m] Substance Abuse and Mental Health Services Administration, National Survey on Drug Use and Health 2016. Final Approved CAI Specifications for Programming (English Version), accessed from http://www.samhsa.gov/data/sites/default/files/NSDUHmrbCAIquex2016v2.pdf on 6/27/2016.

How did you obtain [DRUG] that you used non-medically:

- Prescription from 1 doctor
- Prescription from >1 doctor
- Stole from healthcare facility
- Got from a friend/relative for free
- Bought from friend/relative
- Took without asking from friend/relative
- Bought from dealer/stranger
- Some other way

If you got [DRUG] from a friend/relative for free, how did they obtain [DRUG]:

- Prescription from 1 doctor
- Prescription from >1 doctor
- Stole from healthcare facility
- Got from a friend/relative for free
- Bought from friend/relative
- Took without asking from friend/relative
- Bough from stranger/dealer
- Some other way

If "YES" to past year prescription pain reliever non-medical use:

- Was there a month or more where you spent lots of time getting or using prescription pain relievers? [Y/N]
- Was there a month or more where you spent lots of time getting over the effects of prescription pain relievers? [Y/N]
- Did you try to set limits on how often / how much you would use? [Y/N]
    - Were you usually able to keep limits, or did you often use more than you intended to? [Y/N]
- Did you need to use more prescription pain reliever than previously needed to get desired effect? [Y/N]
    - Did you notice that the same amounts of prescription pain relievers had less effect than previously? [Y/N]
- Did you want to or try to cut down or stop using prescription pain relievers? [Y/N]
    - Were you able to cut down or stop using prescription pain relievers every time you wanted to or tried to? [Y/N]
    - Did you cut down or stop using prescription pain relievers at least one time? [Y/N]
- Did you ever have 3 or more of the following symptoms after cutting back or stopping? [Y/N]
    - Feeling kind of blue or down
    - Vomiting/nausea
    - Cramps/muscle aches
    - Teary eyes, runny nose
    - Sweaty, enlarged pupils, or body hair standing up on skin

    - Diarrhea
    - Yawning
    - Fever
    - Difficulty sleeping
- Same question as above, but did the symptoms last longer than a day? [Y/N]
- Did you have any problems with your emotions, nerves, or mental health that were probably caused or made worse by use of prescription pain relievers? [Y/N]
    - Did you continue to use prescription pain relievers even though you thought this was causing you to have problems with your emotions, nerves, or mental health? [Y/N]
- During past 12 months, did you have any physical health problems that were probably cause or made worse by use of prescription pain relievers? [Y/N]
    - Did you continue to use prescription pain relievers even though you thought this was causing you to have physical problems? [Y/N]
- Did using prescription pain relievers cause you to give up or spend less time doing activities like work, school, taking care of children, hobbies/sports, spending time with friends/family? [Y/N]
- Sometimes people who use prescription pain relievers have serious problems at home/school, such as neglecting their children; missing work/school; doing poorly at work/school; losing a job or dropping out of school. Did using prescription pain relievers cause you to have serious problems like this at home, work, or school? [Y/N]
- Did you regularly use prescription pain relievers and then do something where using prescription pain relievers might have put you in physical danger? [Y/N]
- Did using prescription pain relievers cause you to do things that repeatedly got you in trouble with the law? [Y/N]
- Did you have problems with family or friends that were probably caused by your use of prescription pain relievers? [Y/N]
- Did you continue to use prescription pain relievers even though you thought this caused problems with family or friends? [Y/N]
- Have you needed additional treatment or counseling for prescription pain relievers? [Y/N]

Appendix 3: MTF Non-Heroin Narcotics Question Summary

Description of the monitored variables in the survey (abstracted by DEPI)[n]

Exposure and availability of [DRUG]:

- Exposure to people who use [DRUG]
    - Exposure at parties to [DRUG]
- Proportion of friends who use [DRUG]
- Perceived availability

Use:

- Lifetime/annual/monthly prevalence and frequency of use
- Quantity consumed
- Indirect measures of quantity used per occasion (i.e., degree & duration of high)
- Mode of administration
- Injection of any drug for nonmedical use
- Patterns of multiple drug use: concurrent and not concurrent
- Age at first use
- Attempts to quit
- Felt need to quit or cut back
- Expected future use
- Prescribed use of psychotherapeutic drugs
- Use of OTC psychoactive drugs

Attitudes of significant others:

- Parental awareness of use
- Perceived friends' disapproval of use
- Perceived status attached to use in the school
- Perceived social connotations of use by respondent's acquaintances
- Perceived pressure to use

Exposure to drug education:

- Types
- Rated helpfulness
- Effect on use

Frequency of use in different settings:

- While alone
- With a few friends
- At parties

[n] Johnston L, O'Malley P, Miech R, Bachman J, Schulenberg J. Monitoring the Future: National Survey Results on Drug Use, 1975-2015: Overview, Key Findings on Adolescent Drug Use. Ann Arbor: Institute for Social Research, The University of Michigan. Accessed from http://www.monitoringthefuture.org/pubs/monographs/mtf-overview2015.pdf on 6/27/2016.

- With spouse/date
- With adults
- At home
- At school
- In a car
- During the daytime

Source of substance:
- Where acquired

Drug-related problems:
- Checklist of 15 problems
- Having “bad trips”
- Auto crashes and violations under the influence
- Driving after drinking

Reasons for use, abstention, and termination of use

Attitudes and beliefs regarding the use of various drugs:
- Perceived harmfulness
- Personal disapproval
- Social connotations attached to use
- Preferred legal status
- Preferences re: marijuana decriminalization

Exposure to drug treatment:
- Inpatient
- Outpatient

Exposure to drug testing:
- Pre-employment
- Post-employment

Exposure to antidrug ads:
- Level of recalled exposure
- Credibility of ads
- Judged impact of ads

Appendix 4: Literature review summary table. Epidemiologic studies examining the adverse opioid-related outcomes of misuse, abuse, addiction, overdose, and death in the pediatric (<21 years) population, January 1, 2000 – March 4, 2016. Updated July 21, 2016

Year	First Author	Title	Journal	Study Design	Data & Population	Outcome	Main Findings	Comments
2015	Ali	The mental health consequences of nonmedical prescription drug use among adolescents	Journal of Mental Health Policy and Economics	Cross-sectional	NSDUH 2008-2012 (84,800 12-17 yo)	Major depressive episode	12-17 year olds reporting NMUPO were 33-35% more likely to experience major depressive episodes than those who did not report NMUPO	
2013	Biondo	Discrepancies in prevalence estimates in two national surveys for nonmedical use of a specific opioid product versus any prescription pain reliever	Drug and Alcohol Dependence	Cross-sectional	NSDUH 2005-2010 (n=approximately 3,020 12th graders per year); MTF 2005-2010 (n=approximately 15,127 12th graders per year)	Discrepancies in NMU estimates	Prevalence of past-year oxycodone nonmedical use was relatively steady over the time period in both surveys, but was 2.5-3 times higher in MTF compared to NSDUH. Possible explanations include NSDUH pill cards, setting (household vs. school), mode of administration (computer vs. pencil/paper)	
2014	Bonar	Prescription drug misuse and sexual risk behaviors among adolescents and emerging adults	Journal on Studies of Alcohol and Drugs	Cross-sectional	Electronically-administered survey of adolescents seen in Michigan academic ER (n=2,127 14-20 yo), 2010-2012	SRB (inconsistent condom use, multiple partners, intercourse following drug/EtOH use); AUDIT-C and ASSIST surveys; adapted questions from National Longitudinal Study of Adolescent Health for SRB	Opioid misuse was positively associated with inconsistent condom use, multiple partners, and substance use before sex in this demographic	
2006	Boyd	Adolescents' motivations to abuse prescription medications	Pediatrics	Cross-sectional	Electronically-administered survey of 7-12th graders in MI (n=1,086), 2005	Motivations for Rx nonmedical use / abuse (including opioids); positive DAST score	12% of respondents engaged in NMUPO in the past year; main motivations were pain relief, sleep aid, anxiety, and psychoactive effects. Increasing number of motivations to abuse opioids corresponded to an increased likelihood of a positive DAST score when compared to respondents whose primary NMUPO was self-treatment of pain	Defined NMUPO as using to get high or not as prescribed
2014	Boyd	Psychological and drug abuse symptoms associated with non-medical use of opioid analgesics among adolescents	Substance Abuse	Cross-sectional	SSLS electronically administered to 7-12th graders in MI (n=2,627), 2009-2010	Psychological (assessed by YSR version of CBCL) and DAST score; motivations for Rx nonmedical use / abuse	3.5% of respondents were nonmedical users of opioids, and 1.6% screened positive for opioid abuse. Abusers had greater odds of having psychological (affective, anxiety, somatic, attention-deficit	Defined nonmedical misuse as using someone else's Rx

Year	First Author	Title	Journal	Study Design	Data & Population	Outcome	Main Findings	Comments
						including NYS battery about pain symptoms	hyperactivity, and conduct) symptoms than non-abusers	
2010	Brands	Nonmedical use of opioid analgesics among Ontario students	Canadian Family Physician	Cross-sectional	Electronically-administered survey of 7-12th graders in Ontario (n=2,914), 2007	NMUPO	20.6% respondents reported nonmedical use in last year, female (16.6%) > male (12.0%). Most (72%) got the drugs from home; 6% reported obtaining drugs from friends. NMUPO users had higher past-year prevalences of alcohol use, daily smoking, and other illicit drugs compared to non-users	Defined NMUPO as taking pills without a prescription
2013	Calcaterra	National trends in pharmaceutical opioid related overdose deaths compared to other substance related overdose deaths: 1999-2009	Drug and Alcohol Dependence	Ecologic	CDC WONDER MCOD data, 2005-2009	Unintentional pharmaceutical opioid-related death	Crude overdose death rates per 100,000 persons, 15-24 yo: female 1.32 (CI: 1.25-1.39), male 4.69 (CI: 4.56-4.82). Overall age-adjusted pharmaceutical opioid-related death rate for 15-64 yo over this timeframe was 5.47 (CI:5.42-5.51) per 100,000 person-years	
2015	Cerda	Nonmedical prescription opioid use in childhood and early adolescence predicts transitions to heroin use in young adulthood: a national study	Journal of Pediatrics	Cross-sectional	NSDUH 2004-2011 (n=223,534 12-21 yo)	Heroin initiation with previous NMUPO; age of first NMUPO as a risk function for later heroin initiation	Prior nonmedical use of Rx opioids strongly associated w/ heroin initiation (HR 13.12, CI: 10.73-16.04) in young adulthood. Younger age of NMU of opioids associated with higher risk of heroin initiation (10-12 had highest risk). Black respondents had lowest risk of heroin initiation of all ethnicities. Peak heroin initiation occurs at 17-18 years old. No one who reported zero NMUPO initiated heroin	
2012	Currie	Adolescent use of prescription drugs to get high in Canada	Canadian Journal of Psychiatry	Cross-sectional	Canadian Youth Smoking Survey 2008-2009 (n=44,344 7th-12th graders)	Past-year NMUPO	5.9% overall prevalence; females had higher odds of reporting NMUPO compared to males. Native / First Nations population had higher prevalence as well. Students with high "school connectedness" scores had lower prevalence of abuse	
2013	DeAndrea	Toward primary prevention of extra-	Preventive Medicine	Cross-sectional	NSDUH 2004-2008 (135,552 12-21 yo who had	Incident Oxycontin® abuse	Peak incidence of initiating extra-medical use of Oxycontin® is age	

Year	First Author	Title	Journal	Study Design	Data & Population	Outcome	Main Findings	Comments
		medical Oxycontin use among young people			not used Oxycontin® extra-medically in year prior to survey assessment)		16-18 yo. Pooled estimation vs. meta-analysis approaches yielded similar results	
2015	Edlund	Opioid abuse and depression in adolescents: Results from the NSDUH	Drug and Alcohol Dependence	Cross-sectional	NSDUH 2008-2012 (n=112,600 12-17 yo total sample; n=7,100 12-17 yo reporting past-year NMUPO)	MDE and NMUPO	6% reported past-year NMUPO and 8% reported past year MDE. When NMUPO and MDE were comorbid, respondents reported MDE typically preceded NMUPO. Past-year MDE associated with increased risk for reporting NMUPO	
2015	Fink	Patterns of major depression and nonmedical use of prescription opioids in the United States	Drug and Alcohol Dependence	Cross-sectional	NSDUH 2011-2012 (36,663 12-17 yo)	MDE and NMUPO	Comorbid MDE and NMUPO cluster in lower socioeconomic strata; female adolescents have higher odds (OR 3.7, CI:2.7-5.2) of comorbid NMUPO and MDE than male adolescents. Adolescents reporting EtOH use disorder, any drug use other than NMUPO also had increased odds of comorbid NMUPO and MDE	
2015	Ford	Racial/ethnic differences in factors that place adolescents at risk for prescription opioid misuse	Prevention Science	Cross-sectional	NSDUH 2012 (n=17,399 12-17 yo)	Prevalence of NMUPO by race	Black adolescents (6.08%) have highest prevalence of NMUPO, not statistically significant vs. whites (5.39%) or Hispanics (5.60%). Whites had greatest odds of NMUPO	
2012	Gilchrist	Vital signs: Unintentional injury deaths among persons aged 0-19 years – US, 2000-2009	MMWR	Ecologic	NVSS MCOD file; unintentional injury deaths from 2000-2009 (0-19 yo)	Unintentional injury death	From 2000-2009, poisoning rate among 15-19 year olds nearly doubled (1.7 to 3.33 per 100,000). Percentage of poisoning deaths in this age group w/ Rx drugs as a contributing cause increased from 30% in 2000 to 57% in 2009	
2015	Johnston	Monitoring the Future: Key Findings on Adolescent Drug Use, 2015 Findings	MTF	Cross-sectional	MTF 2015 (n=approximately 13,700 12^{th} graders)	Non-heroin narcotic use without being instructed to take by a doctor	Annual prevalence of 12^{th} grader use of non-heroin narcotics without being instructed to do so: 4.4% used Vicodin, 3.7% used Oxycontin. 2.1% report using any non-heroin narcotic in past 30 days. 39% report obtaining non-heroin narcotic would be "fairly easy" or	

Year	First Author	Title	Journal	Study Design	Data & Population	Outcome	Main Findings	Comments
							"easy"	
2008	McCabe	Screening for drug abuse among medical and nonmedical users of prescription drugs in a probability sample of college students	Archives of Pediatric and Adolescent Medicine	Cross-sectional	Web survey of college students at a "large, Midwestern 4-year university" (n=3,639), 2005	Medical and nonmedical use of prescription drugs; "probable drug abuse" measured using DAST-SF	Non-medical users of Rx drugs are at elevated risk of screening positive for drug abuse; medical users without a Hx of non-medical use are not at increased risk	
2005	McCabe	Sources of prescription drugs for illicit use	Addictive Behaviors	Cross-sectional	Web survey of college students (n=9,161), 2003	Identification of sources for Rx drugs	Broadly, categories are peer (57%) family (12%), and other (30%) for opioid sources. Peer sources were associated with higher rates of all other drug use than other sources	
2009	McCabe	Motives for nonmedical use of prescription opioids among high school seniors in the United States	Archives of Pediatric and Adolescent Medicine	Cross-sectional	MTF 2002-2006 (n=12,441 12th graders)	Identification of motivations for nonmedical Rx	45% of past-year nonmedical users reported pain relief as a primary motivation. Odds of heavy drinking and other drug use were lower among users seeking solely pain relief vs. those seeking highs	
2005	McCabe	Illicit use of opioid analgesics by high school seniors	Journal of Substance Abuse and Treatment	Cross-sectional	MTF 2002 (n=4,522 12th graders)	Identification of correlates for illicit opioid use (using Rx opioid without a prescription)	Illicit users were more likely to be male, white, and have a lower GPA; also have higher rates of tobacco use, EtOH use, MJ use, other illicit drug use, and problematic behaviors	
2007	McCabe	Medical and nonmedical use of prescription drugs among secondary school students	Journal of Adolescent Health	Cross-sectional	Web survey in MI (n=1,086 7-12th graders), 2005	Rx opioid use – medical or nonmedical – and association with positive DAST-SF screen, MJ use, or other illicit drug use	Adolescents reporting [medical or nonmedical] or nonmedical use were significantly more likely to report illicit abuse and screen positive on DAST-SF for probable drug abuse than nonusers	
2014	McCabe	Non-medical use of prescription opioids during the transition to adulthood: a multi-cohort national longitudinal study	Addiction	Cohort	MTF 1976-2005 panel studies (n=27,268 18-25 year olds)	Characteristics of persistent NMUPO users by positive NMUPO reports at any of a series ("wave") of 2-year follow-up surveys following graduation	Majority of wave 1 + users did not continue to use; majority of wave 1-2-3-4 + users (~3% of all NMUPO users) had associations with binge drinking, MJ, and other substance abuse behaviors	
2005	McCabe	Nonmedical use of prescription opioids	Addictive Behaviors	Cross-sectional	CAS 2001 (n=10,904 college students)	NMUPO (use without a doctor's Rx)	Students attending less competitive schools, HBCU had lower	

Year	First Author	Title	Journal	Study Design	Data & Population	Outcome	Main Findings	Comments
		among U.S. college students: prevalence and correlates from a national survey					prevalence of NMUPO. Black, Asian, Hispanic respondents had lower prevalence of NMUPO; higher GPA had lower prevalence of NMUPO; living in off-campus or Greek housing had higher prevalence of NMUPO	
2013	McCabe	Motives for medical misuse of prescription opioids among adolescents	Journal of Pain	Cross-sectional	2011-2012 SSLS (n=2,964 Detroit 7th-12th graders)	Listed motivation for past-year misuse (taking more of one's own pills than prescribed or to get high, e.g.) and nonmedical use (using pills prescribed to someone else)	Misuse: pain relief (84%), to get high (20%) are most common motivations NMU: pain relief (87%), to get high (13%) are most common motivations	
2013	McCabe	Medical use, medical misuse, and nonmedical use of prescription opioids: results from a longitudinal study	Pain	Cohort	2009-2011 SSLS (n=2,050 7th-11th graders at 2 schools in MI)	Past year use; nonmedical use; DAST-10 score for probable drug abuse	Of those reporting past-year NMUPO in year 1, 25% continued in year 2. Odds of a positive DAST in year 2 were greater for adolescents who reported medical misuse or NMUPO for non-pain-relief motives in Year 1 compared to those who did not use Rx opioids	
2013	McCabe	Leftover prescription opioids and nonmedical use among high school seniors: a multi-cohort national study	Journal of Adolescent Health	Cross-sectional	MTF 2007-2010 (n=8,888 12th graders)	Past year NMUPO and sources	36.9% of past year NMUPO users obtained Rx from their own previous prescriptions; 55% received for free from a friend or relative; those who obtained Rx from another source had higher odds of abuse-type behaviors. Most commonly reported motivation was pain relief (72%)	
2007	McCabe	Does early onset of non-medical use of prescription drugs predict subsequent prescription drug abuse and dependence? Results from a national study	Addiction	Cross-sectional	NESARC 2001-2002 (n=43,093 ≥18 yo)	Self-report age of onset of non-medical use of Rx pain reliever; current drug use d/o based on validated AUDADIS-IV instrument	A higher percentage of individuals who began using Rx drugs nonmedically at or before age 13 years had developed Rx drug abuse and dependence compared to those who began using at or after 21 years of age	

Year	First Author	Title	Journal	Study Design	Data & Population	Outcome	Main Findings	Comments
2012	McCabe	Co-ingestion of prescription opioids and other drugs among high school seniors: results from a national study	Drug and Alcohol Dependence	Cross-sectional	MTF 2002-2006 (n=12,441 12th graders)	Report of NMUPO and co-ingestion of other drugs simultaneously	Overall prevalence of NMUPO co-ingestion with other drugs is 4.9%; MJ (58%), alcohol (52%) most commonly reported. Among those who report NMUPO, prevalence of co-ingestion is 70%. Nonmedical users who co-ingested were more likely to snort, use recreationally, and had higher subjective high experiences	
2014	McCabe	Trends in medical use, diversion, and nonmedical use of prescription medications among college students from 2003 to 2013: Connecting the dots	Addictive Behaviors	Cross-sectional	CSLS, conducted odd years inclusive 2003-2013 (n=21,771 undergraduate college students)	Prevalence of past year, lifetime use NMUPO	8.8-16.4% of respondents had used NMUPO in the lifetimes, depending on the year. Past year prevalence of medical use, diversion, and nonmedical use of prescription opioids decreased from 2003-2013. White, male, Greek member, lifetime hx of receiving an Rx have higher odds for nonmedical use	
2012	McCabe	Adolescent nonmedical users of prescription opioids: Brief screening and substance use disorders	Addictive Behaviors	Cross-sectional	SSLS 2009-2010 (n=2,744 7th-12th graders)	Positive CRAFFT screen with h/o NMUPO	35% of NMUPO users screen positive for CRAFFT. Odds of buying, obtaining from multiple sources, snorting, and abusing were higher among those with positive CRAFFT screen	
2014	McCabe	Social contexts of substance use among U.S. high school seniors: a multicohort national study	Journal of Adolescent Health	Cross-sectional	MTF 2002-2011 (n=24,809 12th graders)	Social context of drug use	Alcohol, MJ, and polydrug use most often occur at parties; stimulants, tranquilizers, and opioid use occur most often at home	
2007	McCabe	Trends and college-level characteristics associated with the non-medical use of prescription drugs among US college students from 1993 to 2001	Addiction	Cross-sectional	CAS 1993-2001 inclusive odd years (n=approximately 10,000-15,000 undergraduate college students annually)	Prevalence trends and college-level characteristics of NMUPO	Past-year and lifetime prevalence of NMUPO increased from 1993-2001	
2012	Meier	Extramedical use of prescription pain relievers by youth	Archives of Pediatric and Adolescent Medicine	Cross-sectional	NSDUH 2004-2008 (n=138,729 12-21 yo)	Estimated age-specific risk of initiating extramedical use of	16 years of age is peak year for initiating extramedical use (2-3% become newly incident users);	

Year	First Author	Title	Journal	Study Design	Data & Population	Outcome	Main Findings	Comments
		aged 12 to 21 years in the United States				prescription pain relievers, year by year, and confirmation of peak age risk	smaller risk estimates above and below that age	
2015	Miech	Prescription opioids in adolescence and future opioid misuse	Pediatrics	Cohort	MTF 1990-2012 (n=6,220 who answered questions in at least one of the three follow-up panel surveys)	Past-year opioid misuse at subsequent follow-up	Among 12th graders with little experience with illegal drug use and who strongly disapprove of illegal drugs, a legitimate opioid Rx predicts opioid misuse after HS (RR 1.33, CI: 1.04-1.7)	
2015	Mitra	Drug use patterns predict risk of non-fatal overdose among street-involved youth in a Canadian setting	Drug and Alcohol Dependence	Cohort	Street-involved (homeless or semi-homeless) youth in BC, Canada (At Risk Youth Study) who self-report no history of OD (n=615 14-26 yo)	Self-report of non-fatal OD in past 6 months; aim to determine factors associated with non-fatal OD from 9/2005 – 5/2012. Time to OD event as survival analysis	98 participants (16%) reported non-fatal OD from 2005-2012. Binge drug use, injection Rx opioid use, non-injection meth use, injection heroin use were associated with shorter time to non-fatal overdose	Defined non-fatal OD as "negative reaction from using too much drugs"
2015	Murphy	Opioid misuse among adolescents: new evidence from a misclassification analysis	Applied Health Economics and Health Policy	Cross-sectional	2008 WA State Healthy Youth Survey (n=9,990 8th, 10th, and 12th graders)	Non-medical prescription opioid use; misusing own vs. someone else's prescription, likelihood of misreporting of prescription source	35% of respondents who said they had never misused prescription opioids "most likely had [done so]". 17% claimed to have misused a diverted prescription, but probably had misused their own	
2014	Murphy	Non-medical prescription opioid use and violent behavior among adolescents	Journal of Child and Adolescent Mental Health	Cross-sectional	2008 WA State Healthy Youth Survey (n=10,623 8th, 10th, 12th graders)	Opioid abuse and association with violent behavior or thoughts	Rx opioid abuse associated with violent behavior, attitude, and thoughts	
2012	Nakawaki	Predicting adolescents' persistence, non-persistence, and recent onset of nonmedical use of opioids and stimulants	Addictive Behaviors	Cross-sectional	NSDUH 2003-2009 (n=126,764 12-17 yo)	Persistent, non-persistent, and nonmedical use of Rx opioids	Persistent nonmedical users of MJ/inhalants had greater risk of nonmedical opioid and stimulant use. Non-persistent use of MJ/inhalants was strong predictor of non-persistent opioid and stimulant use	Non-persistent user is someone who used in the past 2 years w/o repeat use; persistent user is someone who used in past 2 years with use in past year
2015	Parker	Epidemiological evidence on extra-medical use of prescription pain	PeerJ	Cross-sectional with pooled meta-analysis	NSDUH 2002-2013 (n=330,983 12-21 yo)	Opioid dependence within 12 months of initiating extramedical use of prescription	Peak risk of transitioning from extramedical use of opioids to opioid dependence seen among 14-15 yo, which is earlier than peak	

Year	First Author	Title	Journal	Study Design	Data & Population	Outcome	Main Findings	Comments
		relievers: transitions from newly incident use to dependence among 12-21 year olds in the United States using meta-analysis, 2002-13				pain relievers	risk for extramedical use initiation, which is typically 16-19 yo. Projected one adolescent transition to adolescent-onset opioid dependence within 12 months for every 11-16 newly incident extramedical users	
2014	Rudd	Increases in heroin overdose deaths – 28 states, 2010 to 2012	MMWR	Ecologic	28 state health department mortality files, 2008-2012	Heroin overdose death	Heroin OD death rate in 15-24 yo stratum increased 86% from 2010 to 2012 ; opioid pain reliever death rate in same stratum decreased 28% in same timeframe	
2008	Schepis	Characterizing adolescent prescription misusers: a population-based study	Journal of the American Academy of Child and Adolescent Psychiatry	Cross-sectional	NSDUH 2005 (n=18,678 12-17 yo)	Predictors of opioid Rx misuse	Predictors of Rx opioid misuse include poor academic performance, past year depression, past-year MJ, EtOH, Tob, cocaine/inhalant use (Table 2)	
2009	Schepis	Sources of prescriptions for misuse by adolescents: Differences in sex, ethnicity, and severity of misuse in a population-based study	Journal of the American Academy of Child and Adolescent Psychiatry	Cross-sectional	NSDUH 2005-2006 (n=36,992 12-17 yo)	Sources of misused Rx opioids	47% of all misusers got Rx opioid for free from friend/relative; 22% from a physician; 13% purchased	
2013	Spoth	Longitudinal effects of universal preventive intervention on prescription drug misuse: three randomized controlled trials with late adolescents and young adults	American Journal of Public Health	Randomized controlled trial	IA, PA 6-12th graders	Self-reported Rx opioid misuse and lifetime Rx drug misuse after randomization to either control group or family-, community-, and peer pressure resisting-related programming	Brief universal interventions – ISFP, SFP 10-14 + LST, SFP + 1 of 3 school-based curricula – were associated with significant reductions in likelihood of misusing opioid Rx in young adulthood	
2010	Subramania m	The added risk of opioid problem use among treatment-seeking youth with marijuana and/or	Addiction	Cross-sectional	Youth recruited from Baltimore-area drug treatment sites (n=475)	Opioid problem use in youth with MJ/EtOH problem use already	Individuals with opioid problem use in conjunction with MJ/EtOH problem use more likely to be older teens (15-17 yo), white, have higher SUD diagnoses, have	

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		alcohol problem use					greater psychiatric symptom severity, engage in higher rates of illegal behaviors	
2005	Sung	Nonmedical use of prescription opioids among teenagers in the United States: trends and correlates	Journal of Adolescent Health	Cross-sectional	2002 NSDUH (n=17,709 12-17 yo) as well as trended NSDUH data from 1965-2001	Past year prevalence of opioid misuse	Highest prevalence groups include females, blacks, lower SES, have favorable attitudes towards illicit drugs, have detached parents, or have friends who use illicit drugs	
2011	Tormehlen	Increased adolescent opioid use and complications reported to a poison control center following the 2000 JCAHO pain initiative	Clinical Toxicology	Ecologic	Poison control center in Indiana from 1994-2000, 2001-2007 (n=1,634 12-18 yo)	Number of opioid calls from the two timeframes involving 12-18 yo	In 2001-2007, there was an increase in the number of calls involving adolescents	
2012	Vaughn	Risk profiles among adolescent nonmedical opioid users in the United States	Addictive Behaviors	Cross-sectional	2008 NSDUH (n=17,842 12-17 yo)	Latent class analysis risk stratification	Four classes of risk exist in this age group: low delinquency/low substance use, high delinquency / low substance use, high substance use / low delinquency, high delinquency/high substance use	
2014	Veliz	Painfully obvious: a longitudinal examination of medical use and misuse of opioid medication among adolescent sports participants	Journal of Adolescent Health	Cross-sectional	SSLS 2009-2012 (n=1,540 14-19 yo)	Misuse of Rx opioids and playing organized sports	Male adolescents who participate in organized sports have higher odds of medical use (OR=1.86, CI:1.23-2.82) and misuse of opioids (OR=10.5, CI:2.42-45 5)	
2013	Veliz	Playing through pain: sports participation and nonmedical use of opioid medications among adolescents	American Journal of Public Health	Cross-sectional	MTF 2010-2011 (n=21,135 8th, 10th, and 12th graders)	Nonmedical use of opioids and participation in an organized sport	Adolescents participating in high-injury sports (wrestling OR1.49, CI:1.01-2.19; football OR=1.50, CI:1.12-1.99) had greater odds of NMUPO than those who did not participate in these sports	
2011	Warner	Drug poisoning deaths in the United States, 1980-2008	NCHS data brief	Ecologic	NVSS	Poisoning deaths; opioid-related poisonings	From 1999-2008, opioid-related poisoning rate in 15-24 yo rose from 3.2 per 100,000 to 8.2 per 100,000	
2013	Whiteside	Nonmedical prescription opioid	Pediatrics	Cross-sectional	Adolescents who presented to Univ. Michigan ED	Prevalence of past-year nonmedical	~10% reported nonmedical prescription opioid use in past year.	

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		and sedative use among adolescents in the emergency department			(n=2,135)	prescription opioid use	Correlates included other substance use, drinking and driving, receiving IV opioids in ED	
2011	Wu	Treatment use and barriers among adolescents with prescription opioid use disorders	Addictive Behaviors	Cross-sectional	NSDUH 2005-2008 (n=1,788 12-17 yo who met at least one of the past-year criteria for Rx opioid abuse or dependence)	Prevalence of treatment use and perceived need by opioid use status; perceived barriers to Tx	About 17% of adolescents with opioid dependence used treatment in the past year for their condition. Under-used among adolescents who would benefit from it, especially black adolescents	
2008	Wu	Prescription pain reliever abuse and dependence among adolescence: a nationally representative study	Journal of the American Academy of Child and Adolescent Psychiatry	Cross-sectional	NSDUH 2005-2006 (n=2,675 12-17 yo who reported past-year nonprescribed prescription pain reliever use)	Opioid misuse, nonmedical use, and subthreshold dependence	Increased odds of abuse among females, those who buy pills, those who report fair/poor health, nonstudents	
2011	Wu	Racial/ethnic variations in substance-related disorders among adolescents in the United States	Archives of General Psychiatry	Cross-sectional	NSDUH 2005-2008 (n=72,561 12-17 yo)	Substance-related disorders by ethnicity/race	Rx opioid misuse prevalence highest among Native Americans (9.7%), lowest among Asian/Pacific Islanders (4.3%)	
2012	Young	Nonmedical use of prescription opioids among adolescents: subtypes based on motivation for use	Journal of Addictive Diseases	Cross-sectional	Web-based survey administered to MI middle and high school students from 2009-2010 (n=2,597)	Profiles of users by those who want to get high or those who are treating themselves	Sensation-seeking nonmedical users were characterized by rule-breaking and aggressive behaviors. Medical and nonmedical self-treating users were characterized by somatic complaints, anxiety/depressive symptoms, and history of sexual victimization	
2013	Zosel	Characterization of adolescent prescription drug abuse and misuse using the RADARS system	Journal of the American Academy of Child and Adolescent Psychiatry	Ecologic	RADARS (n=16,209 poison control center calls involving 13-18 yo and opioids or stimulants)	Opioid-related adolescent calls	10,966 opioid-related adolescent cases, and the most frequently reported drugs were hydrocodone, oxycodone, and tramadol	

ASSIST – Alcohol, Smoking, and Substance Involvement Screening Test
AUDADIS-IV – Alcohol Use Disorder and Associated Disabilities Interview Schedule – DSM-IV version
AUDIT-C – Alcohol Use Disorders Identification Test
CAS – Harvard School of Public Health College Alcohol Study
CBCL – Child Behavior Checklist

CDC – Centers for Disease Control and Prevention
CRAFFT – Adolescent drug survey screen
CSLS – College Student Life Survey
DAST / DAST-10 / DAST-SF – Drug and Alcohol Screening Test
d/o – Disorder
EtOH – Alcohol
h/o – History of
MCOD – Multiple Cause of Death
MDE – Major depressive episode
MI – Michigan
MTF – Monitoring the Future
NESARC – National Epidemiologic Study on Alcohol and Related Conditions
NHAMCS – National Hospital Ambulatory Medical Care Survey
NSDUH – National Survey on Drug Use and Health
NVSS – National Vital Statistics System
NYS – National Youth Survey
Rx – Prescription
SRB – Sexual risk behaviors
SSLS – Secondary Student Life Survey
WONDER – Wide-ranging Online Data for Epidemiologic Research
Yo – Years old
YSR – Youth Self Report

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