FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE (PADAC) AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE (DSaRM)

Thursday, December 10, 2015

8:05 a.m. to 3:12 p.m.

FDA White Oak Campus

Building 31, The Great Room

White Oak Conference Center

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(8:05 a.m.)

Call to Order

Introduction of Committee

DR. OWNBY: Okay. I'd like to first remind everyone to silence your cell phones, smartphones, and any other devices if you've not already done so. I'd also like to identify the FDA press contact, Andrea Fischer. If you are here, please stand up. She's there in the back of the room.

My name is Dennis Ownby. I'm chairperson of the Pulmonary Allergy Drugs Advisory Committee, and I will be chairing this meeting. I will now call the joint meeting of the Pulmonary Allergy Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee to order. We'll start by going around the table and introducing ourselves. We'll start with the FDA on my left, that's way down there somewhere. You can almost see you from here.

DR. SEYMOUR: Hi. My name is Sally Seymour. I'm the Deputy Director for Safety in the Division

of Pulmonary Allergy and Rheumatology Products.

DR. RACOOSIN: Good morning. I'm Judy Racoosin, the deputy director for Safety in the Division of Anesthesia, Analgesia, and Addiction Products.

CDR MOENY: Good morning. I'm David Moeny. I'm the deputy director for epidemiology in the Division of Epidemiology II.

DR. ADAH: Good morning. My name is Steven Adah. I'm an interdisciplinary science team leader in the Division of Nonprescription Drug Products.

DR. LEEDER: My name is Steve Leeder. I'm the director of the Division of Clinical Pharmacology, Toxicology, and Therapeutic Innovation at Children's Mercy Hospital in Kansas City. My area of interest is pharmacogenetics and the ontogeny of drug metabolism in children.

DR. ALEXANDER: I am Caleb Alexander. I'm a practicing general internist and pharmacoepidemiologist at Johns Hopkins.

DR. DRACKER: Bob Dracker. I am a member of the Pediatric Advisory Committee, and I'm a

pediatrician, hematologist and transfusion medicine specialist in Syracuse, New York.

DR. WHITE: Hi. I'm Michael White. I'm from New Orleans Ochsner Health Center in our University of Queensland Medical School. I'm a pediatric cardiologist, and chair of one of our IRB panels.

DR. GUDAS: Hi. I'm Lorraine Gudas. I'm chairman of the pharmacology department at Weill Cornell Medical College in New York City.

DR. ROUMIE: Christianne Roumie. I'm an internist and a pediatrician, and I do a lot of pharmacoepidemiology at Vanderbilt University.

DR. NELSON: I'm Dawn Nelson. I'm a professor of audiology at Central Michigan University. But in my capacity here, I'm a patient representative. I have a daughter with sickle cell anemia.

DR. PERRONE: Good morning. I'm Jeanmarie Perrone. I'm the director of medical toxicology at the University of Pennsylvania and a practicing emergency medicine physician.

DR. GRAYSON: Hi. I'm Mitch Grayson. I'm an immunologist at the Medical College of Wisconsin.

DR. McCORMACK: My name is Frank McCormack. I'm Chief of Pulmonary Critical Care and Sleep at the University of Cincinnati.

DR. TRACY: I'm Jim Tracy. I'm an allergist/immunologist, Creighton University, and a pediatrician.

DR. HARKINS: Michelle Harkins. I'm chief of Pulmonary Critical Care and Sleep at University of New Mexico.

DR. HONG: Morning. Cindy Hong, designated federal officer for the Pulmonary Allergy Drugs Advisory Committee.

DR. OWNBY: Dennis Ownby. I'm a pediatric allergist at the Medical College of Georgia.

DR. GEORAS: Steve Georas. I'm an adult pulmonary and critical care physician in Rochester, New York.

DR. MORRATO: Good morning. I'm Elaine Morrato. I'm an epidemiologist and health services

researcher and the associate dean for public health practice at the Colorado School of Public Health.

DR. CONNETT: I'm John Connett. I'm in biostatistics at the University of Minnesota.

DR. YU: Good morning. I'm Yanling Yu, a research scientist with the University of Washington and consumer rep on the pulmonary committee.

DR. BESCO: Good morning. My name is Kelly Besco. I'm the medication safety coordinator for the Ohio-Health Hospital System in Columbus, Ohio, and I'm a pharmacist by background.

DR. GERHARD: Tobias Gerhard, pharmacoepidemiologist at Rutgers University.

DR. PARKER: Ruth Parker, professor of medicine, pediatrics, public health at Emory; do a lot of work in health literacy.

DR. PRUCHNICKI: I'm Maria Pruchnicki, associate professor at the Ohio State University College of Pharmacy and a clinical pharmacist.

DR. HUDAK: Good morning. I'm Mark Hudak, chair of pediatrics, University of Florida College

of Medicine in Jacksonville.

DR. CATALETTO: Mary Cataletto. I'm a pediatric pulmonologist at Winthrop University Hospital and professor of clinical pediatrics at SUNY Stony Brook.

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz, pharmacoepidemiologist, Harvard T.H. Chan School of Public Health in Boston.

DR. SUAREZ-ALMAZOR: Good morning. I'm Maria Suarez-Almazor. I'm a professor at the University of Texas MD Anderson Cancer Center. And I'm an internist and clinical epidemiologist.

DR. BROWN: I'm Rae Brown. I'm professor of anesthesiology and pediatrics at the University of Kentucky and Kentucky Children's Hospital.

DR. FLICK: Randall Flick. I'm a pediatrician/anesthesiologist/intensivist, and director of the Mayo Clinical Children's Center. I also chair the Anesthetic and Analgesic Life Support, or Drug Products Advisory Committee.

DR. WALCO: Gary Walco, professor of anesthesiology, pediatrics, and psychiatry and

director of pain medicine at Seattle Children's.

DR. FINNEGAN: Maureen Finnegan. I'm an orthopedic surgeon at UT Southwestern practicing at Children's in Parkland.

DR. GREEN: Good morning. I'm Stuart Green. I'm head of late stage clinical development respiratory and immunology at Merck Research labs, and I'm the non-voting industry rep to the committee.

DR. OWNBY: Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee and the Government in the Sunshine Act,

we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of this meeting. We are aware that members of the media are anxious to speak with FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

I will now pass the meeting to Lieutenant Cindy Hong, who will read the Conflict of Interest statement.

Conflict of Interest Statement

DR. HONG: The Food and Drug Administration is convening today's joint meeting of the Pulmonary-Allergy Drugs and Drug Safety and Risk Management Advisory Committees under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committees are special government employees or

regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of these committees' compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of these committees are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and temporary voting members of these committees have been screened for potential

financial conflict of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves the safety of codeine in children 18 years of age and younger. Codeine, most often in combination with acetaminophen, is used for the treatment of pain in children, however it is contraindicated for the management of pain after tonsillectomy and/or adenoidectomy.

Codeine, in combination with other medicines, is used for the relief of cough associated with upper respiratory allergies or the common cold in children. Codeine is available by prescription and also through the over-the-counter drug monograph for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products.

The focus of the meeting will be the risk of serious adverse events, such as respiratory depression and death, including reports in children who are CYP2D6 ultra-rapid metabolizers. The committees will discuss whether the use of codeine in children should be restricted further beyond the current contraindication described previously and whether codeine should be available through the OTC Drug monograph. This is a particular matters meeting during which general issues will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, a conflict of interest waiver has been issued in accordance with 18 U.S.C. Section 208(b)(3) to Dr. James S. Leeder. Dr. Leeder's waiver addresses his employer's contract with a potentially competing firm regarding a product that potentially would compete with the products under review by the committees. The total funding is anticipated to be between $100,001 and $300,000 per year. Dr. Leeder will

not have any role in the actual conduct of the study.

The waiver allows this individual to participate fully in today's deliberations. FDA's reasons for issuing the waiver are described in the waiver documents, which are posted on FDA's website at www.fda.gov/advisorycommittees/committeesmeetingmaterials/drugs/default.htm. Copies of the waiver may also be obtained by submitting a written request to the agency's Freedom of Information Division, 5630 Fishers Lane, Room 1035, Rockville, Maryland 20857, or requests may be sent via fax to 301-827-9267.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the topic at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Stuart Green is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Green's role at

this meeting is to represent industry in general and not any particular company. Dr. Green is employed by Merck Sharp & Dohme Corporation.

We would like to remind members and temporary voting members that if the discussions involve any other topics not already on the agenda, for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committees of any financial relationships that they may have regarding a topic that could be affected by the committee's discussions. Thank you.

DR. OWNBY: Thank you, Lieutenant Hong. We will now proceed with the FDA presentation. I believe Dr. Seymour will start.

FDA Opening Remarks

DR. SEYMOUR: Good morning. My name is Dr. Sally Seymour, and I'm the deputy director for safety in the Division of Pulmonary, Allergy, and Rheumatology Products. I want to welcome you to

today's joint meeting of the Pulmonary, Allergy, Drugs and Drug Safety and Risk Management Advisory Committee meeting. I want to thank you for taking the time out of your schedules to participate in this important meeting and this important discussion.

In the next 10 minutes, I'm going to give just a very brief introduction to the issues for discussion for today's meeting and a very brief background for today's meeting.

The objective of today's meeting is to discuss the safety of codeine for cough or pain in children 18 years of age and younger, and the focus of today's discussion will be on safety and potential regulatory actions. We do not have presentations on efficacy as the agency has previously made a determination of efficacy for codeine for cough and pain. And we're going to be asking for your input on whether the agency should further restrict the use of codeine for cough or pain, and we also seek your feedback on the availability of codeine for children for cough

over the counter.

Codeine is an opioid that's been around for decades, and it's metabolized by CYP2D6, and you're going to hear a lot more about the metabolism of codeine this morning. It's approved for the relief of mild to moderately severe pain where the use of an opioid analgesic is appropriate. And for this indication, codeine is primarily used in combination with acetaminophen.

For cough, codeine is available only in combination with other medications, such as antihistamines, so the indication is for the relief of cough associated with upper respiratory allergies or the common cold. And for cough, codeine is available in both prescription and over the counter through the FDA monograph, and you'll hear more about the FDA monograph for codeine today.

So why are we here today? We're here because of safety issues and concerns with codeine. And the main safety issue of concern is respiratory depression, and we'll present available data

regarding respiratory depression and death in pediatric patients. Part of the concern is because of the variability in codeine metabolism based upon CYP2D6 activity and how this may impact safety. Because of the safety issue, some regulatory agencies have restricted the use of codeine for both cough and analgesia in pediatric patients, and in the next couple of slides, I'm going to walk you briefly through some of the relevant regulatory history.

The relevant regulatory history for codeine safety dates back to 2006-2007 when a death was reported in a nursing infant whose mother took codeine, and she was found to be an ultra-rapid metabolizer. After review of this issue, FDA modified codeine labeling to include this information and warned healthcare providers about this potential risk.

We pick up the safety issue again in 2012 with publication of a case series of deaths with use of codeine in children in the post-tonsillectomy and adenoidectomy setting. FDA

embarked on a review of this issue in 2012, and in 2013 required a contraindication for codeine use in the adenoid/tonsillectomy setting. And you'll hear more about this review and why FDA required contraindication in children in this setting.

Following the FDA action, the EMA, which is the European Medications Agency, and Health Canada recommended the use of codeine for any pain be limited to children 12 years of age and older. And Health Canada went even further and recommended that codeine not be used in children less than 12 years of age for cough.

In 2014, the EMA then embarked on a review of codeine use for cough. And based upon that review, in 2015, they restricted the use of codeine for cough in children less than 12 years of age. And because of this, we decided to reevaluate the use of codeine in children, and that brings us to this advisory committee meeting today.

So the regulatory actions of other agencies is one of the reasons we are here today. And here's a summary of the regulatory agency

recommendations for use of codeine in children for cough and/or analgesia. Please note that these are not all the recommendations, but ones that are important to inform today's discussion, and let me highlight a couple of points.

For analgesia, the FDA has a focused contraindication for the post-tonsillectomy and/or adenoidectomy setting in children, and this would be children of all ages. The EMA and Australia also have similar recommendations. But some regulatory bodies have a broader recommendation to not use codeine for analgesia or cough in children less than 12 years of age, as shown in the red boxes. And for cough, FDA does not have a specific contraindication. So we're here today to ask you whether you recommend we further restrict the use of codeine in children.

Here's an outline of today's presentations. We'll begin with the clinical pharmacology and pharmacogenomics of codeine. The next presentation will discuss codeine for analgesia and focus on the 2012 review that FDA conducted. Then we'll

transition to codeine use for cough. And the codeine for cough presentation will provide more information about the monograph process and specifically focusing on the codeine monograph.

Our safety group will present data from the most recent FDA review, including utilization patterns for codeine products, postmarketing safety data, and epidemiologic data. Note that there are no FDA presentations regarding efficacy. NDA sponsors were asked if they wanted to participate in today's meeting, and they declined.

So we will end the morning with the open public hearing before lunch. And following lunch, I'll give a brief charge to the committee and then the committee discussion voting.

Finally, the topics for discussion are shown on this slide. We'll be asking you to discuss the available safety data for codeine and asking for your feedback on whether codeine should be further restricted in children, and the OTC availability of codeine. And I'll go over the specific questions during the charge to the committee this afternoon.

Thank you, and I'll turn the chair back to Dr. Ownby.

FDA Presentations - Sheetal Agarwal

DR. AGARWAL: Good morning. My name is Sheetal Agarwal. I am a clinical pharmacology reviewer in CDER FDA. Today I'll be presenting a high-level summary of the clinical pharmacology and pharmacogenomic aspects of codeine. This slide enlists the key topics included in my presentation. I will talk about clinical pharmacology of codeine, its pharmacokinetic features, its metabolic pathways, CYP2D6 enzyme related polymorphisms, and finally conclude with some key points.

Codeine is a naturally occurring opium alkaloid. It is used as an analgesic and as an antitussive. Its primary analgesic effect comes from morphine, which is a metabolite of codeine. Codeine has about 200-fold weaker affinity than morphine for the mu opioid receptor. As an antitussive, it is believed to have a direct effect on the cough center.

This slide enlists some of the

pharmacokinetic features of codeine. Orally administered codeine is absorbed quickly with Cmax occurring at about 1 hour. Plasma half-life of codeine is about 3 hours. Codeine is metabolized by glucuronidation and by CYP enzymes.

CYP3A4 converts codeine to norcodeine, and CYP2D6 converts codeine to morphine. Because of the involvement of CYP3A4 and CYP2D6 in codeine metabolism, there is some drug-drug interaction potential when codeine is co-administered with CYP3A4 or CYP2D6 inhibitors. Codeine is renally eliminated, and about 10 percent of that is as unchanged codeine.

This figure depicts the various metabolic pathways of codeine. Norcodeine and codeine-6-glucuronide, which are considered inactive metabolites, are shown on the left-hand side of this picture. About 5 to 15 percent of codeine is metabolized into morphine by a polymorphic enzyme CYP2D6. Morphine and its metabolites are shown on the right-hand side of this picture. The conversion of codeine to

morphine varies with the type of CYP2D6 polymorphism, which you will see on the next slide.

This slide enlists the four different phenotypes related to CYP2D6 polymorphism and prevalence of each of these phenotypes in Caucasians. The phenotype with negligible CYP2D6 activity is termed poor metabolizer, or PM, and the prevalence of this group is about 5 to 10 percent. The phenotype with intermediate CYP2D6 activity is termed intermediate metabolizer, or IM, and the prevalence of this group is about 2 to 11 percent.

The wild type phenotype or the normal phenotype is the extensive metabolizer group, or EM. And the prevalence of this group is about 77 to 92 percent. Lastly, the phenotype with extensive CYP2D6 activity is termed ultra-rapid metabolizer, or UM, and the prevalence for this group is about 1 to 2 percent.

We are the most concerned with the ultra-rapid metabolizer group for codeine safety as this group can convert higher than normal amounts of codeine to the much more potent opioid,

morphine. On the right-hand side of the slide, you will see the prevalence of the ultra-rapid metabolizer group in other ethnic groups.

In African-Americans, the prevalence is about 3 percent. In Arabs, Ethiopians, and North Africans, the prevalence is about 16 to 28 percent. And in Chinese, Hispanic and Japanese, the prevalence is about 0.5 to 1 percent.

This slide shows mean plasma profiles of codeine and morphine in PMs, Ems, and UMs when 30 milligram of codeine was orally administered to each of these groups. Time in hours is shown on the X-axis, and drug concentration in microgram per liter is shown on the Y-axis. Green color represents PM, blue color represents EM, and red color represents UM.

If you look at the top picture, which represents codeine, you will notice that codeine concentrations seem similar in the three groups. If you look at the bottom picture, which represents morphine, you will notice that morphine concentrations are the highest in the UM group

followed by the EM group. Morphine concentrations are almost negligible in the PM group.

Since CYP2D6 plays an important role in codeine metabolism, we searched published literature for articles related to evaluating CYP2D6 activity with increasing age. This picture is borrowed from a recently published article in which the authors concluded that CPY2D6 activity remains constant after 1 week of postnatal age through 18 years. In this scatter plot, age in years is plotted on the Y-axis and CYP2D6 activity, as represented by the formation of the CYP2D6 metabolite of dextromethorphan, is plotted on the Y-axis.

On my final slide, I would like to summarize some key points from my presentation. Codeine is metabolized to a much more potent opioid, morphine, by a polymorphic enzyme CYP2D6, which leads to variability in morphine concentrations in different phenotypes of the CYP2D6 enzyme.

As compared to extensive metabolizers, morphine concentrations are higher in ultra-rapid

metabolizers and almost negligible in poor metabolizers. Finally, published literature indicates that CYP2D6 activity does not seem to change up to 18 years. Thank you.

FDA Presentation - Timothy Jiang

DR. JIANG: Good morning. My name is Timothy Jiang. I'm a medical officer with the Division of Anesthesia, Analgesia, and Addiction Products. My presentation this morning will orient you to what we learned back in 2012 when we conducted our initial evaluation of pediatric toxicity with codeine. The subsequent presentations this morning will orient you to what we have learned in this new broader evaluation that Dr. Seymour just described.

First, I will briefly describe what codeine formulations are available, then I will spend the rest of my talk to describe our evaluation of codeine through 2012 that leads to the current labeling.

Codeine was originally approved in 1950. As an analgesic, it is available as a single

ingredient or in combination with acetaminophen. The single agent product is not approved for use in children less than age of 18. The combination products with acetaminophen is labeled for pediatric use with dosing instructions down to age of 3.

Let me move on to the safety issue affecting pediatric patients. The history of FDA's regulatory actions relating to CYP2D6 ultra-rapid metabolism of codeine goes back to 2007. In 2006, Koren published a case, which described a neonate who died after being exposed to high levels of morphine in breast milk from his mother, who was a CYP2D6 ultra-rapid metabolizer. Following the publication, FDA issued a press release and public health advisory entitled, Use of Codeine by Some Breastfeeding Mothers May Lead to Life-Threatening Side Effects in Nursing Babies. The labeling of codeine containing products was also revised to describe this risk in the subsection of Nursing Mother.

In April 2012, Kelly published a case series

in Pediatrics, which described three children who died or had life-threatening respiratory depression after codeine use for post-adenotonsillectomy pain. Adenotonsillectomy will be referred as AT on the slides. Following the identification of this case series, FDA embarked on an evaluation of this issue. I will summarize the three cases described in this paper.

The first case described a 4-year-old First Nations boy who received codeine post-adenotonsillectomy for obstructive sleep apnea and recurrent tonsillitis. He died on post-op day 2 and was determined to be a CYP2D6 ultra-rapid metabolizer by genotype. Obstructive sleep apnea will be referred to as OSA on the slides.

A second case described a 3-year-old girl of Middle Eastern descent received codeine acetaminophen post-adenotonsillectomy for obstructive sleep apnea. She was found unresponsive on post-op day 2 and was resuscitated at hospital. She was a CYP2D6 extensive metabolizer by genotype, but her morphine level was

consistent with an ultra-rapid metabolizer phenotype.

The third case described a 5-year-old boy who received codeine acetaminophen post-adenotonsillectomy for recurrent tonsillitis and snoring. He died on post-op day 1. He was considered to be a likely CYP2D6 ultra-rapid metabolizer because he had high blood levels of morphine relative to codeine level.

When we searched the medical literature for other cases of codeine toxicity in children suspected to be related to polymorphic metabolism, we identified 4 other cases. The earliest one was published in 2007 by Voronov in Pediatric Anesthesia. The case described a 29-month-old boy of North African descent who received combination codeine acetaminophen post-adenotonsillectomy for recurrent tonsillitis and mild to moderate sleep apnea. He was found unresponsive on the evening of post-op day 1 and was resuscitated. CYP2D6 genotype showed him to be a heterozygous with one gene have normal activity and the other gene have

increased activity.

Another case was published in 2007 by Ciszkowski in the New England Journal of Medicine. The case described a 2-year-old boy who received combination codeine acetaminophen after adenotonsillectomy for obstructive sleep apnea. He died on post-op day 2. Genotype revealed ultra-rapid metabolizer status.

One other literary case identified a time of 2012 literature search described the case of codeine in children as antitussive agents. In 2008, Hermanns-Clausen published a case in the European Journal of Pediatrics, which described 3-year-old twin boys who received codeine drops for cough once daily for 6 days. One twin died. The second twin was found apneic and was resuscitated. They were both extensive metabolizers by genotype. Analysis of size of drops suggests the possibility of inadvertent overdose. However, in some cases, the extensive metabolizer genotype overlaps with ultra-rapid metabolizer phenotype.

Now I will describe the cases that were

submitted to FDA's adverse events reporting system, or AERS as I will be referring to it. The AERS search spanned 1969 to May 1, 2012. Codeine was searched as the active ingredient, and the MedDRA search terms included the outcome death, the high-level terms overdose, death, and sudden death. The search was limited to children age 0 to 17. Intentional overdoses were excluded from the consideration.

Of 13 cases identified, 7 have already been described as they were in the public literature cases that included CYP2D6 metabolizer status. Six other cases, all death, did not Report CYP2D6 metabolizer status. Two of the deaths occurred in children following adenotonsillectomy.

One case was a 9-year-old boy with a history of having significantly enlarged inferior turbinates and adenoids who was found unresponsive after 1 dose of codeine and could not be resuscitated. The other case occurred in a 5-year-old girl with a chromosomal disorder who was treated with codeine acetaminophen combination

every 4 hours following surgery. She died 46 hours after surgery, and it was reported she had high levels of morphine, codeine, and acetaminophen in her blood.

Another death occurred in a 2-year-old boy with a history of convulsions. He was being treated with codeine for oral aphthae. Toxicological results showed high levels of codeine, morphine in post-mortem plasma samples. A fourth death occurred in a hospitalized child who was receiving valproic acid and codeine for an unknown indication. The other two deaths occurred in children receiving codeine for cough or sore throats.

In the process of reviewing codeine cases, we realized it will be beneficial to know if any cases of death or overdose has been reported to AERS related to the therapeutic use of other potential opioids that might be used for pain management in children, including immediate release hydrocodone, oxycodone, and morphine. The AERS search was conducted using the same search strategy

that was used for codeine as I previously described. No similar cases to those described for codeine were identified.

Although CYP2D6 is part of the metabolic pathway for hydrocodone and oxycodone, the relative potencies of the metabolites and the amounts generated would not be expected to cause more respiratory depression in an ultra-rapid metabolizer. In addition, the relative use of morphine and oxycodone in the age groups most likely to get adenotonsillectomy was very low.

One of the communication tools that FDA has to alert the public about new emerging safety issues under evaluation is called a Drug Safety Communication.

In August of 2012, FDA posted a Drug Safety Communication to alert the public that following the recent publication of the Kelly paper in Pediatrics, we were conducting a safety review of codeine to determine if there were additional cases of inadvertent overdose or death in children taking codeine, and if those adverse events occurred

during treatment of other kinds of pain, such as post-operative pain following other types of surgery or procedures.

Shortly after FDA's Drug Safety Communication was released, the American Academy of Otolaryngology Head and Neck Surgery, which will be referred as AAO-HNS, contacted FDA to inform us about the surveys they were conducting that were related to codeine issues we would evaluate at the time.

The patient Safety and Quality Improvement Committee of AAO-HNS had surveyed the physician membership regarding catastrophic outcomes following tonsillectomy, such as deaths or permanent disability. They were still in the process of writing up the survey results, but were able to share summary data with FDA.

Among 39 pediatric cases reported, 8 pediatric cases were classified as being related to opioid medications. The indication for surgery in 6 cases was obstructive sleep apnea, chronic tonsillitis in 1 case, and unknown in 1 case. Four

children were reported as having underlying conditions. Three had Down's syndrome, one had a neurologic disorder. Of the 8 children, 7 died, 1 had anoxic brain injury. Regarding CPY2D6 status, one child was confirmed to be an ultra-rapid metabolizer on postmortem exam, and one was suspected of being an ultra-rapid metabolizer due to high morphine levels.

You are going to hear a presentation later this morning about drug utilization for codeine analgesic and cough and cold products, so I am going to just briefly summarize what we found in 2012 when we first evaluated this issue. Nearly all the codeine for analgesic in children, 98 to 99 percent, was combination products with acetaminophen.

The analysis of prescribing specialty for codeine use in all age groups shows that category of general practitioner, family medicine, and doctor of osteopathy was the top prescribing specialty for oral solid formulation of acetaminophen codeine combination products.

Otolaryngologist was the top specialty for oral liquid formulations of acetaminophen codeine combination products.

The analysis of diagnosis codes associated with the use of acetaminophen codeine combination products in pediatrics shows that the most common diagnosis code was surgical follow-up. Although not commonly mentioned, drug uses associated with acute tonsillitis and chronic disease of tonsils and adenoids were also captured.

I will spend the next few minutes describing what FDA concluded from the evaluation of the pediatric toxicity issue with codeine, and the regulatory actions that were implemented. As I have described this morning, deaths or life threatening respiratory depression has occurred in children with obstructive sleep apnea who received codeine for post-operative pain management after adenoid tonsillectomy.

We did not, however, identify well-documented cases of death or respiratory arrest following after codeine treatment in

children with ultra-rapid metabolizer status outside of the setting of obstructive sleep apnea and post-adenotonsillectomy.

There is evidence that children with recurrent hypoxia as a result of obstructive sleep apnea have reduced opioid requirements for analgesia compared with those without obstructive sleep apnea in some pediatric patients following adenotonsillectomy. Their obstructive sleep apnea does not improve immediately.

In such patients, the sensitivity to opioid combined with higher level of morphine generated by ultra-rapid metabolism may put these children at particularly high risk for respiratory depression following codeine treatment post-adenotonsillectomy.

Therefore, at the time that we were evaluating the evidence in 2012, FDA concluded that our regulatory action should focus on the group of patients identified as being at highest risk by our review of available data.

Regarding the specific regulatory action

that FDA took in February 2013, we request a new boxed warning, FDA's strongest warning, for all the codeine-containing products, analgesia, and cough and cold about the risk of codeine in post-operative pain management in children following tonsillectomy and/or adenoidectomy. A contraindication, which is a formal means for FDA to make a strong recommendation against use of drug in certain patients, was added to restrict codeine being used in this setting.

The warnings and precautions, pediatric use and patient counseling information sections of the drug label were also updated. The language in the boxed warning and contraindication are shown on these slides. Recommendation for routine genotyping prior to receiving codeine was not added to product labeling for several reasons.

First, extensive metabolizers, in some cases, convert codeine to morphine at levels similar to ultra-rapid metabolizers. Second, the positive predictive value of tests is likely lower; thus, the number needed to screen in order to

prevent one event is very high. Third, genotyping may be logistically difficult to implement because preoperative lab tests are not routinely obtained before adenotonsillectomy.

FDA used a variety of methods to get a safety message out regarding pediatric toxicity with codeine. As a follow-up to the drug safety communication issued in August of 2012, FDA issued a second drug safety communication in February 2013 to summarize our findings and regulatory actions.

There was an FDA consumer update released in concert with the February 2013 drug safety communication to describe the codeine safety issue in consumer and patient friendly language. The action was also posted to FDA's MedWatch listserv.

Finally, FDA co-authored a perspective piece in the New England Journal of Medicine with the American Academy of Otolaryngology and Head and Neck Surgery that posted in April 2013 to summarize and highlight this life-threatening risk occurring with codeine. In the publication, AAO-HNS articulated their support of FDA's action to

restrict codeine use in children following adenotonsillectomy.

While FDA was conducting its evaluation of this safety issue, international regulators were also evaluating the same issue. In October 2012, the EMA initiated a review of codeine focused on codeine use in children for pain relief. In June 2013, the EMA's pharmacovigilance Risk Assessment Committee recommended the following, which was endorsed by the Coordinating Group for Mutual Recognition and Decentralized Procedures - Human. The recommendations included the following.

First, codeine-containing medicines should only be used to treat acute, i.e. short-lived, moderate pain in children above 12 years of age, and only if it cannot be relieved by other painkillers, such as acetaminophen or ibuprofen, because of the risk of respiratory depression associated with the codeine use.

Next, codeine should not be used at all in children, i.e., aged below 18 years, who undergo surgeries for removal of tonsils or adenoids to

treat obstructive sleep apnea as these patients are more susceptible to respiratory problems.

Next, the product information of these medicines should carry a warning that children with conditions associated with breathing problems should not use codeine.

Last, not least. The risk of side effects with codeine may also apply to adults. Codeine should therefore not be used in people with any age who are known to be ultra-rapid metabolizers, nor in breastfeeding mothers. The product information for codeine should also include general information for healthcare professionals, patients, and carers on the risk of morphine side effects with codeine and how to recognize their symptoms.

In June 2013, Health Canada announced that it reviewed the safety of prescription pain and cough medication containing codeine and is no longer recommending their use in children less than 12 years of age. This recommendation was based on very real cases of serious side effects and death in children that had been attributed to codeine

when given directly to a child or to babies from breast milk.

As I have described this morning, polymorphic metabolism of codeine has resulted in fatal or life-threatening respiratory adverse events in children when taken directly or exposed through breast milk. Our evaluation in 2012 identified pain management in the post-adenotonsillectomy as the most well-documented setting for pediatric CYP2D6 ultra-rapid metabolizers to have adverse respiratory outcomes from codeine. Opioid sensitivity in children with obstructive sleep apnea may also have contributed to their respiratory adverse events in these patients.

FDA's regulatory action in 2013 focused on preventing exposure to codeine in this sensitive group. As Dr. Seymour described earlier in her introduction, additional attention to the adverse events associated with pediatric codeine exposure in cough and cold products has led FDA to reevaluate codeine's safety in all

codeine-containing products, for analgesia and for cough and colds. You will hear the results of that additional evaluation this morning. Thank you very much.

FDA Presentation - Benjamin Bishop

DR. BISHOP: Good morning. My name is Ben Bishop and I am representing the Division of Nonprescription Drug Products. I will provide an overview of the history and regulations associated with nonprescription codeine as an antitussive agent in the over-the-counter or OTC monograph. Please note that I'll be using the terms "nonprescription," "over the counter," and "OTC" interchangeably.

During my presentation, I will discuss the regulatory background for over-the-counter products, the history of codeine over the counter, and the current regulatory status of OTC codeine and its availability as an over-the-counter antitussive. First, the regulatory background.

The Drug Efficacy Amendment, also known as Kefauver-Harris, and highlighted in this slide,

established the requirement for new drug applications to demonstrate efficacy whereas previously only evidence of safety had been required. The FDA also needed to evaluate the efficacy of drugs already available, which at the time included an estimated 100,000 to 300,000 OTC products.

Since review of these products individually was not feasible, FDA examined 420 representative products in various therapeutic categories and concluded that only one-quarter of the reviewed products had evidence of efficacy. Therefore, the FDA began the OTC drug review, or the monograph process, which assigned active ingredients into therapeutic categories with the intention of establishing a list of safe and effective ingredients for each category. These lists are called monographs, or taken as a whole, the OTC monograph.

The OTC drug review began in 1972 with the formation of advisory panels, which had a different role than today's advisory committee. Each panel

was comprised of scientists and clinicians assigned a therapeutic category. The panel conducted reviews of the existing literature, as well as data submitted by industry. They also evaluated the conditions for use for each active ingredient and recommended a monograph, or list of active ingredients, for each therapeutic category.

The standard for inclusion in a monograph was established as whether the active ingredient was determined to be generally recognized as safe and effective, or GRASE, for OTC use. The FDA began a lengthy rulemaking process to get each monograph established in the Code of Federal Regulations.

This monograph process is lengthy and it involves multiple steps of notice and comment, all published in the Federal Register. The panels' reports were published in an Advance Notice of Proposed Rulemaking, or ANPR, and public comment was invited. Comments were submitted by drug industry, medical professionals, consumers, anyone with an interest in the topic. The FDA considered

the comments received, evaluated any data included, and revised the ANPR as appropriate, publishing the revision as a proposed rule.

This proposed rule, also known as a Tentative Final Monograph, or TFM, was followed by a second round of evaluation of comments and data. The final rule or monograph was then published in the Federal Register and also in the Code of Federal Regulations.

So with that process as a background, I will now describe how codeine came to be an active ingredient in the monograph.

Codeine was reviewed for inclusion in three monographs, the relevant one being cold, cough, allergy, bronchodilator, and anti-asthmatic, CCABA monograph, specifically as an antitussive. The panel recommended that codeine and two salts, codeine phosphate and codeine sulfate, be classified as GRASE, that is Generally Recognized as Safe and Effective. In response to the panel's report published in the Advance Notice of Public Rulemaking, FDA received both positive and negative

comments relating to the over-the-counter status of codeine.

In response to particular comments from pediatricians expressing concern and objecting to the use of codeine as an antitussive in children, the FDA requested a recommendation from the American Academy of Pediatrics, and their response included quote, "We believe there is a preponderance of evidence that codeine-containing cough syrups can be hazardous to young children, even in prescribed doses."

This led the FDA to propose a revision to the OTC label, which removed the recommended dosage for children ages 2 to under 6 years of age and added this statement, "Children under 6 years of age, consult a doctor."

In the Tentative Final Monograph, FDA proposed moving these dosing instructions for children ages 2 to under 6 years of age to appear in the professional labeling only. Certain OTC monographs explicitly permit professional labeling, and codeine is an example.

Professional labeling is labeling that provides specific information to help professionals for uses not included in OTC drug labeling. When professional labeling is permitted, the labeling may be provided solely to healthcare professionals.

In addition, the product itself must remain OTC monograph compliant, meaning the label may only include labeling approved in the monograph for consumer directed labeling. Consumers do not need a prescription to purchase the product for children under 6 years of age. With these revisions, FDA published the Tentative Final Monograph as a Proposed Rule in 1983.

Pursuant to comments received after the Tentative Final Monograph, the FDA made additional revisions before finalizing the monograph in 1987. The OTC label requirements were revised to include this statement. "Children under 6 years of age, consult a doctor. A special measuring device should be used to give an accurate dose of this product to children under 6 years of age. Giving a higher dose than recommended by a doctor could

result in serious side effects for your child."

The FDA also revised the professional labeling requirements to include, quote, "Codeine is not recommended for use in children under 2 years of age. Children under 2 years may be more susceptible to the respiratory depressant effects of codeine, including respiratory arrest, coma and death."

Here, I will discuss additional details of the monograph and how it affects federal and state regulations of codeine as an OTC antitussive. The final monograph includes specific regulations for OTC products which contain codeine. The monograph requires specific language on the Drug Facts label, and in the case of codeine, professional labeling that does not appear on the dispensed product. There are three primary requirements.

Number one, codeine may only appear in preparations combined with at least one non-narcotic active ingredient, examples of which are listed on the slide. Number two, the other non-narcotic active ingredient must confer, quote,

"Valuable medicinal qualities other than those possessed by codeine alone." And third, that codeine must be limited in concentration to no more than 200 milligrams per 100 milliliters or 100 grams.

These are the dosing directions required to be on the label for any monograph product containing codeine. As you can see, it is an age-based dosing schedule. The directions also state to consult a doctor before giving the product to children under 6 years of age.

Other warnings and precautions related to codeine are listed in your background package, one of which is, "Adults and children who have a chronic pulmonary disease or shortness of breath, or children who are taking other drugs, should not take this product unless directed by a doctor."

These are the dosing directions required to be included in the professional labeling for any monograph product containing codeine. For children ages 2 to under 6 years of age, a weight-based dosing schedule is provided, along with average

body weights for different age groups.

Federal regulations established additional requirements that must be met for codeine to be sold without a prescription. The purchaser's identifying information and details of the sale must be recorded and maintained.

Two hundred and forty milliliters is the maximum quantity which may be purchased at once. Consumers must wait at least 48 hours before purchasing additional products containing codeine. And the purchaser must be at least 18 years of age.

Individual states may prohibit the over-the-counter sale of codeine, however the states which permit it must either follow the federal regulations or impose more stringent restrictions. The most stringent of the state restrictions are listed here with other states varying between these and the federal restrictions.

In some states, a pharmacist may be required to personally perform the transaction. Some states reduce the limit on the maximum quantity per purchase from 240 milliliters to 60 milliliters.

The minimum time between purchases may be increased from 48 hours up to as long as 96 hours. And some states increase the minimum age for the purchaser from 18 to 21 years.

Fourth and finally, I will summarize the current availability of codeine as an OTC antitussive. Data from a 2015 survey by the National Association of Boards of Pharmacy indicate that 28 states and the District of Columbia permit the over-the-counter sale of codeine, while 22 states and Puerto Rico prohibit the over-the-counter sale of codeine. I'll briefly pause on this slide for a moment while you find your home or favorite state.

These are two examples of labels. They are provided as larger handouts in your materials for easier reading. Based on a search of over-the-counter labeling including codeine, there are currently 45 products registered with the FDA as codeine-containing over-the-counter combinations. These products are registered by 18 different sponsors. Some of these products may no

longer be marketed or available.

So in summary, the regulatory pathway for OTC products in the monograph involves a public rulemaking process and changes to the monograph take time. The FDA has established monograph requirements to regulate the sale of OTC products containing codeine indicated for antitussive use. The Drug Facts label for OTC products containing codeine includes directions for ages 6 and older, while directions for ages 2 to under 6 years of age are included in the professional labeling only. Thank you.

FDA Presentation – Peter Starke

DR. STARKE: Good morning. I'm Dr. Peter Starke. I'm a pediatrician, medical officer, and associate director for labeling in the Division of Pulmonary, Allergy, and Rheumatology Products. This morning I will talk about the clinical considerations for codeine use as an antitussive agent.

Here's an agenda for my discussion. My discussion builds upon the previous two

presentations; so as I go through my slides, I'll try to tie my discussion with the previous ones as much as possible, with the hope that when I am done, you will have a good sense of the full picture of the landscape of codeine use, both as an analgesic and as an antitussive, and both by over-the-counter and by prescription use.

I'll first outline the available prescription codeine-containing antitussive products and highlight pertinent aspects of the labeling of these products as prescription antitussives. Then I'll cover more or less in chronological order what various professional societies and regulatory agencies, including the FDA, has said about these as well as other antitussive products, bringing in the specific steps that Health Canada, European Medicines Agency, and just last month -- actually two months ago now, we're in December -- the Australian Therapeutic Goods Administration took that prompted this advisory committee meeting. Again, when we get to the regulatory aspects, I'll try to tie this

in with what you've heard about in the previous presentations.

Finally, I will discuss the alternative prescription antitussive products, highlighting some of the safety issues with these drugs. Because, if one contemplates taking any action with respect to codeine-containing antitussives, this might impact the use of these alternative products.

This is a listing of the approved codeine-containing antitussive products. As you've heard, over-the-counter antitussive use of codeine is allowed in combination with other monographed ingredients when the product matches the requirements of the over-the-counter monograph. If it does not, it must be by prescription.

There are two sets of prescription codeine antitussive products: immediate release products that are in combination with other non-monographed drugs, and extended-release products that may be in combination with monographed drugs but are in non-monographed dosage form, such as extended-release dosage forms. Again, note that

the single ingredient codeine is not approved as an antitussive, so the only products available as an antitussive are combination products.

Immediate release combinations include combinations with promethazine, with or without a decongestant, and combinations with triprolidine and a decongestant pseudoephedrine. The extended-release dosage forms include codeine chlorpheniramine combinations, either as a suspension or as a tablet.

For convenience, I've placed the initial date of approval of the products after each as that becomes relevant when we get to the labeling of the individual products. Note that the currently marketed extended-release combinations were approved in 2015, and are only approved for adult use. I'll discuss this a bit further on the next slide.

This slide is a bit complicated, and I'll walk you through it. It summarizes the labeling of the codeine containing antitussives. In each of the columns, you'll see the listing by active

ingredient, lowest approved age, and relevant labeling.

This section summarizes the class labeling for the products. These products do include the class labeling that was instituted that's common to all the codeine containing products, prescription products, and it's the same regardless of whether the indication is an antitussive or as an analgesic. And as you've heard, this includes a boxed warning and a warning regarding deaths related to ultra-rapid metabolism, and a contraindication for post-operative pain management for tonsillectomy and adenoidectomy.

Now let's talk about the labeling of the specific products that is in addition to the class labeling of which there are now three sets. Again, you'll see the lower age threshold and relevant labeling listed.

The differences in the age ranges allowed in the labeling of these products relate to the year of first approval, which for the codeine promethazine combinations was in 1952, and for the

triprolidine combination was 1960, whereas both, as I mentioned before, of the extended-release combinations with chlorpheniramine that are now currently marketed were approved this year.

Codeine promethazine combinations are all immediate release combinations that are approved for patients 6 years of age and older. For these combinations, in addition to the codeine class labeling, there is a contraindication for use in patients less than 6 years of age, along with a boxed warning and a warning statement regarding respiratory depression related to the use of promethazine. And that's in children, and there's also a pediatric use warning about the combination of promethazine and codeine being associated with respiratory depression in children. The dosing information is shown, which also includes maximum daily dosages that should not be exceeded.

The codeine triprolidine pseudoephedrine combination includes dosing information for 2 years of age and older, as shown on this slide.

With regard to the extended-release

products, the agency did not allow an indication for pediatric use of these combinations, which were both approved this year. The agency now has the regularly authority to require companies to obtain pediatric data under the Pediatric Research Equity Act, or PREA, if the product triggers PREA.

In this case, we took the regulatory approach of setting the lowest age at 18 years and not allowing a pediatric indication without pediatric PK and safety data. So when pediatric studies are submitted, it is possible that these extended-release products could be labeled for use in younger ages.

I can discuss PREA and the regulatory actions and PREA requirements for these drugs later if you have any questions, but it is important that you understand that your recommendations today could also impact the age range allowed for these extended-release products in addition to the immediate release products.

So much for the codeine antitussives and their current labeling. Now I'll discuss what

professional societies have recommended and what actions various regulatory agencies have taken with regard to antitussive use in children.

I've placed the slides in relative chronological order so you can get a sense of what happened over time. As we get into the discussion, you'll see that there's significant overlap with regard to the regulatory actions and recommendations regarding use of codeine as an antitussive and as an analgesic, so my discussion will pick up from the information that was discussed in the several earlier talks.

Going back to 1997, the American Academy of Pediatrics Committee on Drugs issued a statement that included a formal caution against the use of antitussives, including codeine and dextromethorphan, in children, and the position statement was reaffirmed in 2006.

Among other things, and here I'm paraphrasing the document, it states that acute cough is frequent, usually associated with an upper respiratory tract viral infection, and in that

respect it's self-limited.

Whereas chronic cough is different, and the treatment should be directed at the underlying disease. They went on to suggest that cough during an upper respiratory tract infection is a normal and healthy reaction to the cold, and that suppression of the cough may actually lead to unintended health consequences. Further, there may be adverse effects and over dosage associated with the use of antitussives.

With regard to support for their use, they noted that there are no well-controlled efficacy or safety studies and that the dosage guidelines for children are not based on PK data, but are in fact derived from dosing in adults.

This slide is not part of the AAP position document, but it summarizes some of the points made by the AAP about the transient nature of colds with symptoms varying over the course of the disease, but tapering fairly rapidly over about a 10- to 14-day period.

These data are actually data from adults,

but we know that a similar course of disease is common in children. Cough is the symptom shown with a continuous line and circles. Note that not every patient gets a cough, but for many it continues for two weeks or more, so cough can be an annoying symptom even though it's not harmful.

In 2006, the American College of Chest Physicians issued guidelines for evaluating chronic cough in pediatric patients. While I emphasize that these guidelines are for chronic cough, they do contain the following statement, and I quote. "In children with cough, cough suppressants and other over-the-counter medications should not be used as patients, especially young children, may experience significant morbidity and mortality."

Moving on, in October of 2007, in response to a citizen's petition, the FDA convened a joint Nonprescription and Pediatric Advisory Committee to discuss the safety and efficacy of over-the-counter cough and cold products in children.

The main topics of discussion were the available efficacy and safety data to support use

of these medications, and whether extrapolation of efficacy data from adults, or even from adolescents, to younger children was possible. As such, the efficacy and safety of codeine products was not a specific focus of the discussion.

That said, the committee voted that antihistamines, nasal decongestants, and antitussives should not be used for the common cold in the following age groups, and you can see the results of the voting at the bottom of the slide.

The committee overwhelmingly voted against use of these products in children less than 2 years of age, whereas the voting was somewhat mixed, but leaning against use in children 2 through 5, and leaning more in favor of use in children 6 years of age and older.

There are a number of events that occurred surrounding the 2007 advisory committee meeting, and this slide summarizes what happened around that time. In October of that year, shortly before the advisory committee meeting, the Consumer Healthcare Products Association, which is a national trade

association that represents the leading manufacturers and distributors of over-the-counter medicines and dietary supplements in the United States, which includes the cough and cold medicines, announced a voluntary withdrawal of all over-the-counter cough and cold medicines that have labels, including pictures, or use the term "infants."

Combined with the publicity around the advisory committee meeting, which included a public health advisory issued by the FDA, stating that children younger than 2 years of age should not be given cold medicines because of potential serious and life-threatening side effects, and a supporting statement issued by the American Academy of Pediatrics, this recall changed the over-the-counter availability of cough and cold medicines that were marketed specifically to children less than 2 years of age.

Later in 2008, the manufacturers association went one step further and announced a voluntary transition to labeling that states, "Do not use"

over-the-counter cough and cold medicines in children under 4 years of age. Again, this was a voluntary transition. The hope was that this would decrease such use.

Earlier you've heard about what the FDA did to change the labeling for the codeine-containing products in 2007 and 2013, primarily because of issues related to codeine when used as an analgesic.

This slide relates to codeine for pain rather than for cough, but I've included it here for completeness. The World Health Organization, or WHO, maintains a list of essential medicines, which are those medicines that satisfy the priority healthcare needs of the population and are intended to be available within the context of functioning healthcare systems.

These medicines are selected based on public health relevance, evidence of efficacy and safety, and comparative cost effectiveness. In 2011, the WHO removed codeine for pain from the list of essential medicines for children, and their

reasoning is shown on this slide.

Now you saw this slide earlier as well. In June of 2013, Health Canada announced that they had reviewed the safety of prescription codeine medications that are used for both the cough and pain indications, stating that they are no longer recommended for use in children less than 12 years of age for either indication.

They also recommended a caution for use in children of all ages who have compromised respiratory function. This was followed by similar announcements, as you heard, by the European and Australian regulatory agencies, and I'll summarize these on the next slides.

You also recall hearing earlier that in 2013 the EMA Pharmacovigilance Risk Assessment Committee, or PRAC, issued an assessment report with regard to use of codeine for pain in children. In April of 2014, the EMA PRAC initiated a similar review of the available efficacy and safety data to support use of codeine-containing products for cough in children, and they issued their assessment

report earlier this year.

With regard to efficacy, they reviewed the available literature and only found four published cases regarding codeine use as an antitussive agent in children and two in adults. The report is in your briefing packet, and I will not try to summarize the specific studies. The PRAC concluded that the evidence to support efficacy of codeine as an antitussive agent is limited.

With regard to safety, they reviewed the available Euro vigilance data and the published literature. Briefly among the literature reports, they found 4 deaths and 10 life-threatening cases associated with the use of codeine-containing products for cough and cold.

Their conclusion was that poor metabolizers would get no benefit, whereas ultra-rapid metabolizers are at high risk. So they made the following recommendations for these products.

They instituted a contraindication for use of codeine-containing products in children less than 12 years of age, both for cough and cold, and

as you know already, they have done so for pain. They instituted a not recommended for use in patients 12 to 18 years of age with compromised respiratory function.

Similar to the actions that the FDA had already taken for the codeine-containing products, they instituted a contraindication for use in patients of any age who are known to be CYP2D6 ultra-rapid metabolizers and a contraindication for women who are breastfeeding.

Although they took -- as you see that next to the last bullet, they went further than we did in terms of restricting use for all ultra-rapid metabolizers rather than just certain individuals, or after a tonsillectomy/adenoidectomy.

In July of this year, the Australian Therapeutic Goods Administration convened an advisory committee on the safety of medicines -- it's similar to the advisory committee meeting today -- after which their conclusions were published back in October of 2015.

Because it's so recent, we did not include

this information in your briefing document, but you will see that the recommendations are virtually identical to those issued by the EMA PRAC and very similar to those issued by Health Canada. With regard to recommendation number 3, you'll note that the U.S. labeling requirements for the prescription codeine-containing products are fairly consistent with this recommendation, spanning both the cough and pain indications.

I come back now to Dr. Seymour's introductory summary slide that basically summarizes the regulatory recommendations from the other agencies, and just note that there is a blank under the cough with regard to what the FDA has recommended.

Moving on, I want to bring your attentions to labeling of the alternative prescription on over-the-counter antitussives. Later, we'll be asking you to provide recommendations about the use of the codeine-containing products in children. If the recommendation is to restrict use in certain age groups, there is the concern that this might

indirectly cause an increase in the use of alternative products.

There are basically two sets of prescription antitussive products, one non-narcotic, benzonatate, and one set of narcotic products where hydrocodone has been substituted for codeine. Note that except for the single ingredient product, which is combined with homatropine, the combinations are with ingredients that are in the cough/cold monograph. However, since hydrocodone is not in the OTC monograph, all of these products are by prescription only. We'll cover benzonatate first.

Benzonatate is a peripheral anesthetic that acts by anesthetizing the stretch receptors located in the respiratory passages, lungs, and pleura. It's approved for use in adults and children 10 years of age and older, and the labeling includes a pediatric use statement that safety and effectiveness in children below the age of 10 have not been established. Benzonatate has significant risks, particularly for use in children.

These products come as perles, which if you're not aware of what perles are, they are basically soft gel, or sort of soft gelatin capsules, and they also come as capsules. The products contain a warning about the safety concerns if these capsules are sucked or chewed, namely, and I quote, "that severe hypersensitivity reactions, including bronchospasm, laryngospasm, and cardiovascular collapse, have been reported, which are possibly related to local anesthesia from sucking or chewing the capsule instead of swallowing it. Severe reactions of required intervention with vasopressor agents and supportive measures."

In short, the reactions range from a dive-like reaction, to full-blown bronchospasm, laryngospasm, and cardiovascular collapse. So these can be quite serious and life-threatening. Further, the labeling contains the statements that over dosage has been associated with death, and accidental ingestion resulting in death has been reported in children less than 10 years of age.

Hydrocodone-containing antitussives are summarized on this slide.

Hydrocodone is a centrally-acting opioid that has similar effects on the respiratory drive center in the brain as codeine. Hydrocodone metabolism is also by CYP3A4 and 2D6, so it has potential drug-drug interaction risks.

Hydrocodone products come as immediate release products in combination with homatropine, antihistamines, decongestants, or expectorants, and as extended-release products in combination with chlorpheniramine. So the range of products is relatively similar to that for the codeine-containing antitussives.

With homatropine, labeling includes dosing information for adults and children 6 years of age and older, a warning about respiratory depression in patients less than 6 years, and a pediatric use statement to use with caution in children greater than 6 years of age.

The extended-release combinations with chlorpheniramine include a contraindication for use

in patients less than 6 years because use is associated with cases of fatal respiratory depression.

The immediate release combinations, of which a number were approved in the last few years, are not indicated for children less than 18 years of age, and contain the same warning about respiratory depression that I just mentioned, including fatalities in children less than 6 years of age. These recent approvals are labeled differently because of the required pediatric assessments if they triggered PREA.

This slide just summarizes the information that I just reviewed regarding the prescription antitussive products that are alternatives to codeine. The active ingredient is listed, the class, the lower age bound, and the relevant labeling.

Now, it wasn't covered in previous talks, so I'm going to cover it here. This slide summarizes the over-the-counter antitussive alternatives permitted under the cough/cold monograph, again by

active ingredient, class, the lower age bound allowed without professional labeling, and relevant labeling.

You'll see that there are basically three alternative antitussives, or antitussive classes, chlophedianol, dextromethorphan and salts, and diphenhydramine and salts. I'm not aware of any currently marketed chlophedianol products.

Dextromethorphan is the only antitussive that is allowed to be marketed directly down to 2 years of age, whereas the minimum age for both the others is 6 years, with professional labeling in the monograph for dosing in children 2 through 5 years of age.

The OTC monograph also allows topical agents, including camphor and menthol, for patients 2 years of age and older. These are sold as topical ointments, lozenges, and for steam inhalation use, depending upon the ingredient and the formulation. Note that the ointments and the steam inhalation products are required by the monograph to have a flammability warning.

In summary, codeine-containing prescription antitussive products are available in combination with other medications such as antihistamines and decongestants, and I've shown you the relevant labeling that's currently under labeling for use in children. Professional societies have voiced significant concerns for the use of all cough and cold medicines in children.

The FDA advisory committee held in 2007, as well as the labeling steps that FDA took for the prescription codeine-containing products in 2007 and 2013, led to a series of evaluations of the safety of these products. And while the advisory committee did not discuss the use of codeine specifically, it highlighted that there are safety risks with the use of all of the cough and cold products.

Health Canada, the EMA, and Australia have recently singled out codeine-containing antitussives as having limited efficacy, as well as presenting a safety risk for use in children. As a result, they have contraindicated or not

recommended their use in children less than 12 years of age. And finally, I've highlighted some of the risks associated with the use of alternative prescription and nonprescription antitussive products. Thank you for your attention.

Clarifying Questions to the Presenters

DR. OWNBY: Thank you very much. We're a few minutes ahead of schedule. I'd like to remind everyone that as you can see, this is a large committee, so please try to make any comments or questions succinct so that we have adequate time, but we do have the afternoon.

So are there any clarifying questions for the FDA speakers? Please state your name for the record as you speak. And if you can, please direct your questions to a specific presenter. Yes?

DR. SUAREZ-ALMAZOR: Yes. Maria Suarez-Almazor. I realize that it's a choice of the FDA not to discuss efficacy, but it's a little difficult to make a decision or to have an opinion on the safety without really having an idea of the

risk/benefit ratio. So I was wondering if in the FDA's view, there are any unique situations where codeine would be the preferred agent, either as an antitussive or for pain control in children.

DR. SEYMOUR: Hi. This is Sally Seymour from FDA. And I had a feeling efficacy was going to come up in the discussion, but I didn't think it would come up quite so soon. So let me mention the position about efficacy, and then I'll address your second question as well for antitussive, and then see if others have comments about the analgesia.

So we're not presenting efficacy because we have previously made a determination of efficacy for both cough and analgesia. And we generally don't revisit that decision, but obviously, as you've said, that's going to be part of the risk/benefit consideration.

These are old medications, approved in the 1950s -- some of them go back that far -- and clinical practice may have changed over time, availability of other medications may have changed over time, and all those things may factor into

your risk/benefit consideration.

The EMA did a review for codeine for an antitussive, and looking at the antitussive data and they made some statements about the efficacy in their document, which is included in the briefing package. So certainly that is going to be part of the risk/benefit consideration, all those things, the known efficacy, the use and the armamentarium for other available medications for cough or for analgesia, and clinical practice as well.

As you've seen, some recent recommendations from different professional societies have made statements about whether you should treat cough at all, so I think things have changed over time.

Your question about if it's preferred for codeine in cough in any situation, I'm not aware of any situation for the use for cough, if it's a preferred medication. You certainly heard that some professional societies now don't recommend treating acute cough at all in children. So I think I don't have a recommendation where codeine could specifically be preferred medication for

cough.

DR. RACOOSIN: Let me just add something there about the efficacy. So in 2009, an NDA for a single ingredient codeine product that had been previously marketed and approved, it went through the NDA process, and the submission included no new studies but a literature review of the published efficacy studies that included codeine and codeine/acetaminophen combination products.

The division made the determination, based on the sponsor's literature review and FDA reviewing what was available in that literature review, that the product was efficacious for use in adults.

So that product was approved for adults, and it triggered the PREA rule that Dr. Starke mentioned about requiring pediatric studies. So the evidence base for efficacy in pediatrics was not very -- there are very few studies included in that sponsor's literature review, and rather, these PREA studies were required for pediatrics, and those are still in process.

So I just wanted to add that bit about the recent review for that particular single agent codeine NDA that was approved in 2009.

DR. SUAREZ-ALMAZOR: So approved for pain? For pain?

DR. RACOOSIN Yes, for pain.

DR. OWNBY: Dr. Perrone?

DR. PERRONE: Thank you. Jeanmarie Perrone. My first question is built on what Dr. Starke mentioned about alternatives to codeine as an antitussive. And really, have we looked at the alternatives to codeine for pain?

Because when you do the calculations, I asked my clinical colleagues at Children's Hospital of Philadelphia what they're using now that codeine has had these restrictions for the past few years. And they said they pretty much eliminated their codeine use and have switched to oxycodone.

Thinking about this in terms of prescribing, oxycodone is 5 or 6 times more potent than codeine. And I don't think that a clinician, at least a non-pediatrician clinician, is going to keep those

proportions in mind, at least routinely, when it comes to prescribing and dosing these medications.

So while codeine may have this problem, I'm really concerned that the alternatives would have much bigger problems, especially in this scenario of risk of respiratory depression associated with obstructive sleep apnea.

So my real question is to Dr. Jiang. Since we've made this recommendation, have we looked for signals from oxycodone or hydrocodone prescribing in the post-op OSA patients that are similar? Because really, when you have this problem with codeine metabolism, you're really just getting closer to hydrocodone therapeutic dose range. So, thank you.

DR. RACOOSIN: So let me respond to that. Judy Racoosin. There's going to be a discussion of drug utilization that will follow later this morning, and some of those issues could be addressed I think in that presentation, or in the follow-up slides to that presentation.

DR. PERRONE: Okay.

DR. OWNBY: Dr. Gerhard?

DR. GERHARD: Tobias Gerhard. Just one quick question for clarification. As you presented data from what were the actions of other regulatory agencies regarding both the cough and cold indication also pain, from Europe, Canada, and Australia, do I understand correctly that these are all relating to prescription uses and that neither of these countries have OTC products available? And if there are OTC products, how would they be affected by these labeling changes?

DR. SEYMOUR: This is Dr. Seymour from the FDA. I will double check on the EMA and the OTC availability of codeine and see if I can get back to you after the next break, because I don't want to misspeak. At this point I'm not sure.

DR. OWNBY: Dr. Morrato?

DR. MORRATO: This is Elaine Morrato. I had a similar question, so that will be very helpful. I'm also trying to sort of synthesize difference, and better understand the differences between the prescription and the over-the-counter labeling.

And I thought it might be helpful to understand kind of FDA's thinking in terms of how they approach consistency between those two labels.

I do recognize the long regulatory history and products are coming through at different points, and that's when determinations are being made. But specifically, are there examples in which you have prescription products that have boxed warnings, or contraindications in specific age groups, at the prescription side but are more lenient on the OTC side or equally lenient?

I could think of acetaminophen, and where you have a boxed warning for potential for severe liver failure, that's allowed OTC. Ibuprofen or non-aspirin NSAIDs are similar in terms of the heart attack or stroke warning, but if the products are used as indicated in OTC, it's allowed.

The reason why I'm asking this is that helps us as we think about the prescription and what we might be hearing in Europe and others, and the precedents being set there and how we translate that over to OTC labeling. I'm concerned about

like inconsistencies in that. And it sounds like the most recent product approval for extended release is barring all use under 18.

So how does the FDA think about that when they think about generally regarded as safe and translating the prescription to the OTC side? Are there examples or context we can draw upon?

DR. SEYMOUR: This is Sally Seymour again. I'll start, and if someone else from OTC wants to weigh in on the monograph -- I mean, you've identified a number of inconsistencies already in the Rx versus OTC. In the cough/cold codeine products, there are already differences. Even within the prescription products, there are differences in age cutoffs.

So we're aware of the inconsistencies. Some of that has been impacted by the time of approval. The more recent approval, as Dr. Starke mentioned, we have the ability to ask for a pediatric study, so we limited the age cutoff to 18. That's inconsistent with other prescription products for codeine. That's inconsistent with a monograph

labeling. There's boxed warnings that are not included in the monograph.

But the monograph process and to update the labeling is quite extensive and lengthy. So I'm not sure that that process could actually keep up to date to be consistent with prescription labeling. We have a lot more power within the prescription products to be more consistent. And you can see even with the cough/cold products we've laid out, there's some inconsistencies in age cutoffs.

So based upon the feedback today, I think we will be looking at the labeling for those for pediatric patients and try and see if we can be a little more consistent in what we're recommending. And then I think the over-the-counter division will take the feedback as well to see if there's an impact or anything they need to do to implement with the monograph.

DR. ADAH: So let me comment also, if that would be okay, since I represent the OTC division. We do recognize that there are the inconsistencies

and we do try to address them. But as Dr. Seymour said, the timing for action is very different, and we struggle with that daily. And if you notice recently, these are not necessarily boxed warnings, but we've issued a number of drug safety communications, acetaminophen being one, and have addressed how the labeling will be handled with OTC monograph products.

So we do try to correlate and make things as consistent as possible. It's just the monograph system, currently as it's designed, isn't really receptive to quick changes.

DR. MORRATO: And I understand that this meeting is the opportunity to help bring the thinking up-to-date, but would you say then that the extended-release evaluations that you've just done for the prescription represents the most up-to-date thinking on the agency's thought about use in children?

DR. SEYMOUR: I think we have required studies in children down to 6 years of age for those extended-release formulations. Those are

pharmacokinetic studies looking at dosing information as well as safety studies.

As Dr. Starke mentioned, based upon the results of those studies, we would be considering whether to extend the indication down to 6 years of age.

So I think we haven't shut that door on that age range, and that would make it more consistent with the older products then extending the indication down to 6 years of age. So that is still an option on the table for those products, so we haven't cut off the age at 18 and shut that door for the lower age group.

DR. MORRATO: And just my last question. Was that influenced because it was extended release versus immediate release, or was it more driven by your thinking about data for the active in general?

DR. SEYMOUR: I think it's just more general thinking about we are trying to ask for more pediatric data in general. And there's a lot of interest in the cough/cold medications and getting more data as well, so this is an opportunity to

evaluate both.

DR. OWNBY: Dr. Besco?

DR. BESCO: Yes, Kelly Besco. First of all I concur with some of the earlier comments about the transfer of risk to other opioid pain medications and other analgesics. One noted thing I picked up on is that we haven't really discussed tramadol. Tramadol is metabolized also by the CYP2D6, and there have been some documented off-label use in pediatric patients for pain management.

In fact, I think FDA also recently issued an alert about tramadol use in pediatric patients. So I wondered if you were able to include review of adverse events associated with tramadol, or if we're expected to discuss that during the utilization discussion.

DR. RACOOSIN: So, Judy Racoosin. Let me address that. Tramadol does not have an approved -- there's no pediatric formulation that is approved, and the formulations that are approved are not approved in children.

So when we did this evaluation of codeine and the other potential opioids that might be used to treat pain in children back in 2012, we didn't include tramadol in that evaluation because we didn't think that it was being -- that it would be likely to be commonly used in that setting.

Since then, as you point out, there's a publication this past spring of a similar case, post-tonsillectomy case, where a child with ultra-rapid metabolism got into trouble having been treated with tramadol.

So FDA began to do a similar evaluation of this issue, and in September we actually posted a drug safety communication describing that that is an ongoing evaluation, which it is. And yet we are not to the point of being ready to discuss it, you know, in this setting because our evaluation is still in progress.

But, importantly, what the committee recommends today will definitely be taken into consideration as we continue our evaluation of tramadol. So I'll just leave it at that.

DR. BESCO: Yeah, I guess too, and potentially the other opioids, I know we don't have documented case reports, but it seems like this risk could be applicable to all agents, based on the fact that they're all metabolized by the same enzyme.

DR. RACOOSIN: Well, I'll defer to my clinical pharmacology colleagues, but I think that is a bit of an over-generalization. Different opioids do have -- CYP2D6 is certainly involved in some of them, but the amounts of the active metabolites and the potencies of those active metabolites do not put all opioids at the same risk related to the polymorphic metabolism with CYP2D6.

So there's certainly data out there that suggests that other opioids may be potentially problematic for children with obstructive sleep apnea who've just had their tonsils removed, there is some literature supporting that. But I think we have to be a little bit careful about attributing all the problems to ultra-rapid metabolism because for codeine and tramadol, where the parent compound

has little affinity for the opioid mu receptor and the primary metabolite has substantially more potency at the mu opioid receptor, those are the ones that are going to be most risky in an ultra-rapid metabolizer.

DR. OWNBY: Dr. Connett?

DR. CONNETT: Well, my concern here is, I think as Dr. Perrone suggested, that maybe the alternatives are actually more dangerous, and we have, I guess, data from 1969 to 2012 on codeine. I don't know. I have the impression that there's a similar volume of data on the other drugs, benzonatate and some of these others that look like they're fairly -- there is some information there.

But if we don't know something about how many serious adverse events happen per prescription, we could make a rather bad decision to recommend alternatives that are actually worse. Maybe we're going to hear data on that.

DR. OWNBY: Does anyone from the FDA want to respond to that concern now or are we waiting?

DR. RACOOSIN: Well, as Dr. Jiang pointed

out in his talk, at the time that we did the original codeine review in 2012, we also looked at hydrocodone, oxycodone, and morphine using the same search strategy, and we did not identify similar cases. As I pointed out, because of the differences in the metabolism, we may not have been expecting that we would see cases with those.

Also, morphine and oxycodone's use in the younger age group of the pediatric age group is very uncommon. I understand the concern about unintended consequences of making one recommendation or the other, but in 2012, we didn't see evidence of these kinds of cases with those comparator products.

DR. CONNETT: One other minor point. Dr. Jiang I think on page 5 of his presentation referred to the exclusion of intentional overdoses, and I'm wondering what that means with intentional overdose. Is that somebody trying to do harm to somebody else or themselves? And why are they excluded? I mean, intentional overdoses are, with a dangerous drug, evidence that maybe it shouldn't

be on the market.

DR. RACOOSIN: So the reason that we excluded those cases is because we were looking for cases related to ultra-rapid metabolism. So we're looking for deaths or respiratory depression related to what we believed to be a potential problem with polymorphic metabolism of codeine and CYP2D6 ultra-rapid metabolizers.

So if we included intentional overdoses, we would not be able to separate out these -- I mean, when someone is intentionally taking more drug than is prescribed with an opioid, the likelihood of respiratory depression or death is -- I mean, that's a pharmacologic effect of the product.

But we were specifically looking for cases where a prescribed appropriate dose was given and the child had respiratory arrest or death. That's why we excluded intentional overdoses.

DR. CONNETT: How many were you able to document as being intentional overdoses? A large number or --

DR. RACOOSIN: I'll have to go back and see

if we can pull that review.

DR. OWNBY: Okay. I realize we're at time for a 10:00 break, but I have six more people. We'll go another five minutes, but then I think we'll have to cut it off and take our break. So I have Dr. Yu next.

DR. YU: Thank you. I also have a question about the codeine, but it's more a clarification. In one of the -- Dr. Jiang's presentation, on page 6, he said the review of AERS and review in 2012 of other opioids, medication, he said and no similar cases were identified for codeine. I just wanted to clarify whether does this only include the case of the death of children or includes all the adverse events looked at in an AERS?

DR. RACOOSIN: Can you identify the slide number?

DR. YU: Six in Dr. Jiang's presentation, on page 6. It's the second slide on page 6.

DR. RACOOSIN: Okay. Yes.

DR. YU: The second line. It said, "No similar cases to those described for codeine were

identified." I just wanted clarification; is it only referred to death?

DR. RACOOSIN: So if you look at the slide 10 on the bottom of page 5 that describes the search strategy that we used, MedDRA search terms, we used the outcome of death and we used the high level terms of overdose, death, and sudden death.

So when we ran that same search strategy, and used the same exclusions. So that was what we originally did for codeine, we ran the same search strategy for the comparators, hydrocodone, oxycodone, and morphine, and we did not identify similar cases that we did find with codeine. We did not find with these comparators. That's what that slide is saying.

DR. YU: Okay. So this is not only -- it's restricted to the deaths, the search for --

DR. RACOOSIN: Deaths, overdoses.

DR. YU: Yes.

DR. RACOOSIN: Again excluding intentional overdoses because we're looking again for cases where children got the prescribed appropriate dose,

but had one of these severe outcomes of overdose or death.

DR. YU: Yes. Okay. Thank you. My second question is related to this map that shows codeine availability in different states, you know red and blue. I found this very intriguing. And just from the regulatory point of view, I was just wondering, for over-the-counter availability, did FDA do any study or demonstrate and show adverse events and deaths associated with over-the-counter codeine displayed or presented in a map fashion that we can look at to compare among different states, and just say -- as additional information to evaluate over the counter?

DR. ADAH: So a little bit about OTC monographs and adverse event reporting. Reporting wasn't even required until 2007. And the only thing we do get are serious adverse events. And even in those cases, we don't tend to see a lot of those events. It's just the nature of the way things are. And it's one of the things I think we'd like to address if we ever are able to make

the monograph process change.

So we do take a look at the events that are submitted. Oftentimes, we can't relate them to what type of product it is. It's a codeine product, but we don't know was it OTC or was it prescription. And also in many cases, we can't even tell under the conditions of use or anything like that. It's just very limited data for these products, and including sales. We even have a tough time with sales.

DR. YU: Okay. Thank you. Just one quick clarification, and I will shut up. There was a plot that's showing duration of a co-symptom, and shows how many days the symptom subsided as compared to cold and sore throat, and that was on page 4 of his presentation.

I was just wondering, is this plot shown with the intervention or no intervention? Just naturally the symptom just subside?

DR. STARKE: That comes from a publication from Gwaltney that looked at the natural history of colds -- this is Dr. Starke speaking -- in an

industrial setting in adults. And the slide actually comes from the CDC that summarized the findings in the study. I don't recall whether there was any treatment involved. It was a natural history type of study.

DR. YU: Okay. Thank you.

DR. OWNBY: Okay. I'll ask the rest of you to please hold your questions. I realize a number of you didn't get a chance. Let's take a 10-minute break and reconvene at 10:15. I'm sure there will be plenty of time this afternoon for many more questions.

(Whereupon, at 10:06 a.m., a recess was taken.)

DR. OWNBY: Okay. We'll go back and proceed with the FDA presentations. I believe Dr. Gill is the next presenter from FDA.

FDA Presentation - Rajdeep Gill

DR. GILL: Good morning. My name is Rajdeep Gill, and I'm a drug utilization data analysis team leader in the Division of Epidemiology II in the Office of Surveillance and Epidemiology. Earlier

you heard a presentation on FDA evaluations on codeine safety in children conducted in 2012. Now we will present recent analyses of pediatric utilization, pharmacovigilance, and epi data on codeine-containing products.

I will provide utilization trends for codeine-containing products. This information can serve as a context for the upcoming discussion regarding the risk of respiratory depression following codeine use in children.

The outline of my presentation is as follows. I will provide utilization patterns of over-the-counter sales and prescription codeine product use from retail settings, followed by limitations of these analyses and a summary of my presentation.

For the purpose of these analyses, cough and cold versus analgesic codeine-containing products were grouped based on active ingredient. For example, combination acetaminophen with codeine and single ingredient codeine were grouped into analgesic category and combination

codeine-guaifenesin, and codeine-promethazine were grouped into cough and cold category.

First we analyzed sales distribution data to assess where the majority of all codeine-containing products were distributed based on sales from the manufacturers to different settings of care.

Our analyses focused on outpatient retail settings, which accounted for the majority of codeine-containing product sales in year 2013. Drug use analyses will include over-the-counter sales of cough and cold codeine products and pediatric prescription use of both analgesic and cough and cold products.

The IMS OTC International Market Tracking database was used to provide OTC retail sales of cough and cold codeine products to consumers in recent years. Please note that OTC retails sales data could not be stratified by patient age.

This figure shows the sales of over-the-counter cough and cold codeine products sold to consumers from retail stores. OTC sales to consumers decreased by 85 percent from 2010 to

2014.

In the next few slides, I will present U.S. outpatient retail utilization of codeine-containing products in the pediatric population. The IMS Total Patient Tracker database was used to provide national estimates of pediatric patients who received dispensed prescriptions for analgesic or cough and cold codeine products from U.S. outpatient retail pharmacies in recent years.

This figure shows the number of pediatric patients 0 to 18 years who received any codeine-containing product prescription from U.S. outpatient retail pharmacies over time. Please note the Y-axis representing pediatric patients in millions.

Pediatric utilization decreased by 40 percent from 3.1 million patients in 2010 to 1.9 million patients in 2014. Pediatric patients 0 to 11 years received the majority of prescriptions for codeine-containing products throughout the examined time.

This figure provides utilization of

codeine-containing products in pediatric patients aged 0 to 1, 2 to 5, and 6 to 11 years. In general, the utilization decreased across these younger age groups. Among the younger pediatric patients, the majority of codeine utilization was observed in patients 6 to 11 years, as shown in the purple bars.

In the next two slides, I will present pediatric use of analgesic versus cough and cold codeine products. This slide provides total pediatric use by active ingredient from 2010 through 2014. Of the total pediatric codeine-containing analgesic use, over 99 percent of pediatric patients received combination codeine acetaminophen. Of the total pediatric cough and cold use, more than half of the pediatric patients received combination codeine guaifenesin.

These figures show pediatric utilization of codeine-containing analgesic and cough and cold products. In 2014, nearly triple the number of pediatric patients received analgesic codeine prescriptions compared to cough and cold codeine

prescriptions.

Stratifying by age, patients aged 0 to 11 accounted for the majority of pediatric patients who received either analgesic or cough and cold codeine products. However, for cough and cold codeine prescription use, the number of pediatric patients aged 0 to 11 years decreased below the number of patients aged to 18 years in 2014.

Now I will present limitations of my analyses. The OTC data do not have information on patient demographics and direct patient use is unknown. We analyzed outpatient retail pharmacy data only, and these data may not be generalized to other settings of care.

From our analysis, we could not provide linkage between a dispensed prescription and a diagnosis. Codeine products were grouped based on active ingredients, and it is unknown if a patient actually took an analgesic codeine product for pain related conditions or a cough and cold codeine product for respiratory related conditions.

In summary, from 2010 through 2014, there

was a decrease in over-the-counter retail sales of cough and cold codeine products. Pediatric use of prescription codeine products decreased as well. Of the prescription use, the majority of pediatric patients were 12 years and younger and the majority of pediatric patients received combination codeine acetaminophen products. Despite a decrease in utilization, there still remains a considerable pediatric utilization of prescription codeine products. Thank you.

FDA Presentation – Annie Nguyen

MS. NGUYEN: Good morning. My name is Annie Nguyen. I am a safety evaluator with the Division of Pharmacovigilance in the Office of Surveillance and Epidemiology. For the next 15 minutes, I will provide an overview of the postmarketing safety data for codeine-containing products.

Earlier this morning, Dr. Jiang provided a high level summary of the postmarketing safety data that were evaluated as part of the 2013 FDA regulatory action. We expanded upon that evaluation for our current analysis. Please keep

in mind that there will be some overlap in the identified cases.

Here's the outline that I will follow for my presentation. First, I will provide an overview of the FDA adverse event reporting system, also known as FAERS and previously known as AERS.

You have heard the previous speakers discuss the potential for respiratory depression reported with codeine-containing products. I will therefore continue this topic with an analysis of pediatric postmarketing reports of respiratory depression in the FAERS database and medical literature. Finally, I will conclude the presentation with a summary of the findings.

Before I present our findings, it may be helpful to provide an overview of the database that houses all of the postmarketing adverse event reports received by the FDA. In the next two slides, I will discuss the strengths and limitations of the FAERS data.

FAERS is a computerized database which contains over 11 million adverse event reports from

various sources, such as healthcare providers and consumers. It has many strengths that allows the FDA to use it as a postmarketing drug safety surveillance tool.

FAERS includes all U.S. marketed products, and may include foreign products, as well as all uses for both approved indications and off-label use. It includes broad patient populations, such as elderly, children, pregnant women, and patients with comorbidities who are often excluded for clinical trials.

It allows for detection of events not seen in clinical trials or events with a rare background rate. FAERS is useful in identification of report trends, possible risk factors, at risk populations, and other clinically important emerging safety concerns.

While FAERS has many strengths, it does have some limitations. For example, for reporting purposes, the FDA does not require a causal relationship between an event and product to be proven. Some reports do not contain enough

information or detail to fully evaluate an event.

Further, the FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about a drug or event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event in the U.S. population.

Now that I have provided you with the strengths and limitations associated with the data, I will discuss the cases of potential respiratory depression that were received in the FAERS database. This slide shows you the search parameters we used to identify pediatric cases of respiratory depression from the FAERS database and medical literature.

In our current analysis, we searched the FAERS database for all codeine-containing products through May 26, 2015 that involved patients 18 years and below and with a serious outcome such as death or hospitalization. We also looked through

medical literature for any recent case reports involving pediatric patients and codeine that were published after the review that resulted in the 2013 FDA regulatory action.

For the purposes of the current analysis, we identified those cases where there was a temporal association following codeine-containing product administration and one of the following: signs or symptoms consistent with respiratory depression, such as slow or shallow breathing; difficult or noisy breathing, or unusual sleepiness; naloxone administration; a diagnosis of respiratory depression; or a death outcome that did not have a clear alternative reason.

We identified 64 serious pediatric cases of respiratory depression from the FAERS database. This table shows several descriptive characteristics of the cases we identified. I will walk through each of them.

Fifty of the 64 cases involved children under the age of 12. The most frequent one reported codeine-containing product was

acetaminophen with codeine. A temporal relationship was observed with the events occurring as early as after 1 dose of a codeine-containing product.

There were 10 of 64 cases that mentioned CYP2D6 genotyping. Cases involved ultra-rapid metabolizers as well as extensive metabolizers. There were 48 of 64 cases that reported reason for use; 34 in the pain management setting, and 14 were in the cough and cold setting.

In the next two slides, I will provide additional details in these two settings. Here we present 34 serious pediatric cases of respiratory depression when a codeine-containing product was reported for analgesic use. Since respiratory depression in the setting of pain management was the focus of Dr. Jiang's presentation earlier this morning, I would just like to point out that the majority of cases occurred in children under the age of 12.

I will now move on to the cough and cold setting. This table shows several descriptive

characteristics of the 14 cases that occurred in the cough and cold setting. All 14 cases involved children under the age of 12. Eleven of the 14 cases were U.S. cases. The most frequently reported codeine-containing product was promethazine with codeine, with and without phenylephrine. There were 7 cases with an outcome of death.

In the next slide, I will go back to the overall 64 cases of respiratory depression and discuss their outcomes by age. This table summarizes the outcomes of the 64 cases of respiratory depression with codeine-containing products reported by age.

There were 24 deaths. Of those, 17 occurred in patients under the age of 6; 4 occurred in patients 6 to less than 12 years of age; and 3 occurred in patients 12 to less than 18 years of age. Please note that one report may include more than one outcome.

In the next slide, I will discuss the 24 deaths and the reported reasons for codeine use.

Of the 24 cases with a reported outcome of death, the reasons for use were reported in various clinical settings, such as cough and cold and pain management. It is noteworthy to mention that 21 of the deaths occurred in children under the age of 12.

I will now present some representative case reports. There was a literature article identified in the Journal of Opioid Management by Friedrichsdorf et al. that discusses codeine associated pediatric deaths in various clinical settings, despite using recommend dosing guidelines.

The article describes three children, 4 to 10 years of age, who reported codeine toxicity at home. All three children were overweight or obese, however the codeine doses were within recommended dose ranges for adjusted lean weight. Two of the cases were reported in FAERS. I will provide the case details for these three children in the next three slides.

The first case involved a 10-year-old female

of Guatemalan descent who was discharged home 5 days after orthopedic surgery for bilateral hip subluxation. She was prescribed acetaminophen with codeine for pain and diazepam for spasms.

She was found unresponsive after 2 doses of acetaminophen with codeine and 1 dose of diazepam. Her postmortem codeine and morphine concentrations were in the toxic range. She was noted to have reactive airway disease and probable obstructive sleep apnea.

The second case report involved a 4-year-old female who received a total of 4 doses of acetaminophen with codeine post-tonsillectomy and adenoidectomy and was found unresponsive the following morning. Of interest, genetic testing found this patient to be CYP2D6 extensive or normal metabolizer.

The third case I'd like to present involved a 6-year-old overweight female who was prescribed guaifenesin with codeine for severe cough and respiratory infection. She received a total of 3 doses throughout the day and was found dead the

following morning by her mother. Her postmortem codeine and morphine blood concentrations were in the toxic range.

Earlier I presented a case involving a CYP2D6 extensive or normal metabolizer that resulted in death. Now I'd like to present a non-fatal case involving a 13-year-old African-American female who was determined by genetic testing to be a CYP2D6 ultra-rapid metabolizer.

She received 1 dose of acetaminophen with codeine for pain management of her sickle cell disease and was noted by her mother to be extremely drowsy and difficult to arouse. This child had previously taken acetaminophen with codeine and drowsiness was observed at that time as well.

In summary, we noted that there is some case report evidence of respiratory depression that sometimes results in a death following codeine-containing product use. Our pediatric case series primarily involved children less than 12 years of age.

The cases of pediatric death occurred after

codeine-containing product exposure when the products were used not only for pain management following tonsillectomy and/or adenoidectomy, but also for other pain management and for cough and cold management.

Lastly, CYP2D6 genotyping does not reliably predict outcome. There were 2 non-fatal cases of ultra-rapid metabolizers and 2 fatal cases of extensive or normal metabolizers in our case series. Thank you for your attention.

FDA Presentation - Catherine Dormitzer

DR. DORMITZER: Hello. My name is Cathy Dormitzer, and I'm an epidemiologist from the Division of Epidemiology II in the Office of Surveillance and Epidemiology. And I'll be reviewing the epidemiologic data on pediatric emergency room visits related to codeine-containing cough and cold and analgesic products.

First I'll discuss data from the Drug Abuse Warning Network. I'll discuss its background, its methodology, findings, strengths, and limitations, and then what conclusions can be

drawn from these data. After that, I'll do the same for the NEISS-CADES data set.

The Drug Abuse Warning Network is a data set usually referred to as DAWN. It's administered by the Substance Abuse Mental Health Services Administration, also known as SAMHSA. It provides published national estimates of emergency room or emergency department visits -- they're also called EDs -- that were induced or related to a drug.

These data are drawn from a multi-stage probability sample of 233 hospitals. It provides these estimates by drug substance and by case type. National estimates are not published if the counts are below 30 or where the estimates are too imprecise. Also, it only provides data on patients that survived long enough to make it to the emergency department, so it is not a good measure of drug-related deaths.

National estimates are classified and published by case type, and one of these case types is adverse drug reaction, which are ED visits that were the result of either an allergic reaction, a

drug-drug interaction, or a side effect of the drug.

The national estimates of this case construct is what I will be presenting next. Unfortunately, these data are no longer being collected due to lack of funding, so only data from 2004 through 2011 are available.

This slide presents national estimates for analgesic products. And as you can see, there are lots of asterisks on this table, and that indicates that the estimates were too imprecise to publish. I'm also not presenting cough and cold estimates because these estimates by age group were also suppressed.

When you examine the table, what you see is that in the 12 to 17 age group, there were roughly a thousand ED visits for each year for the years 2004 through 2011, and the estimates were somewhat lower in the younger age groups. But when you examine the confidence intervals of each estimate across the years and between age groups, they all overlap. So that indicates that the estimates

between years and even age groups aren't remarkably different.

The strength of this data set is that it is a public health surveillance system of serious adverse drug events that resulted in an emergency department visit, and these events were captured by medical professionals. They were derived from a large sample of 233 hospitals that are nationally representative.

The biggest limitation is that these data are no longer being collected. Another limitation is with the case type adverse drug reaction. That case construct does not provide granular detail on the case type and is going to include visits that are related to respiratory depression but others that are not, such as a drug-drug interaction or an allergic reaction. Lastly, these data are not likely to capture information on deaths that occurred outside of the emergency department, and that's a huge limitation.

So in summary, there are no published national estimates of adverse drug reaction ED

visits associated with the cough and cold products for the pediatric population, and there were roughly 1000 adverse drug reaction ED visits in the older children related to codeine-containing analgesic products.

Now, I will discuss findings from the National Electronic Injury Surveillance System - Cooperative Adverse Drug Event Surveillance data set. It's also called NEISS-CADES. And it's a joint effort of the U.S. Consumer Product Safety Commission, the CDC, and the FDA. It collects data on emergency department visits where the clinician explicitly attributed the visit to the use of a drug.

These events include allergic reaction, adverse effects, unintentional overdoses, or secondary effects such as coughing. It excludes ED visits that are the result of intentional self-harm, drug abuse, drug therapeutic failures, drug withdrawal, as well as ED visits that resulted in a death.

Clinical detail for each ED visit are

available with these data and are collected from a national stratified sample of 63 emergency department hospitals. And we have data for these from 2004 through 2013.

I will be presenting counts of these events because the national estimates were too imprecise to -- well, given the low numbers of events, the national estimates would just have been too imprecise. I will present the ED visits by ADE mechanism as specified by CDC, which is the global judgment of the mechanism by which the drug caused the adverse event or ED visits.

They include unintentional or accidental, which are unsupervised ingestion on the part of the child or if the parent made a mistake and gave the wrong medication or a wrong dose; allergic reaction, which is immunologically-mediated effects, such as a rash or hives, and adverse effect, which is an undesirable pharmacological or idiosyncratic effect at recommended doses.

So this table shows you the counts of NEISS-CADES ED visits for both cough and cold and

analgesic products. And in the 10-year period, there were 73 ED visits for cough and cold products and 261 visits for analgesic products.

This bar graph depicts the 73 visits for cough and cold products by ADE mechanism, and as you can see by the green bar, 70 [sic] of these 73 visits were accidental or unintentional. They were primarily in the younger age groups followed by allergic reaction, which is the yellow bar, and that occurred mostly in the 12 to 18-year-olds. There were 9 cases that were determined to be the result of an adverse effect, and I'll provide more details in the next slide.

This is a pie chart of the ED visits by ADE mechanism. And as you can see, 55 percent of the visits were accidental or unintentional, 33 percent allergic reaction, and 12 were adverse effect ED visits. The table provides a listing of the clinical symptoms the physician noted in the adverse drug effect ED visit. Two of these ED visits, the physician reported symptoms that may be related to respiratory depression.

This is a bar graph for the codeine-containing analgesic products, where there were 261, and this time the largest proportion of ED visits were related to allergic reaction. There were 117.

The number of ED visits for accidental unintentional adverse effect were roughly the same, 74 for accidental, 70 for adverse effect. Most of the accidental unintentional ED visits involved children under 5. There were 70 adverse effect ED visits, and most of those were in the older age groups, and none occurred in the under 2-year-old population.

This is the pie chart for the analgesic products. As you can see, 45 percent of the ED visits were related to allergic reaction, 28 percent to accidental, and 27 for the adverse effects. Now what you can see in the table, is that there are 130 symptoms for these 70 adverse effect ED visits. That's because there were many ED visits where the physician recorded more than one symptom per ED visit, and all symptoms are

presented in this table.

As you can see, there were 13 cases where the physician reported symptoms that may be related to respiratory depression. There were 8 where the physician reported dyspnea, 3 involving somnolence or sedation, and 2 where the physician reported decreased breathing or abnormal breathing.

So the strengths of NEISS-CADES is that it provides clinical detail on the ED visits, and these were recorded by a trained medical professional. It is an active surveillance system from a nationally representative sample.

The limitations are that it is still only a sample of 63 hospitals, so it makes it more difficult to provide national estimates. A huge limitation of these data are that it's collected at discharge, and no deaths are recorded in these data.

So to summarize, there were pediatric ED visits for both cough and cold and analgesic products in the NEISS-CADES data set. Accidental and unintentional ingestions accounted for the

largest proportion of ED visits related to cough and cold, and allergic reaction accounted for the largest proportion of ED visits for analgesic products. There were ED visits found that maybe likely related to respiratory depression for both cough and cold and analgesic products.

So both DAWN and NEISS-CADES found pediatric ED visits associated with analgesic products, and there were ED visits for cough and cold products in the NEISS-CADES data set as well. These data are not likely to provide a complete picture. Although it is active surveillance, the NEISS-CADES data set is small, so it is difficult to compute national estimates.

Furthermore, there are limitations with emergency department data. If an event results in a death, little to no data will be derived from these emergency department visits because emergency departments just won't gather these data. Thank you.

FDA Presentation - Margie Goulding

DR. GOULDING: Good morning. Just want to

reassure you, you're in the final stretch on the data, at least from FDA presentations. My name is Margie Goulding. I am also an epidemiologist, and I'm going to provide a very brief wrap up with a summary and takeaway points on the various data that you've heard about from my colleagues in the past half hour.

These takeaway points are first, over the period 2010 to 2014, although total OTC sales of codeine-containing products and prescription use by pediatric patients decreased, pediatric prescription use remains high.

Second, there are both FAERS and epidemiological emergency department data case reports of respiratory depression or respiratory depression related problems in pediatric patients after use of codeine-containing products, both for cold/cough and analgesic uses.

Third, two emergency department data sources, that is DAWN and NEISS-CADES, showed pediatric ED visits for adverse reactions or adverse events associated with codeine-containing

analgesics.

Our points on interpretation of these data. The FAERS, NEISS-CADES, and DAWN case data largely cannot be used to generate reliable national estimates of codeine-containing product related adverse events in pediatric patients. But still, there are cases of respiratory depression or respiratory depression related problems, such as dyspnea, following codeine-containing product use in pediatric patients in both the FAERS and the NEISS-CADES emergency department visits data.

We cannot determine the true magnitude of the problem. That is, we cannot get reliable incidence rates, but we also cannot conclude from these data that there is not a significant risk. That is, we cannot interpret these data as evidence of no problem or no risk.

Therefore, taking all this information together, we conclude that given continuing high pediatric use of codeine-containing products, these data do raise concern and interest in consideration of further regulatory action to promote safer use

of codeine products in the pediatric population.

We'd like to acknowledge these additional contributors to the work we've presented. And I believe we have some time for questions. Thank you.

Clarifying Questions to the Presenters

DR. OWNBY: Thank you very much. Are there any clarifying questions for the FDA or the speaker? Please state your name for the record before you speak. If you can, please direct the question to a specific presenter. Yes?

DR. FINNEGAN: I actually have one for the first person who spoke. I'm wondering if you can do the same studies on oxycodone and hydrocodone that you did to find the pediatric prescription rate in the U.S. population. Because your numbers are so low as far as incidence of depression or concern that it may be you didn't see any because there aren't enough prescriptions in the pediatric population for that.

DR. GILL: Hi. This is Rajdeep Gill. Could you clarify your question? Is it around use of

oxycodone acetaminophen?

DR. FINNEGAN: If I understand you correctly, you looked at the looked at the retail prescriptions for codeine analgesics. My question is -- because from my interpretation the number of patients that have to get the drug in order for you to have an adverse effect is pretty high.

So I'm wondering if you did not see any adverse effects with the other medications because they haven't been previously routinely prescribed, and therefore you need a larger number of patients to get the medication before you get the adverse events. Does that make sense?

DR. RACOOSIN: Yes. Cindy, can you pull up the backup slide that I sent you the other day? I don't know what number it is. We just had one for DAAP, the backup slide.

We did that analysis back in 2012. We didn't repeat it with this analysis, this 2015 review, but I have this slide from that that we're trying to pull up.

DR. FINNEGAN: And do you have

[inaudible - off mic]?

DR. RACOOSIN: Well, I think it's easier if we just look at the numbers on the slide.

Okay. So this is the year 2011; that was at the time that we did the analysis. And 2012, this is the last year that we had the full data for. And you can see that -- did you guys want to describe this?

DR. GILL: That's fine. As you can see, the oxycodone acetaminophen use in the older population, or older pediatric population, which is 11 to 17 is -- actually, all age groups is way lower than codeine acetaminophen, all the pediatric age groups.

This is just -- can you see the colors actually? Just 0 to 1, 2 to 5, 6 to 10, and 11 to 17, and the total use obviously is lower. And then if you were just comparing oxycodone acetaminophen and codeine acetaminophen, it is pretty low.

DR. RACOOSIN: So I think the point here is that codeine acetaminophen combination is the most commonly used one up and through 10 years old. But

then when you get to the 11 to 17, hydrocodone way exceeds codeine -- hydrocodone acetaminophen way exceeds codeine acetaminophen, and it's only in that oldest age group where you start to see any use of oxycodone/APAP. Morphine is not on this slide, but it was on the order of codeine single ingredient, so we don't have it broken out.

DR. OWNBY: Okay. Dr. Cataletto?

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. I wanted to ask the FDA epidemiologists their thoughts about the possibility of some of these cases potentially being attributed to the indication for the use of the medications. Do you think that's possible?

DR. RACOOSIN: So just to understand, you mean the fact that they had some sort of upper respiratory infection or cough, that that would be the explanation for why they had respiratory depression as opposed to attributing it to some effect of the medication?

DR. HERNANDEZ-DIAZ: Correct. Do you have any thoughts about that possibility?

DR. SEYMOUR: This is Dr. Seymour. So I mean I think that's difficult to tease out in these case reports. Certainly, on the patients post-tonsillectomy and adenoidectomy, in the presentations, they described that there was some sensitivity in these patients and swelling. There could be some increased risk because of their underlying condition.

I think the same goes with cough and cold, that it would be difficult to tease that out. But this is the population that these drugs are indicated for and they're being used in, so I don't know that we can tease it out.

DR. RACOOSIN: But I do think that in the post-tonsillectomy setting, with airway swelling and this opioid sensitivity in the children who have obstructive sleep apnea, that those things combined with the higher levels of morphine and the ultra-rapid metabolizers, that those three things may -- because again, we couldn't find cases where -- or in our initial evaluation, we didn't see cases of children getting codeine for dental

surgery or some other kind of surgery. We didn't see that, and so it's hard to know. But we did have cases in this second evaluation with the cough and cold.

So whether there's some sort of contributory factor that there's already something going on in the airway or the respiratory system is a contributory factor, but as Dr. Seymour says, it's hard to tease out each one of these.

DR. HERNANDEZ-DIAZ: Okay. So I can see how it can be hard, but do you know if there is any data for post-adenotonsillectomy? What is the natural history of the kids post-surgery? If there is any data of mortality with and without these drugs or specifically for these kids. There is a high risk of death already based on the --

DR. RACOOSIN: There is a paper published in this last year by Dr. Koren's group, and Dr. Kelly was the first author of the same group that published that case series in 2012, where they did a randomized controlled trial comparing morphine to ibuprofen and acetaminophen for post-tonsillectomy

pain, and they measured desaturations, oxygen desaturations.

In the ibuprofen group, there was like a 68 percent decrease in the desaturations in that first night post-tonsillectomy, compared to I think only 14 percent had improvements in their desaturation in the morphine group.

So if you use desaturations as a measure of continuing respiratory problem, then it suggests that the group on the opioid did not show as much improvement in their respiratory status post-surgery in that first post-operative night as the group that got the NSAID and the acetaminophen. So that doesn't look at a long-term outcome, but in that immediate post-operative setting, the non-opioid group, their respiratory status seemed to fair better than the opioid group.

DR. OWNBY: Dr. Flick?

DR. FLICK: So just a couple of comments from a pediatric pain management perspective. For those of us who manage acute pediatric pain, there are a couple things that I think are useful.

First of all, the metabolism of oxycodone is fundamentally different than the metabolism of codeine, so we should not be comparing those two drugs as having a similar risk profile. They clearly do not.

Among pediatric pain providers, the preferred oral pain medication is oxycodone, and oxycodone is used preferentially by virtually all of my colleagues across the country in children, in very young children down to toddlers. My colleagues on either side of me can amplify that. So oxycodone is the prevalent drug for post-operative pain in children.

I would also ask, is there something fundamentally different about codeine in terms of cough suppression than any other opioid? If there is, I'm not aware of it. And when we have a discussion of risk and benefit, we also have to have a discussion of alternatives, unless there is no benefit.

So if we think there's some benefit to opioids in the management of cough, then we should

be thinking of what those alternatives are and what the risk associated with those alternatives might be.

I'll make one final comment. We talk a lot about the risk in the setting of tonsillectomy when in fact we may be talking about the risk in the setting of obesity, because obesity is highly correlated with tonsillectomy, especially in older children, non-toddlers.

So obesity and obstructive sleep apnea lead to tonsillectomy. So the risk factor may not be tonsillectomy/adenoidectomy. We know from Karen Brown's work that opioid sensitivity is increased in the setting of sleep apnea. So what I'm saying is there's a much broader risk group than simply tonsillectomy. It's obesity, in my view, that is the risk, and we should think about that as we consider the discussion.

DR. OWNBY: Thank you. Dr. Leeder? I believe you're next.

DR. LEEDER: Steve Leeder. Actually my question and comment was actually related to the

obesity as well. The three Friedrichsdorf cases were all obese or overweight children. Two of the three cases in Kelly, if you actually look at the weights and then estimate whether they're overweight based on their percentile, two of them were -- cases 1 and 3 were greater than the 95th percentile. And case 2, which was a female, 14.4 kilo female, was not. She was between the 50th and 75th percentile.

My question was to Annie Nguyen as to whether obesity had come up as a signal for the larger set of cases that had been looked at.

MS. NGUYEN: Hi. Annie Nguyen. To be honest, a lot of -- you heard the FAERS limitations. Unfortunately, the cases that we receive, not all the cases provide us with the weight of the child. They provide the event; sometimes it's very limited in data. So we didn't find a signal. It doesn't mean that it wasn't there, it's just that we didn't have any weights reported.

DR. OWNBY: Dr. Alexander?

DR. ALEXANDER: Just one or two comments about the potential for unanticipated consequences, or unintended. So there were huge changes in Rx and OTC use over five years. It sounds like 40 percent reduction in Rx and 85 percent in OTC.

So if one assumes that these are true, then it might be of interest to look at the changes in use of other products that would be substitutes for these products. That might be especially informative for analgesia where we've heard that, maybe arguably, there's a greater concern about unintended consequences of further restrictions on codeine-containing products.

I find it really remarkable that there were no FAERS events when searching for alternative opioids using the same strategy. It's hard for me to believe if there were really 2 million patients that were exposed to hydrocodone. But the data is what it is.

But one could also use FAERS or other data sources to look at a broader set of comparator products. It sounds like you guys have looked at

whether or not -- you've used FAERS to look at whether or not using a similar search strategy there were signals for three opioids. But given that there have been concerns expressed about the potential safety profile and adverse effect profile of a broader group of substitutes for codeine-containing products, one could also use these types of data sources to look for that.

If you really believe that there's an 85 percent reduction in the OTC use and 40 percent reduction in Rx use, those might be helpful analyses to do to further reassure you about unintended consequences.

I'll hold the comments on monograph, although I have a few. So the last is just a very pointed question, which is just, is there any professional society or guideline that's provided vocal opposition to the general path or pattern that we've seen over the past decade or more, which you nicely explicated, which is greater and greater restrictions, regulatory restrictions on these products?

DR. RACOOSIN: To clarify your last question, do you mean are there professional societies that have encouraged continued use of codeine? Is that what you're asking?

DR. ALEXANDER: Yes. I mean, we heard -- you provided -- essentially, it looks like all of the other major regulators -- we've only seen examples of regulatory agencies that have more restrictive policies than the FDA. And if I'm correct, if I caught what was presented, all of the professional societies and sort of influential bodies, WHO, or head and neck surgeons, or whatever else, all of them appear to be supportive of the types of restrictions that have put in place.

So what I'm asking is, are there any professional societies that have spoken out and said in fact we think this is a mistake, or that these products are too tightly regulated, or that we think that the risks are being overestimated, and that in fact, we need less of an emphasis on this, not more?

DR. RACOOSIN: So no, we have not found

professional societies or other relevant groups who have advocated that position. In addition to the ones that Dr. Starke presented in his presentation, I also mentioned that the American Academy of Otolaryngologists concurred with FDA's approach to restricting or contraindicating codeine after tonsillectomy/adenoidectomy.

So I am not aware, and I think as we've sort of scanned the literature and the professional society recommendations, we've not found any group to advocate for sort of the continued use at prior levels or to soften these recommendations about codeine.

To your other point about the unintended consequences of shifting things, I do want to point out that between the review that we did in 2012 and this one that you heard about today that we've just completed, the search strategy broadened.

When we initially were looking at this, based on the cases that were in the literature that we were aware of, we took a fairly narrow view. We looked at deaths and we looked at overdoses.

In this review, to broaden the potential number of cases that we could identify, we went to serious outcomes. So the regulatory definition of serious I think is on one of the slides, so let me just point that to you. It's on slide 21 of Dr. Nguyen's presentation.

The serious outcome of death, life-threatening events, hospitalization, disability, congenital anomaly, and other serious important medical events; we took this broader approach in this evaluation.

So I just want to remind you that when we did not find cases for hydrocodone, oxycodone, or morphine, that was the original search strategy, which was all deaths and the high level terms of overdose.

So it's possible there could have been additional cases we might have identified, and perhaps we're going to need to do that as one of our action items out of this meeting so that we do have an idea of what the potential unintended effects might be.

So I think I just want to reiterate that when we were in our fairly narrow effort to identify cases potentially related to ultra-rapid metabolism of codeine, when we took that approach and looked at these comparators at that time, we didn't find cases that met that case definition.

This broader case definition hasn't been evaluated for those alternative products, so I can't even begin to say what we would find, but it's certainly something that we could consider looking at as we're exploring the potential implications of unintended consequences.

DR. OWNBY: Dr. Morrato, you're next.

DR. MORRATO: Thank you. Dr. Morrato. I wanted to just echo I think the analysis that Dr. Alexander was recommending and just add a couple of thoughts to that to expand on it. Sales data, you can be looking also at states in which OTC is not -- you have to have a prescription or not.

So there is ability to have greater granularity, and it gets at the point, are you

seeing differential effects depending upon the state regulation. I think it will be --

DR. RACOOSIN: Can I just say --

DR. MORRATO: Yes.

DR. RACOOSIN: For the data resources that we have for the OTC products, we are not able to break it down by state. So we're limited in that by the data that we have available.

DR. MORRATO: By the data that the FDA has contracted? Is that -- because manufacturers can look down at finer granularity, so maybe just the -- so maybe there are ways that you might get access to that information.

I know there's statistical units where you can look at major metropolitan areas and look at sales within those. So those data are available, maybe researchers can get it.

But I think it would also be important to know in the time period in which you are looking at changes, were there any states that flipped over and changed their state policy making some things now requiring a prescription? Just to make sure

that you're understanding the impact of the time trend, is it due to market forces in which people are changing based on the labeling changes, or is it due to other state regulatory forces? Do you know? Or is that all those states --

DR. RACOOSIN: So I think one thing that we need to perhaps recognize is that that trend of declining use of codeine predated anything that we did with our labeling. So that trend, you started to see the decline in like 2011, 2012. We didn't take our action until 2013. So there's other -- in the medical literature, people have been talking about concerns about codeine for some time, so that could be playing in. So there's a lot of different things that could be going on.

DR. MORRATO: Exactly. But if you could at least do an analysis of which states were switching their policies during that time frame, it does allow you to sort of estimate the incremental impact then of FDA making its federal level decisions around some of these labels. So that was just some additional thought.

But I just wanted to confirm, so we're understanding the biologic plausibility of the safety signal as it relates to genetic variability and metabolism, but we're being asked to be very specific on age groups, less than 6, less than 12, less than 18.

Is there any data -- and we've seen case reports across the age range. Is there any data, PK, pharmacology or any others, that would say that this adverse event is age dependent, or is it more just a matter of the size of the person as they get older? I mean, what is the evidence that would suggest why it's a 12 cut point versus an 18 from a risk standpoint?

DR. SEYMOUR: So I think that's a challenge with the data that we have, and certainly other regulatory bodies did make an age cutoff. The case reports that you've seen are primarily in the 12 and younger. There are a few in the 12 and older age groups.

We, when we originally made the contraindication didn't put an age range on it. It

was all children who had gone post-tonsillectomy or adenoidectomy. I don't think there was an age group that we felt could be isolated, so it was all children. But, you know, unfortunately this is the data we have. It's postmarketing reports. It's literature reports. The majority of them, though, are in 12 and younger.

DR. MORRATO: So in the other regulatory considerations, was there any biological basis for why they made that, or is it more or less convention in those markets of how they are defining pediatric?

DR. SEYMOUR: I don't recall reading anything in the EMA about the age cutoff. They had the most, I think, largest document in the PRAC report about their assessment. And I don't recall if there was any information about why they chose 12 versus 6 versus 18.

DR. RACOOSIN: But I think that to some extent, at least the tonsillectomy and adenoidectomy, it tends to be the younger age groups that are getting those procedures done. So

that partly may explain why we saw most of the cases under 12 because many of them were related to that procedure.

DR. OWNBY: Okay. I know it's time that we were scheduled, but we're going to continue the questions for another 15 minutes or so. And I believe Dr. White is the next one with a question.

DR. WHITE: I think I'm going to defer. Dr. Flick answered a lot of the information. But if the FDA has a slide that would show the metabolic pathways for hydrocodone, oxycodone, and codeine, that would be great.

DR. OWNBY: Okay. Do you have that available from the FDA or --

DR. SEYMOUR: In the interest of time, I think let's work on that, and we'll let you know when we have that slide available.

Can I answer Dr. Gerhard's question, though, that he asked earlier about the EMA over-the-counter use? They actually published -- there was an article published in 2015 about the EMA availability of codeine, and they surveyed their

different member states, of which there are 28.

So it is available over the counter. Fifteen of the member states did not permit over-the-counter sales. And just like our states, there are different restrictions, who can buy it, labeling throughout differs, but it is allowed over the counter in some of their states.

DR. OWNBY: Okay, Dr. Roumie, I have you next.

DR. ROUMIE: My question was really touched on a little bit by Dr. Alexander and related to this. On Dr. Gill's slide 8, it shows the OTC retail sales that really plummet about 85 percent between 2011 and '12. And I guess I'm thinking more of the monograph and the policy implications.

Were there other -- or are you aware of any other state-level restrictions that occurred at that time? Because that seems to be really before the 2012 FDA kind of advisory and lots of other kind of governmental policy implementation? So that was really end of 2011 it looks like that started to go down.

DR. ADAH: So let me comment. Steve Adah. Let me comment for a minute on how we generated that table. We actually went through a number of different databases to try to figure out what states allowed for what.

We didn't, to my knowledge, really look at if there were shifts in time, and in a couple cases, it was really difficult to even get the states to respond to tell us what their policy was. We did see, I thought, a couple states that may have changed during the time period, but I wouldn't want to hang my hat on any of that.

DR. ALEXANDER: Did you guys look at other products just to be sure that that wasn't -- the way that these data are derived by IMS, they essentially -- they're data aggregators.

So, you know, they'll get different feeds. One year Walmart will be in; one year, you know, Walgreens will be out. So I just wonder if you looked at other products to be sure that there weren't large changes in other products that would raise concern about the sample changing year-to-

year.

CDR MOENY: Right. This is David Moeny from DEPI. It's true that their sample does change over time. They attempt to correct for that in their projection methodology. But to answer the question directly, no, we focused simply on codeine for this meeting, and we haven't looked at the other products since the 2012.

DR. ALEXANDER: With some of their products, they allow for one to look at, for example, constant store panels and using the national prescription audit. So I don't know if there is something similar where you could just identify a single vendor that accounts for a large market share in the U.S., and then you'd have, greater ability -- if you can identify that, you'd have -- it would increase one's confidence that these are true changes in consumer utilization.

DR. ROUMIE: I guess part of my concern with this data is I'm not sure how accurate it's reflecting all the over-the-counter use. And if we're going to discuss kind of monograph issues,

that's obviously a multi-step process. If we were to believe this, we would say, oh, well not many people are using it anyway. But I guess I'm just wary a little bit.

CDR MOENY: Yes. Rajdeep can speak to this perhaps a little bit more. But we did look at the sales distribution on a wholesale level with these products and found that the preponderance of them went into the retail channels, and then these OTC are the retail channels coming out as well.

DR. OWNBY: Did that answer the question? Do you have one quick comment, Dr. Morrato?

DR. MORRATO: Related to that, were manufacturers reformulating during this time period, therefore your set of drugs is also getting smaller?

DR. ADAH: For clarification, when you say manufacturers, are you talking OTC or in general?

DR. MORRATO: Well this is OTC retail sales, right? So is this a constant set of products throughout? I know the category -- so it could be a collapsing of the categories getting smaller

because there are fewer medicines being marketed, too, as well as what I was saying as state changes.

Are manufacturers changing when you look over this time period? They're reformulating the active out and they're using other products.

DR. CHAI: Hi. My name is Grace Chai. I'm the deputy director for drug utilization. We actually have a backup slide of the database description. If you don't mind going to -- I think it's slide number 66 under Rajdeep Gill's presentation. Yes. It says "Database Description, OTC International Marketing."

So to your question, we queried this database for all codeine-containing products that are sold over the counter. And once a site populates, what it does state is that it is based on a sample of over 70 percent of the OTC retail universe that is being sold. And it is projected up, the remainder, but it is a very robust sample.

There are many factors that could be contributing to the decline, including differing state regulations, but as it was mentioned

previously, I think there were attempts to try to talk to the states about that, but I think you can speak further about that.

DR. ADAH: I don't think so.

DR. CHAI: No, this is not the slide. I'm sorry.

DR. ADAH: I don't believe so. I think we just looked to see what regulations were on what states. We never looked beyond that.

CDR MOENY: To go back to the question about products dropping out of the market, we did roll these into these large aggregate groups of analgesic, cough/cold. But yes, you did see some of the lesser used products drop out of the sample, and you're not really seeing them in the later years.

I'm sorry, I don't have a slide to show you, but that's what we were generally seeing. The major players that we listed, like the guaifenesin, codeine, they were fairly consistently the major products in the past as well.

DR. OWNBY: Did that answer the question

then?

DR. CHAI: This is the slide.

DR. OWNBY: Do you want to comment on the slide or?

DR. CHAI: It basically states what I mentioned before, that it is a very robust sample, and we did query for any codeine containing products that is sold over the counter.

DR. OWNBY: Okay. Dr. Besco, I believe I had you next.

DR. BESCO: Kelly Besco. And I was glad to hear some others comment on the role of obesity for risk of respiratory depression when opioids are used. I also wondered, and my guess is it was probably difficult to ascertain if there was any effect of concomitant use of sedating medications and used in these cases that could have contributed to the excessive sedation.

Then also, since there were so many accidental events that occurred that were reported from the ED point of care, I wondered how many of those potentially were a result of a parent

administering an incorrect dose. As we know, that's quite prevalent; errors in the home have some bearing on the availability of these from a nonprescription standpoint or if they were just accidental ingestions.

CDR MOENY: We can answer the question, I believe, about the detail to obtain who administered the product.

DR. DORMITZER: With the accidental, it was -- I wish I could give the exact split. But it was more with the child found with the bottle all over its shirt of something like that. But there were times where the parent either gave something different; they gave the cough and cold product instead of the Zantac, or was listed that, oh, I gave the wrong medication, or they gave the wrong dose. So with the parent, it's a mistake, and with the child it's unsupervised.

DR. BESCO: And was there any information on concomitant use of sedating medications in these cases? I saw one that referenced valproic acid, but that could potentially heighten the level of

sedation and induce respiratory depression. So just wondering if that was a trend that was noted in the data?

DR. DORMITZER: No, no. No, the accidental ingestions, that's the mechanism that caused the ED visit. None of those had respiratory depression, because if there were respiratory depression, then it would be an adverse drug effect. So even if they did it accidentally, they would wind up in the adverse drug effect category.

DR. BESCO: I guess it was two different questions, sorry. It might have blended together. So you answered my question on the accidental events. I was more wondering if any of the events that you looked at from an aggregate standpoint, if there was a trend with use of concomitant sedating medications that could have also exacerbated the respiratory depression.

CDR MOENY: Are you referring to the FAERS cases or to the hospital data?

DR. BESCO: Yes, I was thinking about the FAERS cases; I'm sorry.

UNIDENTIFIED MALE SPEAKER: The child with cerebral palsy also got valium as well as the codeine, so there are at least two.

MS. NGUYEN: I'm sorry. Annie Nguyen, again. Could you just repeat your question just so I can make sure I understand what you're asking?

DR. BESCO: Sure. I was just wondering how many of the FAERS cases, if you found that the child was also, at the same time, getting another agent that is known to cause sedation, that could have exacerbated that respiratory depression in addition to the use of the codeine.

MS. NGUYEN: Yes. So I did mention that promethazine with codeine was reported in a large majority of the cough and cold cases, and promethazine is noted to cause respiratory depression as well.

DR. RACOOSIN: The other issue about the valproic acid, there are actually three cases where children were on concomitant valproic acid in the original case series; the six cases that didn't have the CYP2D6 phenotyping or genotyping. And at

the time we discussed this -- this is in the background package, the question of whether the valproic acid played some role in those cases.

Our advice from our colleagues in the Office of Clinical Pharmacology was that valproic acid can play a minimal role in inhibiting the UGT-mediated clearance of morphine, but that they didn't think that it was clinically significant.

So we can put it up there again, but the metabolic pathway of codeine, once it gets to morphine, it has these additional enzyme breakdown of the morphine. So the valproic acid could potentially play some minor role in that latter part of the process, but it wasn't considered to be clinically significant.

DR. BESCO: I've just experienced cases in the adult population where we've seen multiple sedating medications given at the same time, and then a patient has a respiratory depression event. So just wondering if that came out as a trend at all, to potentially consider like a staggering administration recommendation, but --

DR. RACOOSIN: Well the thing is, at least post-tonsillectomy, most of these children are being discharged to home. So they're being given pain medication, but beyond that it's not clear that they would be getting the kinds of additional medications you're suggesting.

DR. SEYMOUR: But all the codeine cough/cold medications are in combination with an antihistamine or some other medication. So there is concomitant use.

DR. OWNBY: Okay. Dr. Yu, you're next.

DR. YU: Thank you. My two questions related to data. The first one is just a clarification. On a National Electronic Injury Surveillance System, you said the data is currently available for 2004 to 2013. I'm just wondering if you have any data actually collected to present, like 2015.

DR. DORMITZER: We will be getting 2014 data very soon. It's a continuous program, and they're continuing to collect data.

DR. YU: Okay.

DR. DORMITZER: So we just haven't gotten 2014 all clean yet.

DR. YU: Okay. My second question is, the National Electronic Injury Surveillance data.

DR. DORMITZER: NEISS-CADES.

DR. YU: Yes, that's it. It collect accidental, unintentional. Does FAERS data also include those types of category, accidental, unintentional? Do they include it?

DR. DORMITZER: How FAERS is collected is different. Yes.

MS. NGUYEN: So there were a few cases of accidental or overdose or ingestion. There were three non-fatal cases of accidental, and four death cases of accidental ingestion.

DR. YU: Okay. All right. Thank you.

MS. NGUYEN: Sure.

DR. YU: My third question, I hope is short.

DR. RACOOSIN: Can I just go back for a one second to your last question? I think it's important to recognize the different ways that these data sources -- so the FAERS data that we're

talking about is all spontaneously reported either by a physician, a healthcare provider, or patient, or there are requirements for pharmaceutical companies that they have to report the adverse events that come to them.

But it is not the same as the NEISS-CADES, which is actually an active surveillance system where they're combing through the patients who come through the 63 emergency departments looking for cases that are related to some sort of drug exposure. So you have to separate those two things because they are completely different in how that data is collected.

DR. YU: Yes. That brings me up to my third question. Now we have three major data sets presented to us, and it all shows some evidence of the problem. But just like any data set, they always have the drawbacks and have something incomplete.

So in FDA's perspective, or your perspective, which data set among the three do you think is the most helpful to guide us to give a

more complete picture or more evidence picture on a national level for this type of problem we are looking at?

CDR MOENY: I think your question had the crux of the answer in it. To get as complete a picture as we have, we have to basically combine aspects from all three of them and glean the data we can from each one. There's no one magic bullet that's going to let us get a complete picture of the issue, unfortunately.

DR. YU: Yes. From a consumer's point of view, and the same as providers, we all wish that we have a national very comprehensive adverse drug event surveillance system that we can track, systematically, we can look at a risk/benefit in a full comparison with different drugs; or when we have one drug and we have a problem, we can pull out another one. We can compare the same, the risk and benefit and to evaluate this. But I feel like I'm frustrated looking at all the data and have it collected in a different way.

The last thing I saw, different hospitals,

they all collect their -- they have their own surveillance system. I just wonder whether there are professional societies, organizations, actually, like a pediatric society, do they actually collect some -- do some surveillance, tracking the data, the drug adverse events for that type thing?

CDR MOENY: First of all, I'd like to say that we share your frustration with being able to get the complete picture. To the second question about societies collecting these types of data independently, I'm not aware of any, no.

DR. YU: Okay. Thank you.

DR. OWNBY: I have Dr. -- I believe it was Dr. Brown down here on this side that was next.

DR. BROWN: I've got a lot to say. One thing that's bothersome to me -- I want to ask some questions about over the counter and about prescription. One thing that bothers me is that in the face of an international attempt to reduce the use of codeine, that there are still a couple million prescriptions in the United States that are

for codeine in children.

One thing that I think the FDA has done a very nice job of is teasing out who are the prescribers. Most of the people who are sitting around the table here today are pediatricians, and if you look at the data, it's mostly not pediatricians that are prescribing these compounds.

This gets to the issue of the professional organizations. Whereas I don't think you're going to see professional organizations that are against any reduction in the use of codeine, the data that the FDA has given us suggests that the professional organizations differ in their ability to get the message out to the rest of the practitioners. And these practitioners, some of whom are physicians, some of whom are nurse practitioners, that all varies.

One comment about over-the-counter codeine. In the face of this international drive to reduce the amount of codeine that is prescribed to children certainly, does it make any sense for us to still allow over-the-counter codeine in the

United States? I guess I just throw that question out.

It seems like we're sending two messages here. As a pediatric pain practitioner, I don't use codeine anymore because I agree completely with Dr. Flick's comments. But if we allow over-the-counter codeine to be sold, one thing that we know about narcotics is that if it is out there, it will be used.

Does it make sense for us to allow that to be sold over the counter with the implication that it is innocuous?

DR. ADAH: That is exactly one of the questions we're asking this panel today. And it is a specific question about OTC separate from codeine in general in children. That is a very specific question partially for that reason I think. I mean, we do share that concern.

DR. OWNBY: Dr. Perrone, I believe you're next. And just short because we have to move on to the open public hearing.

DR. PERRONE: Very short. I think the FDA

answered my questions about utilization.

DR. OWNBY: Dr. Leeder? You have a short question?

DR. LEEDER: Actually, I don't have a question at all. I was just going to help out with the age -- the issues related to drug metabolism, drug clearance that might be relevant to the age issue of the younger subjects, younger patients being involved.

There's been a lot of attention paid to the cytochrome P450 2D6 status of the cases being ultra-rapid metabolizers and extensive. There are a couple of comments that are relevant here.

The activity of the enzyme is a continuous sort of thing. So there's a considerable amount of overlap between those individuals who have two copies, functional copies, of the gene or more than two copies of the gene. And this is one of the reasons why you'll see some cases showing up as extensive metabolizers.

The other issue, though, is that to the extent that we believe that morphine is responsible

for the therapeutic action of codeine and its toxicity, there are two factors -- well there are two primary factors involved. One is its formation, which is the 2D6 issue. The other is its elimination. And the primary routes of elimination are 3-glucuronide formation and 6-glucuronide formation. And the more relevant developmental issue relates to the maturation of these glucuronosyltransferases.

I went back and looked at the EMA assessment, and they actually have a section 2.2.2 on the effect of age. And they basically are using the 12-year time point as being the point at which the pathways, all the pathways, involved in morphine -- well codeine disposition, but that includes morphine -- are fully mature.

In some of the cases where there are both high codeine and high morphine concentrations, it implies that maybe the elimination of the morphine is an issue in addition to the formation, in that orally absorbed codeine can be glucuronidated both in the gut and by the liver.

So the age-related issues I think reflect more the elimination of the morphine than the formation of the morphine, but both likely are determinants of risk in as much as renal elimination also is associated with higher systemic exposure to morphine.

Open Public Hearing

DR. OWNBY: Okay, thank you. We'll move on to the open public hearing portion. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at open public hearing sessions of the advisory committee meeting, FDA believes it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with any company or group that is likely to be impacted by the topic of this meeting.

For example, the financial information may include the company or group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their considerations of the issues before them. That said, in many instances and for many topics there will be a variety of opinions.

One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when

recognized by the chairperson. Thank you for your cooperation.

Will speaker number 1 step to the podium and introduce yourself. Please state your name and any organization you are representing for the record.

DR. HOWARD: Good morning, and thank you for the opportunity to speak. My name is Marcia Howard, and I am the senior director of regulatory and scientific affairs at the Consumer Healthcare Products Association.

Founded in 1881, CHPA is a U.S. based trade organization that represents manufacturers of over-the-counter medicines and dietary supplements.

Today, I am here to emphasize the changes to any OTC monograph, including the one for cough and cold products, must be based on sound scientific evidence. The OTC monograph review process for cough ingredients was a thorough, multi-step process and included the use of an FDA advisory committee, not unlike the committee that is convened here today.

The ingredients included in the OTC

monograph were determined to be generally recognized as safe and effective, or GRASE, based on review of the data provided to the FDA at the time of the OTC review.

Any changes to the regulatory status of an ingredient currently found as GRASE must also go through a multi-step process, including a proposal to amend the cough and cold monograph and a period of time for interested parties to submit further data and comments to the agency.

The procedural protections of this rulemaking process are important to assure notice is given and that there is transparency. While we acknowledge that the time to finalize a change to the OTC monograph may be lengthy, industry can and have worked with the FDA to implement changes on a voluntary basis when made aware of a safety concern.

In closing, cough and cold ingredients listed at 21 CFR 341 are generally recognized as safe and effective. Any changes to the OTC monograph for cough and cold products should be

based on scientific evidence and must follow the appropriate rulemaking procedures.

Industry can and has worked with the agency to implement changes on a voluntary basis when a safety concern is identified for products marketed under an OTC monograph. Thank you for your time and attention.

DR. OWNBY: Thank you. Will speaker number 2 step to the podium and introduce yourself. Please state your name, any organization you are representing for the record.

DR. RUPP: Hi. My name is Tracy Rupp. Thank you for the opportunity to speak today. I was previously clinical pharmacist and pediatric nutritionist at Duke University Medical Center, and I'm now the director of public health policy initiatives at the National Center for Health Research.

Our research center analyzes scientific and medical data and provides objective health information to patients, providers, and policy makers. We do not accept funding from the drug or

medical device industry, and I have no conflicts of interest.

We strongly support access to safe and effective medications for children. Codeine is one of the most widely prescribed opioids and is frequently chosen because it is perceived to have a wide margin of safety.

Over the past decade, however, serious concerns have been raised about its safety in children. As we have heard today, the safety risks with codeine are largely due to the substantial variability in how it is metabolized.

One study found oral codeine led to a 20-fold higher morphine exposure in extensive metabolizers, the most common genetic variation, compared to poor metabolizers. Ultra-metabolizers experience the highest risk of harm from codeine since they could have morphine levels almost 50 percent higher than extensive metabolizers.

Children who are ultra-metabolizers can convert too much of their codeine dose to morphine with catastrophic consequences, including death.

Unfortunately, physicians usually don't know how fast a child will metabolize codeine.

From the information presented today, we have learned the risk of codeine can outweigh the benefits. A review of the FDA Adverse Event Report System found that most cases of respiratory depression in 21 of 24 deaths occurred in children less than 12 years of age. Cough and pain were two of the common reasons for use of codeine in these children.

Since the safety and effectiveness of codeine is unpredictable in children, even when prescribed correctly, the World Health Organization has removed codeine from its list of essential medicines for pain in children. They note that acetaminophen or ibuprofen may be just as effective for musculoskeletal pain, but without the same risks.

The AAP cautions about the lack of evidence for the safety and effectiveness of opioids like codeine for cough, and the American College of Chest Physicians states that children may

experience significant morbidity and mortality with the use of cough suppressants.

The European Medicines Agency has stated that codeine is contraindicated for cough and pain in children less than 12 years of age, and in women who are breastfeeding.

We strongly urge the FDA to require labeling that states that codeine is contraindicated for cough and pain in children less than 12 years of age. We also strongly urge the FDA to remove codeine from the OTC monograph.

To be marketed as an OTC drug, a drug must be generally recognized as safe and effective. Nearly half of the states already recognize that codeine is not safe enough for over-the-counter status. The children in the other states deserve the same protection by removing codeine from the OTC monograph.

Lastly, we strongly urge the FDA to require prescription codeine labeling to state that codeine is contraindicated in women who are breastfeeding.

Codeine is currently one of the most

commonly prescribed opioids for women after Caesarian section births. Many providers appear to be unaware of the risks of prescribing codeine to these women. At least one infant has died after receiving a lethal dose of opioid from his mother's breast milk. Many other safer pain relief options are available.

Thank you for the opportunity to comment today and for the consideration of our views.

DR. OWNBY: Thank you. Will speaker number 3 step to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. HOUCK: Good morning. My name is Dr. Connie Houck, and I am a practicing pediatric anesthesiologist at Boston Children's Hospital and an associate professor in anesthesia at Harvard Medical School.

Thank you for allowing me to speak here today on the use of codeine in children. I am here in an official capacity representing the American Academy of Pediatrics.

The AAP is a nonprofit professional medical organization representing over 64,000 primary care pediatricians and pediatric medical and surgical sub-specialists. I am the current chair of the AAP Surgical Advisory Panel, and I also serve on the AAP Committee on Drugs.

We greatly appreciate that the Food and Drug Administration is calling attention to the important issue of codeine safety and efficacy in children.

The members of the academy have been concerned for a number of years about the potential adverse effects of codeine-containing medications administered to children. Though studies in adults in the 1960s had shown some efficacy of opioid-containing medications in the suppression of cough related to acute respiratory infections, no such efficacy has been found for children.

A randomized study by Taylor and colleagues in 1993 found no improvement in cold symptoms compared to placebo in children receiving codeine-containing preparations.

Subsequently, in 1997, the AAP Committee on Drugs published a policy statement that discouraged the use of both codeine and dextromethorphan-containing medications for treatment of cough in children, citing both the lack of efficacy and the concern about serious adverse effects, including respiratory depression, with the use of these medications, especially in young children.

In 2006, a set of evidence-based guidelines was issued by the American College of Chest Physicians warning against the use of codeine-containing medications for the suppression of cough for acute respiratory infections in children.

As a prodrug, codeine is dependent on cytochrome P450 CYP2D6 metabolism for its opioid effects, making the drug with significant genetic variability in both its efficacy and side effects. There's increased conversion of codeine to morphine in ultra-rapid metabolizers, 1 to 2 percent of patients, which increases the risk of codeine

toxicity. In addition, patients who are poor metabolizers will have ineffective analgesia following codeine administration.

There are case reports of morphine toxicity, and even death, in breastfed infants of ultra-rapid mothers who have been prescribed and taken codeine. In fact, the FDA warned against codeine use in nursing women in 2007.

Sadly, there have been more than a dozen deaths in the literature attributed to the use of codeine over the past decade, and children are disproportionately overrepresented in these cases. Unfortunately, these guidelines, case reports, and warnings have not had a significant impact on the prescription of codeine-containing medications to children.

A 2014 study published in Pediatrics, using a large national database, showed no significant decline from 2001 to 2010 in the number of prescriptions for codeine in children 3 to 17 years of age for cough related to acute respiratory illness. Though a small decline in prescriptions

occurred after the 2006 national guidelines were released, the change was not statistically significant.

With regard to post-operative pain management, the use of codeine for the treatment of pain in children in the perioperative period after adenotonsillectomy appears to have decreased since the black boxed warning was issued in 2012. But due to its continued ease of availability compared to other oral opioids in children, many practitioners have continued to use codeine-containing medications for the treatment of both acute pain and cough, despite the many warnings from national organizations about its potential toxicity in children.

In order to address the increasing concerns about the risks posed by the use of codeine, the number of international organizations have responded by discouraging all use of codeine in children. In 2011, the World Health Organization removed codeine from its analgesic ladder, and in 2013, the Canadian Ministry of Health recommended

against the use of codeine in children less than 12 years. Most recently in 2015, the European Medicines Agency restricted codeine use to only those aged over 12 years.

In the last several years, a number of children's hospitals throughout the U.S., including the one that I work in, have completely eliminated codeine from their pharmacies and have educated their physicians not only about the dangers of codeine, but about alternative oral opioids that can be used for pain management in children.

Because of its variability in metabolism, the increased risk of adverse effects in children and the lack of data showing efficacy for treating cough in children, the use of codeine or any other opioid cannot be recommended for the treatment of cough in children.

Likewise, for acute and post-operative pain in children, alternative strategies should be recommended, including other opioids. Therefore, the American Academy of Pediatrics recommends that codeine be contraindicated for the treatment of

both cough and pain in all children, and further recommends that codeine and codeine-containing products be removed from the over-the-counter monograph for the treatment of cough in all children.

Thank you for your time and consideration. We look forward to continuing to work with the FDA to ensure the safe and effective use of medications in children.

Clarifying Questions (continued)

DR. OWNBY: Thank you very much. The open public hearing portion of this meeting is now concluded. We will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee.

We have four more people that had questions, and I believe we have about 15 minutes before we are due to break for lunch. So the next person I have on the list for a question/clarification is Dr. Parker.

DR. PARKER: Thank you. So my question, I

wanted to drill down just a little more on the age, and it's sort of from a practicality standpoint. I understand that the focus is on pediatric, and that is defined as 18 and under by the purview of the FDA.

But I'm just trying to think about how this hits the ground and the public, and what it means to say up to 18, but hey, you're 18.1 and now it's different, and what that looks like and feels like in a practical way.

I just want you to help me think about the safety issue, because I know that's the focus specifically. And you helped begin to drill down on that in the 12 to 18, because it does look like there's some variability on what we see around the world according to age.

I just want to make sure I understand the safety issues and whether or not it really does change at age 18, or do we have evidence that it may be -- there's a spectrum, and it seems to be whatever the safety thing is may have a different -- if you can help me a little more in

how I think about age, and also just maybe just make me feel better about what's going to happen if you're 18.1 and older.

DR. SEYMOUR: Okay. Well, we have to make a decision on a cutoff, unless you say don't use codeine in anyone. So we try to provide what we think are sort of logical age cutoffs. I think Dr. Leeder summarized some of the information that may help inform some metabolism differences as you age. You obviously can look at where the data suggests the risk is most from the FAERS and other data sources we have.

But we will communicate this as best -- whatever decision is ultimately made and whatever age cutoff, we will try and communicate it so it's clear why we made the decision we did, similar to in 2012-13, there was a publication explaining why FDA made the decision about contraindicating in the post-adenoidectomy/tonsillectomy age, or setting.

So I think we have to make a cutoff somewhere, and we'll do the best we can to

communicate that. I know that's one of your concerns. And obviously, if you say 12, there may be kids who are 12 or 13 who could still be at risk. It's always going to be a spectrum, but we have to make a decision on a cutoff.

DR. PARKER: So if you could just kind of summarize for me the safety -- I don't want to call it signals, but the safety concerns under 12 versus over 12, or is it 15? We got it a little bit with the variability and the metabolism, but I just want to know if that needs to be in my mind or if I just need to understand that we've got to make the cutoff somewhere; we're able to do it up to 18, that's why we're doing it. I want to make sure I'm not missing anything. Sorry to be picky about it, but I want to make sure I'm not missing anything in that.

DR. RACOOSIN: So if you look at the recent FAERS review, I think that that may be what Dr. Nguyen tried to point out, slide 27. When you look at the pediatric death cases, 21 of 24 were in the less than 12 years of age.

So again, we have the data that we have, and that's the published literature and that's the FAERS cases. And the FAERS signal, as far as the most severe outcome of death, points to the less than 12 as -- again, this is all -- this is spontaneously reported cases and cases submitted by pharmaceutical companies. But that's where this part of the signal is in the less than 12.

I can say that in our original literature search, we found one published case of an adult who was an ultra-rapid metabolizer, who was hospitalized for a respiratory condition, and also was on some other medication that interacted with the pathway in addition to getting codeine.

So we're not overwhelmed with literature cases in adults, but the advice that the EMA gives, which is that someone known to be an ultra-rapid metabolizer, probably shouldn't get codeine, and that seems like a reasonable recommendation and something we can certainly consider.

But adults have not been the focus of this review; we've been focused on the children and our

review, this recent review, at least the cases that we're aware of, point to the less than 12.

DR. OWNBY: Dr. Tracy?

DR. TRACY: Some of this has already been addressed, and it's kind of actually a yes/no question. As Dr. Goulding mentioned, we really don't have a true incidence of this problem, and part of it is both numerator and the denominator are kind of fuzzy.

But when you look at Dr. Gill's number of prescriptions written for analgesia between 2010 and 2014, it's somewhere between 1.5 and 2 million every year. Then you look at the FAERS data, and your N for respiratory events is 64 with deaths of 24. And I was just wondering if the agency would be willing to hazard a guess as to the incidence?

UNIDENTIFIED FEMALE SPEAKER: No, we don't guess.

(Laughter).

CDR MOENY: This is David Moeny. The hazard guess is yeah. The problem we have, especially when we're looking at the data we've got in front

of us, is that the FAERS reports go way, way back, and we only have the most recent years of utilization data available. So even trying to draw a conclusion from that, we don't really know about the long historical trends of codeine use among children. So I think it would be very difficult for us to hazard a guess on incidence from these data, outside of to say, fairly rare.

DR. GOULDING: Yes, the numerator and the denominator come from come from different sources. They have different limitations. None of them are national. So no, we wouldn't put one on top of the other and come up with an incidence rate.

DR. OWNBY: Thank you. Dr. Connett?

DR. CONNETT: I had mainly a question on clarification on Dr. Dormitzer's presentation on ED visits. It's on pages 22 and 23 in this book here.

The question is, it says ED visits by adverse event and age group for cough and cold products, but it doesn't say whether those cough and cold products are codeine-containing or not.

DR. DORMITZER: No, those are

codeine-containing products. I have a backup slide. For the cough and cold containing products, it was codeine/promethazine. There were 31 cases for codeine/promethazine, 25 for codeine/guaifenesin, 3 for codeine/guaifenesin/pseudoephedrine, and then 14 where it was codeine-containing unspecified. It's in my backup slides. It's one of the tables in my review.

DR. CONNETT: Okay. So do we have similar data for non-codeine-containing products?

DR. DORMITZER: Well, I didn't examine those data. So you asked about cough and cold non-codeine products?

DR. CONNETT: Yes.

DR. DORMITZER: That's not included in the review. I was looking very specifically for codeine.

DR. OWNBY: Dr. Alexander?

DR. ALEXANDER: Yes, I have a question about the monograph. It's fascinating to learn about the different regulatory parameters that govern the

monograph versus the ANDA and NDA products.

So the first is a comment, which is even if the process is a bit archaic or it takes forever, it kind of feels to me a little bit like the FDA is obligated to try to update it to make it as concordant as possible with the labeled changes. And I am interested in whether manufacturers would voluntarily modify their labels for OTC products even if they're not sort of mandated or legally obligated to do so.

But the question is really about the data that's provided on dosing, and I'm just trying to understand how conservative the dosing recommendations are in the monograph, and then also how closely they're followed.

The presentations included a remarkable amount of very helpful contextual information about a lot of different things to help us think about the question that we've been posed. But it would be helpful to know how well patients and their families and caregivers actually follow the directions that are in the monograph, dosing

guidelines.

DR. ADAH: So let me comment on monograph products in general. I really don't know if I can speak to codeine products, but we deal with a number of adverse events each year, which are related to consumers not following the dosing directions well. So we do know that's a problem. I can't really tell you how it relates in this particular instance because I really don't have any data to support anything on.

As far as your comment about given the timelines, we agree we have an obligation to update the monograph, and we try to do that. When we can't, we try to find alternative mechanisms to get the information out there because the concern for safety is greater -- becomes a greater issue than worrying about the codifying it in the monograph, although we try to do both.

DR. ALEXANDER: And how about this question of how conservative the dosing guidelines are?

DR. ADAH: I'm not sure what you mean. Could you clarify?

DR. ALEXANDER: If you follow them, how are they derived? I mean one presentation included information that they're derived at -- maybe not the monograph data, but there was a comment about data for children being derived from pharmacokinetic and pharmacodynamic data for adults.

So I guess I'm trying to understand, when we look at the monograph data and it says less than 2, don't use or something, ages 2 to 6, dose at this level, et cetera, how conservative are those? How likely if you take 100 or 1000 kids, is one likely to experience an adverse effect from an overdose, inadvertent or not, based on the criteria that are in the monograph for dosing recommendations?

DR. STARKE: This is Dr. Starke. And I'll try to answer it as best I can, but quite frankly, the data is limited in terms of giving you a specific answer.

First, it's important to say that there is very little PK data with regard to codeine in children, and what you see in the monograph is

likely derived data from adults. And what I mean by derived, I don't want to use the word "extrapolation" in terms of pediatric extrapolation like we do with PREA or efficacy, but in fact you could say it was extrapolated from data in adults.

In other words, you have dosing -- and this happens for many, many drugs. In fact, in the '90s, there were at least two advisory committees that discussed pediatric dosing schedules that were extrapolated or derived from data in adults. So we have dosing in adults going back to before you usually did PK data as part of an NDA, for many, many drugs.

Then what happened was they picked a half a dose for certain age groups, say 6 to 11, and then a quarter dose for under that. It's all guesswork is what it comes down to. And it is likely that the over-the-counter monograph simply incorporated that same kind of guesswork. I hope that answers your question.

DR. ALEXANDER: Thank you.

DR. OWNBY: Okay. We're approaching our

lunch hour, but I have Drs. Flick, Walco, Georas, and Brown. Dr. Flick?

DR. FLICK: Judy or Sally, in your black box warning and the contraindication, you refer to children. And as I look at the questions and the discussion here, we're going to be addressing specific ages. Does the agency have a definition for children? And did you make a conscious decision not to use an age? Because all the other worldwide agencies specify an age, but you simply use the term "children."

DR. RACOOSIN: So when we wrote that labeling, it was not a specific action to not quantify. It was the sense that the population that we were seeing having problems were children getting tonsillectomy and/or adenoidectomy. But moving forward, we are trying to be more specific about the ages, so less than 18 is our cutoff for children.

DR. FLICK: So the committee shouldn't think of a recommendation that is specific to children. It should focus on ages, specific ages.

DR. RACOOSIN: Yes.

DR. OWNBY: Dr. Walco?

DR. WALCO: My question has been answered. Thank you.

DR. OWNBY: Okay. Dr. Georas?

DR. GEORAS: Let me just preface my remarks by saying I'm not a pediatrician, but I take care of a lot of adults with cough. And participating in this panel has made me rethink my use of codeine, which is very rare in that population.

But I just want to restate and make sure I understand the arguments and that I'm not missing an argument because what I'm hearing is a drug that has unpredictable metabolism, and the cough indication on certain and possibly non-existent efficacy, and comments from experts in the room that there are alternative agents for pain, that would be preferred.

So I haven't heard in the deliberations today a compelling reason to vote yes for under 18, and I'm wondering if there are members of the panel that feel that way. If you could articulate the

basis for that so at least I could understand it. Thank you.

DR. OWNBY: Does anyone want to speak to that question specifically?

DR. FLICK: Can you restate the question?

DR. GEORAS: I'm trying to understand -- I understand we're grappling with age, but if there are alternative agents and concerns about metabolism and questions about efficacy, I'm having a hard time understanding why we would vote yes for under 18, but I acknowledge I'm not a pediatrician nor an expert in pharmacoepidemiology. So if there is somebody who feels that way, I'd be just curious to understand the basis for your thinking so I can consider it.

DR. ALEXANDER: Well, I can play a devil's advocate, although I'm not suggesting that this is how I would feel. The events are very rare. They're relatively rare. They are serious, but all drugs have risks.

DR. OWNBY: I've been informed that we should not discuss this right now, so we'll go

back. Our last person with a question was Dr. Brown.

DR. BROWN: Some people are asking questions about the correct dosing, and I just want to reiterate something that we've heard today. And that is that there are case reports of children who have been dosed absolutely correctly according to the labeling who have had serious outcomes, including death.

On the OTC monographs, some of the dosing is actually per age rather than per weight. And in my mind that, especially given the wide variation in size of particular children in the United States now at particular ages, that likely seems to me like quite inaccurate.

One small comment about dosing relating to parents. Parents are making assertions about the appropriate dose without a lot of ability to discern what is right for their child. I don't think there are lots of parents that -- or really very few parents that read the small print. And their knowledge about the variable pharmacokinetics

and pharmacodynamics of these individual drugs is meager.

DR. OWNBY: Okay, thank you. We have one clarification from the FDA before we break for lunch.

DR. AGARWAL: There was a question about oxycodone and hydrocodone metabolism, so I just have a couple of slides. So hydrocodone goes to norhydrocodone, which is an inactive metabolite through the CYP34A pathway, and it goes through hydromorphone through CYP2D6.

The amount of hydromorphone in plasma levels in humans is really low, so one of the most recently approved hydrocodone extended-release tablets label says that hydromorphone is less than 3 percent of the circulating parent hydrocodone.

If you go to the next slide. This slide shows the metabolism for oxycodone. I did not see percentages of oxycodone that's metabolized to morphone and noroxycodone. However, the labels indicate that the majority of oxycodone goes into noroxycodone, which is a CYP3A4 metabolite, which

is inactive, and very less amount goes to oxymorphone, which is the 2D6 metabolite.

The label indicates that oxymorphone is present in the plasma only at low concentrations, and very low circulating concentrations of oxymorphone have been observed following a single oral dose of oxycodone.

Just wanted to present the metabolic pathways of these two drugs. Thank you.

DR. OWNBY: Okay, thank you for that clarification. We will now break for lunch. We will reconvene again in this room at 1:00 p.m. Please take any personal belongings you may want with you at this time. Committee members, please remember that there should be no discussion of the meeting during lunch amongst yourselves, with the press, or with any member of the audience. Thank you.

(Whereupon, at 12:20 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:01 p.m.)

DR. OWNBY: Next on the agenda, Dr. Sally Seymour will provide us with a charge to the committee.

Charge to the Committee - Sally Seymour

DR. SEYMOUR: Good afternoon. Before you begin your deliberations and discussion this afternoon, I wanted to take a moment to introduce the questions for discussion. So let me summarize a few key points from this morning's presentations and your discussions so far.

You've heard about the variability in codeine metabolism based upon CYP2D6 activity, and how this may impact safety. We reviewed available data and presented information on postmarketing reports and FAERS, available literature, and epidemiologic data regarding respiratory depression and death in pediatric patients, and some cases do suggest a role of CYP2D6 activity.

You've heard about the current use patterns of codeine utilization in pediatric patients. And

while codeine use has decreased in children, in 2014, approximately 1.9 million pediatric patients, 0 to 18 years, received dispensed prescriptions for codeine products. Given this use, the number of reports that you've seen for postmarketing cases, these cases do appear to be rare.

Based upon a review completed in 2012, FDA contraindicated the use of codeine for post-operative pain management in children who have undergone tonsillectomy and/or adenoidectomy, and this is a very focused contraindication.

But you've heard that some regulatory agencies have restricted the use of codeine for both cough and analgesia in pediatric patients, which is a much broader restriction of the use of codeine. So we seek your input on the following questions.

Question 1 is a discussion question. These questions are broken up for the cough and pain indication because the risk/benefit discussions may be different in those different indications.

Question 1: Discuss the available data on the

safety of codeine use for cough in pediatric patients. And we ask that you address the following age groups in your discussion: children 0 to 6 years of age; children 6 to 12 years of age; and children 12 to 18 years of age. Discussing the available data in these age brackets may help inform your voting questions for the other questions.

Question 2 is also a discussion question, but this is for the indication for pain. And we ask that you discuss the available data on the safety of codeine use for pain in pediatric patients, also looking at the same age brackets.

Question 3 is the first voting question. And we ask that based upon the discussion of the available safety data with codeine, should the current contraindication for codeine, which is for pain management in the post-tonsillectomy and adenoidectomy setting, be expanded to a contraindication for codeine use for any pain management in children?

We've included the CFR definition for

contraindication, which really is for only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit. Only known hazards and not theoretical possibilities can be the basis of a contraindication.

So if you think the contraindication should be expanded, there are several options, (a), (b) and (c), depending upon the age for cutoff.

Option (a) is yes, expand the contraindication for any pain management in children younger than 6 years of age; (b) would be yes for children younger than 12 years of age; (c) would be yes, expand the contraindication to include all children younger than 18 years of age; and (d) would be no; no change to the current contraindication.

We ask that regardless what you vote you have, you provide the rationale for your recommendation and any other labeling recommendations you may have.

Question 4 is a similar type question, but

it is for the treatment of cough in children. And I won't go through the details, but again, you have the same options for the different age brackets for children younger than 6, 12, or 18; or if you don't think there should be a contraindication for cough, you would respond (d) and provide the rationale for your recommendation.

Question 5 is a voting question specific to the FDA monograph or over-the-counter availability of codeine for children. The question is, based upon the discussion of the available safety data with codeine, should codeine be removed from the FDA monograph for over-the-counter use for the treatment of cough in children?

It's formatted similar to the previous questions. If you think it should be removed, you would vote (a), (b) or (c). And depending upon the age cutoff, you would vote accordingly: (a) remove codeine from the monograph for children younger than 6; (b) remove codeine from the monograph for children younger than 12 years of age; (c) remove codeine from the monograph for children younger

than 18 years of age. Or, if you think no change to the current monograph for codeine, you would vote (d), and again provide the rationale for your recommendation.

Thank you again for your participation in this meeting today, and we look forward to your discussion on these topics.

DR. OWNBY: Thank you, Dr. Seymour. Are there any panel members who want to ask any specific questions or general observations before we start through the questions that Dr. Seymour just outlined? Yes?

DR. FINNEGAN: I have a question about regulatory language. Health Canada did not recommend the use, but it did not contraindicate. So is that regulatory language that you are interested in or you use, or how -- because that obviously means they can prescribe it, they just don't recommend it.

DR. SEYMOUR: Right. The language for the different regulatory agencies does differ. We are asking specifically about a contraindication, which

I provided the regulations for that. Now, if you prefer to have a recommendation of do not recommend, we certainly are interested in that, and you can provide that in your comments when you vote on the question.

DR. RACOOSIN: Can I just respond to that as well? Judy Racoosin. So there's limitations of use that we can -- there are other ways that we can incorporate recommendations into labeling. One of the options is that you don't recommend a contraindication, but you could recommend something else.

DR. ALEXANDER: But I think it's important to just state, to be clear, doctors are free to prescribe as they wish, and other licensed prescribers. So there was some language about wouldn't allow, and there's nothing in this that would allow or disallow a prescriber to make an educated informed decision to use a product. Just to be clear.

DR. SEYMOUR: That's correct. Prescribers can choose to make decisions outside of the

labeling recommendations to prescribe medications. But the contraindication is a very strong statement in the label about the use in children, and what pharmacy practices, et cetera, how they handle that, may help enforce that within their own systems. But it is a very strong statement.

DR. OWNBY: Dr. Roumie?

DR. ROUMIE: My question is clarifying question 5, or number 5, which relates to the monograph. And we're just discussing codeine use in the monograph with children, not codeine in the monograph.

DR. SEYMOUR: So the question and the topic for today is really for pediatric use and codeine. That being said, we are asking you specifically about your voting and the use of codeine in children. But you do have the option when you go around and provide your comments, if you have recommendations that codeine shouldn't be in the monograph in general, for adults either, I think that's the opportunity for you to make those comments and we can take that under advisement.

DR. OWNBY: Dr. Morrato?

DR. MORRATO: Yes, I just wanted to clarify. So in the newly approved extended-release combinations in adults, that wasn't a contraindication, it was just an indication in adults and it was silent on kids. Is that correct?

DR. SEYMOUR: Correct.

DR. MORRATO: Okay.

DR. OWNBY: Dr. White?

DR. WHITE: Michael White. This is totally off the wall, and I don't know that you can respond. The industry representative alluded to the fact that the monograph was formed in order to use the "generally recognized as safe and effective" as a blanket for the drugs that are included in the monographs.

Have there been any spectacular failures in the monograph system where something generally recognized as safe and effective at the time it was started has been found to be really, really not a good idea?

DR. ADAH: To my knowledge, no. And it's

never that simple. I mean, but no, there's nothing that I can think of that we've pulled out. Can you -- I'm going to defer to Dr. Terri Michele, the division director.

DR. MICHELE: Hi. Terri Michele, Division of Nonprescription Drug Products. So the monograph is not a static system. When it was put in place back in the '70s, the panels made recommendations, and FDA took action based on those recommendations, based on the best knowledge that was available at the time.

As you all know, science doesn't stand still. It keeps changing. And part of the struggle that we have with the monograph system is that the regulatory process that's in place for the monograph isn't always as facile as we would like it to be to keep up with the changing science. But we frequently can and do make changes to the monograph and change the status of ingredients.

For example, just recently, we published proposed rules for healthcare antiseptics and consumer antiseptics, asking for more data for

ingredients that were previously categorized as category 1 or generally recognized as safe and effective.

That's based on the changing use of these ingredients, as well as the changing science and the better understanding we now have about absorption of these ingredients, which is particularly relevant for pregnant women.

So these things do change, and certainly based on changing adverse event profiles, we have taken things that we've changed to a category 3 based on new data.

DR. OWNBY: Are there any other questions right now of a general nature?

(No response).

Questions to the Committee and Discussion

DR. OWNBY: Okay. We would now like to proceed with the questions to the committee and the panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the

panel. As we get to the voting questions, I'll go over the voting instructions.

But now we have question 1, which is a discussion question. Discuss the available data on the safety of codeine use for cough in pediatric patients. Please address the following age groups in your discussion: the 0 to 6 years of age; the 6 to 12 years of age; and the 12 to 18 years of age. Does anyone want to comment on that? I see Dr. Flick --

DR. SUAREZ-ALMAZOR: This is Maria Suarez-Almazor. Yes, I have a -- I mean, this is both a comment and a question, and I didn't ask it before because we were running a little longer. But it relates to the safety in general, and one of the aspects of safety that was brought up early one, which is the misuse or inappropriate dosing of other narcotics if these are used instead of codeine.

So I was wondering if there can be some discussion or if there is any knowledge around the table whether in countries where the labeling has

changed, there's been any evidence of any misuse or inadequate dosing of other narcotics in children such as oxycodone or hydrocodone.

I consider that a little parallel but also an aspect of safety brought before but not really discussed in detail.

DR. OWNBY: Does anyone want to comment on the question? Yes?

DR. DRACKER: Bob Dracker. It's a practical comment. It's just that we treat approximately 50,000 children a year in my practice, and for the past 10 years, we have not used one codeine product on any of them, whether they've been positive for pertussis or otherwise. We've never had a clinical need to even use it under 12 years of age.

DR. GEORAS: I think the concern might be in a less experienced practice out in a community, practitioners changing over on a broad level from familiarity with codeine to more potent narcotics, are we opening -- what is the quantification of that risk, and is that manageable.

Perhaps some people around the room have

experience or can quantify that risk. I think -- was that what the question was getting at? I think so.

DR. OWNBY: Anyone else want to comment on this question specifically?

DR. GRAYSON: Yes, so Mitch Grayson. I was just fine with what Dr. Georas said. So I think when we're talking about -- this is an issue for pain maybe, but for a cough, there isn't really any narcotic, other alternative, and so it really is just a pain issue. And I don't know the answer, except that everybody that seems to deal with pain seems to suggest that codeine is not what they would be using. But I don't know if that, again, gets at it or not.

DR. OWNBY: Dr. Gerhard?

DR. GERHARD: Just a quick follow-up to Dr. Dracker. The statement that you just made, could you comment on the population from 13 to 18 use of codeine for cough from your experience? Is there a need for that product in this population that is different from the younger population?

DR. DRACKER: Previously, and I will admit to this, over 10 years ago, we were already using Tussionex in some of the smaller children because it was very effective and the parents would beg you for it, and it worked; including myself, I use it on my own children. It works great.

But beyond that, at this point, we are still on occasion using it for young adults. We treat children to 22 years of age. So you'll have the 16 to 18-year-old kid who can't sleep, and we're fairly comfortable dosing it appropriately for them.

DR. OWNBY: Dr. Cataletto, you had a question?

DR. CATALETTO: This is more clarification on question 1 and on discussion 1 and 2. It's clear to me that we're covering the neonates in the children 0 to younger than 6, but is there a caveat or a section somewhere, in your understanding of what you want in this question about teen mothers and breastfeeding?

DR. RACOOSIN: So I think breastfeeding is a

different issue, and we're really focused on pediatric patients for whom we are treating the child, and let's distinguish that as non-pregnant children.

DR. OWNBY: Dr. Flick, you had a comment?

DR. FLICK: I think it's helpful to put this in the context that for those of us who practice pediatric pain, codeine has not been used for 20 years. So when I trained 20 years ago, we weren't using codeine for these reasons. So this is nothing new. It's a settled issue.

There are very few children hospitals in the country who allow or don't severely restrict the use of codeine. So from the perspective of pain, this is really an issue that's sort of passé.

From the perspective of cough, if one thinks of this obviously as a risk/benefit, we have a defined risk; it's low, and we have uncertain benefit. Then the question that always comes up is alternative.

The use of codeine for cough, if it's efficacious at all, there's no reason to think that

other narcotics or opiates are not equally efficacious; it's simply that they have not been studied for that particular indication. There's nothing peculiar about codeine that would suggest that it's a better cough suppressant than morphine, for example.

So when I look at this, I say there's really -- we'll get to the question of pain, but for cough, it really seems pretty straightforward that we don't really need this for cough. It probably is of no benefit. It's probably a separate question whether it should be on over the counter, but that seems fairly simple as well. So I'll stop there.

DR. OWNBY: Dr. Parker?

DR. PARKER: So I just wanted to be clear that -- and this follows really well with what you just said separating the pain versus the cough the antitussive.

As I understand it, Dr. Starke, from what you presented, the alternative prescription antitussives to codeine, there's the non-narcotic

and the narcotic, that I assume the hydrocodone in these formulations that you listed on that slide on page 9, you don't list there the hydrocodone with acetaminophen as having an approved indication for an antitussive.

But I guess in my mind, what I'm thinking is -- I'm thinking about the 12 to 18-year-old, and when you no longer -- or you make it contraindicated, and maybe behavior follows that, we can hope so -- does it drive increased use in the alternatives? Because you did mention safety concerns with the non-narcotic alternative and the narcotic alternative.

So it's sort of should we be thinking about potential adverse consequences of getting rid of it when we look at what the alternatives are that do remain available?

DR. STARKE: So this is Dr. Starke. The first question I think you asked is, what are the products that are approved for cough? And there are a lot of codeine-containing products that I did not list. The reason they're not listed is they do

not have an indication for cough. They have an indication for pain.

The codeine with acetaminophen does not have an indication for cough. Single ingredient codeine does not have an indication for cough. Not to say that it isn't used, but it does not have the indication.

What you see is benzonatate and the hydrocodone-containing products, of which there is a whole gamut, including the one that was just mentioned a moment ago by someone who said they were using it for themselves and their children.

Does that answer -- was there another part to the question that I missed?

DR. PARKER: Well, just presumably, there could be an increased use of these alternative prescription products that do have approved use for cough if you get rid of one that used to be and is no longer available. These products remain available.

DR. STARKE: That's correct.

DR. PARKER: And are approved for cough.

And I was thinking about -- in my mind, I was trying to be sure, because there are safety concerns with those, and could you end up with -- it would be an unintended consequence of more safety issues on something else where you're driving use in that direction, especially, I was thinking, with the hydrocodone in the 12 to 18-year-olds specifically.

DR. STARKE: Well, hydrocodone is an alternative opiate. I think from the point of view of respiratory depression, it has a similar risk in terms of suppression of the cough reflex and the respiratory depression as well. It may or may not suffer the same 2D6 issues because it isn't metabolized specifically to morphine, but it has its own risks, and it's labeled for those risks. There are over-the-counter alternatives as well, and I listed those, including dextromethorphan and diphenhydramine and so on.

DR. OWNBY: Okay, I have Dr. Brown next.

DR. BROWN: We've heard a lot of information this morning about the lack of efficacy of

codeine -- demonstrated efficacy of codeine for cough. And that in concert with the EMA writings makes me think that we should be more worried about leaving a drug on the market for a group of children that are at risk than the alternatives to that drug.

Many children, I believe, who get narcotics for cough don't cough because they're somnolent, and with the burgeoning number of cases of obstructive sleep apnea in the population of the United States, that is a problem.

We're not charged with dealing with that issue today, but it is a problem. The focus of my comment is that I've not heard anybody give information that applauds the use of codeine for cough because it was efficacious in reducing cough in children, especially those below 12 years of age.

DR. OWNBY: Dr. Finnegan, I believe you're next.

DR. FINNEGAN: So I'm going to politely disagree with my colleague from the Mayo Clinic. I

think one of the issues is that pediatric pain doctors see those patients who are in relatively chronic pain. Well, okay, in our experience, codeine with acetaminophen is a very effective pain reliever for patients with acute short-term musculoskeletal issues.

One of the problems we have seen, while there is some addiction trend with Tylenol with codeine, there's a much larger addiction trend with both the hydrocodone and particularly the oxycodone. So I think that we need to look at the unintended consequences, and I think that saying that there are no children's hospitals that are providing codeine with acetaminophen is probably not totally accurate.

DR. WALCO: May I respond?

DR. OWNBY: Okay, do you want to respond to that? Or excuse me. Dr. Walco --

DR. FLICK: Yes, I feel like I'm at the Republican debate here. Do I get a chance to respond? Yes.

When I talk about pain management, I talk

about acute pain management, not chronic pain management. That's a very different practice and would obviously not include the use of codeine in that practice either.

So acute pain management, again, I will reiterate that I'm not aware -- and I travel to a lot of children hospitals continuously. I'm not aware of children hospitals that have not restricted, or at least are not in the process of restricting, the use of codeine for the reasons that we've discussed here today.

So with regard to addiction potential of oxycodone versus codeine, these are both opiates. To suggest that there's something fundamentally different about them in terms of addiction potential probably can't be supported by the literature, and I would let my colleague here comment on that.

So in my view, there is no benefit to codeine that -- everything has to be put in the context. I think, Sally, everything has to be put in the context of the alternative. If we're not

talking about -- if we don't include alternative in the discussion, it's a very different discussion.

But for every indication that we are talking about here, there is a better alternative. And so when we balance the risk and benefit of codeine in the setting of available alternatives, it simply doesn't make sense. And I would say it doesn't make sense even for adults. It simply doesn't make sense because there are better drugs.

So I'll, again, leave it at that. But I would ask, I guess, at least to clarify it for me, are we talking -- do we need to include in this available alternatives in the discussion? If we're not, then that's, again, different.

DR. SEYMOUR: Well, I think that's part of your risk/benefit consideration, is the change in practice over time, the armamentarium available with other products that can treat pain or cough. How has the treatment of pain, in this case cough, changed over time? Because some professional societies are not even recommending treatment, pharmaceutical treatment of cough these days.

So yes, I think you have to take all those things into consideration when you make your recommendations.

DR. OWNBY: Remember, we're talking about cough. We have a whole another slide on pain. So I have Dr. Walco, Dr. Morrato, and Dr. Tracy.

DR. WALCO: So the FDA formed a scientific workshop to look at issues of -- and I know we're not talking about analgesics yet, but there's method to my madness -- to specifically talk about the issues of extrapolation and different designs one could do to study analgesics.

The group was exceedingly clear in talking about the differences between efficacy and safety. And what we're being asked about here is specifically safety. And what we've heard is that there are not a lot of PK and PD data on codeine in younger patients. We know, from the available data, that there are some catastrophic outcomes.

So I'm sitting here thinking to myself, the available safety data would say that this is a dangerous drug to be using. We know that 1 percent

of the population hypometabolizes. We also know that 10 to 15 percent hypometabolize and get no benefit. So then you're potentially prescribing a drug that's going to be essentially inert for people.

When that panel met, and the paper's published in Pediatrics in 2012, the issue of codeine actually came up. And it's exactly what Dr. Flick is saying, and that is that the pain experts from around the country were quite clear, quite clear, in saying that the safety profile of codeine should make it never to be on the formularies of children's hospitals. And in fact, I think that is very clearly the trend for most major children's hospitals.

So we could talk more about the pain element in a minute, but if we just focus on safety, which is the question we're being asked, I don't see how you can dismiss very serious safety concerns about this medication.

DR. OWNBY: Dr. Morrato?

DR. MORRATO: Yes, I wanted to address the

point where you're asking us to look at the available data on safety as it relates to age and just kind of summarize my thinking on that. It's similar I think maybe to what others are saying, but maybe a little different.

So yes, we see cases. Yes, there's a biologic plausibility in terms of the genetic metabolism and perhaps the elimination pathways. This, as mentioned, is not as developed until ages of 12.

The case reports that we see, although sparse and rare, is consistent with that, as well as the national surveillance data that we presented. None of it is really looking at it in a cause and effect way, but if you're looking at the totality of the safety data, I think we would agree that there is a signal. And there is some suggestion that, biologically speaking, children less than 12 may be different than 12 and above in terms of some of that risk.

I did find the EMA statement on this, just so that we have that in front of us. In their

determination, they stated that although morphine-induced side effects may occur in patients of all ages, the way codeine is converted into morphine in children below 12 years is more variable and unpredictable, making this population at special risk of such side effects.

I would have like to have seen the data that they considered when they came to this conclusion, and that may be a nice follow-up as the FDA is doing their determination of age and justification.

I do acknowledge the point that the industry was making that these need to be as evidence- and data-based as possible so people are understanding when changes are occurring. But for that reason, just based on the safety data, not the consideration around effectiveness and other consistency of label, it seems that those under 12 are particularly at risk.

DR. OWNBY: Dr. Tracy?

DR. TRACY: So kind of in the interest of full disclosure, I really don't use a lot of codeine for anything. But I have practiced

pediatrics and allergy for about 25 years now, and I will say that I will occasionally use codeine in that 12- to 18-year group, certainly not very much. You get a string of pertussis patients, and it gets pretty rough. And trust me, the non-narcotics do not work. They're disappointingly ineffective with that class of patients.

So it becomes an invaluable addition that I think you have to be careful about taking away. If there's better narcotic or effective agents, I'm all open to that. But I think blatantly just stopping it or getting rid of it all together, I think puts practitioners at a disadvantage. Thank you.

DR. OWNBY: Dr. Yu?

DR. YU: Thank you. Because the question is really focused around the age group, the risk to different age groups, my question is oriented towards that. We have three data sets we're looking at. The first one, FAERS, because it is reported by patients, majority of it, and the providers and the pharmaceutical companies, there's

not really reliable information on causation. So that's how I interpret it. Correct me if I'm wrong.

Then I look at the data set, DAWN, that was emergency visits. The statistics shows -- it also stratifies with an age group. But that's three data sets with age stratifications, which is nice.

But the error bar when looking at it is big from each age group. And it's so hard, at least for me, to draw any conclusion from that. So now, the things left for me to look at it, I think to maybe have a better guidance, depend on looking at age stratification, what's called a NEISS-CADES -- that one what is called surveillance, and was called NEISS, was the acronym. How do you say it?

But anyway, if you look at that data, the number put out based on the age group stratification, you can get different numbers based on how you group them.

So if I look at the -- for example, if I just look at cold medication for allergic reaction,

and I have group age 0 to 5, I get 5, and 6 to 11 as 6, and age 12 to 18, I get 13. So I if group them just under 12, I get 11. And then age 12 to 18, I get 13. But if I group just age under 5 and then any age older than 6, I get 19.

So you see a different signal of the actually observed adverse events depending on how you look at the stratification. So to me, the age group, if based on how you look at it, between 12 and 18, it doesn't necessarily show it actually has a lower observed adverse event than the younger group.

Correct me if I'm wrong. And that's the same as for the pain medication, not just cold. And also, for the cold medication, occurred under the category of accidental/unintentional. I'm a little puzzled about that, how much this can prevent through the regulation because the definition is someone, not children, accidentally grabs it without supervision of mothers, and caretakers just gave the medication unintentionally. This is my question. Thank you.

CDR MOENY: Yes. So you bring up a couple of points there that -- you're looking at three data sources, but these are three different data sources, So we can't really necessarily compare one to the other.

The NEISS-CADES that you're looking at are just counts. They're just raw counts from these hospitals that are surveyed. Whereas the DAWN, they attempt to do national estimates, but as you point out, the confidence intervals are quite wide, right, so you don't have a lot of precision in that estimate. And you're true when you say you can group these things in many, many different ways.

Our intent here was to try and show general trends rather than absolute amounts of adverse events occurring. So you do see these accidental/unintentional occurring more frequently in the younger groups, and it trends the other direction for adverse event and allergic reaction.

So that's what we're trying to do with those rather than being able to give you exact rate of occurrence of an adverse event.

DR. YU: Okay. As far as the trends -- and I think the data is inconclusive if you really look at it. You mean temporal trends, right? And you look at how risky a drug to a particular population in terms of age group, and that's the only thing we get is the incident reports. That's the evidence based on whether you put a confidence interval on those ones and how reliable those observations are, and that's a different story.

CDR MOENY: Yes. The NEISS-CADES and DAWN are being generated from hospitals by healthcare practitioners. And so we have a better confidence that the way they're being coded is probably correct to what's happening in clinical practice there. But when we get to the spontaneous reports -- and our colleagues from the DPV could speak more to that if you'd like -- it starts to get a little messier because you're having reports from many, many different sources, some healthcare practitioners some not healthcare practitioners. So it is what it is; it can be very messy data.

DR. YU: Thank you.

DR. OWNBY: Dr. White is next.

DR. WHITE: Thank you. Michael White, New Orleans. I have three things I'd -- I'm going to be a heretic, unfortunately. I don't quite understand the magnitude of the problem. I understand that we're worried about it, but the data that you're presenting is 64 serious respiratory depression cases from the FAERS system from 1965 to 2015.

I understand that this system is not a particularly sensitive system, but that's not a very high risk profile for most any drug that we give. We had 24 deaths. If we're looking at the age of the 24 deaths, the majority of them were reported to be -- and the serious side effects were reported to be under 12 years of age. So I think the use of 12 years of age as a cutoff is a reasonable one if we're going to have prescriptions or concerns.

The second issue I had is who's giving this drug? And it turns out the people that you have in this room are probably not the people that are

likely to be writing these prescriptions. If we go to -- let me see if I can find the data. It's mostly primary care physicians and doctors of osteopathy, not pediatricians, that are writing these prescriptions. So part of the problem can be probably managed just by education of a different group of people that are giving these meds.

The final thing I have concerns about is the warnings that we give to families, if you are a CYP2D6 rapid metabolizer you shouldn't take this. There's really no way, other than having had a really bad experience, that one's going to know, since we're not testing for it, that you actually are. And the other warning is, if your child has these problems, you should be wary.

Well, the problems that we're looking for are the ones that we're trying to get. We want children to be calm and quiet and not coughing. That's what's going to happen if you're in -- I think you pointed that out, that that's what's going to happen if you're getting too much of the morphine.

Actually a fourth point, which I'm sorry for my ADHD as well, we don't know what the mechanism is in cough that's the suppressant. Is it the codeine itself, or is it the metabolite morphine? If it's the codeine, then maybe we do get an effect from codeine specifically that we may not be getting any other way.

If it's the morphine, then the point that just that was with pain, we're going to miss a huge number of people because we're not getting them to metabolize to morphine, and we're going to make some of those kids toxic.

Dr. Flick, do you know the morphine/codeine question?

DR. FLICK: Sure, I can respond. But I think Gary has a comment he'd like to make, too. So anyone who practices anesthesia knows that narcotics are very potent in terms of suppressing airway reflexes. It doesn't matter what narcotic, they all are potent suppressors of airway reflexes.

We use that day in, day out. That's part of the business. So, I don't think there's probably

any one of us who practice anesthesia would think that one narcotic or opiate is more or less effective than another in terms of suppressing those reflexes.

I would say that codeine would be fine if it was the only choice, but it's not the only choice. So even though these are -- and when I commented before, I said that the risk is low. None of us would suggest that the risk is high. The risk is low. In fact it's probably very low.

But the benefit is, in my view, non-existent. There is no benefit to using codeine in any one of these settings because there are better available alternatives, or one could argue in terms of cough, there is no reason to use an opiate to suppress cough. That's what the American Academy of Pediatrics would say. That's what the American College of Chest Physicians would say.

So we're having a little bit of an argument about something that outside this room is pretty much settled. I think there is something, in my view, to discuss about what age, but the overall

issue, in my view, is fairly straightforward. The question to me is, what's the appropriate age?

DR. OWNBY: Dr. Georas?

DR. GEORAS: Yes. Well, I think I'll pass on the question because I think some of the issues I wanted to bring up have been discussed. Thank you.

DR. OWNBY: Dr. Grayson, you're next.

DR. GRAYSON: Okay, thanks. One thing we haven't mentioned, we've been focused on the risk of death with codeine, and that's great. But being an allergist, and I need to like disclaim that, one of the things I'm concerned about is that when -- and just the whole monogram [sic] issue, and when it was first done maybe the incidence of asthma was lower. Asthma has increased.

People are coughing. Kids are coughing. And I have an issue with this being available over the counter when they probably should be evaluated by somebody and see why they might be coughing. And it's something we haven't really brought up.

So that's another piece that -- I mean I honestly don't think that codeine does anything for cough, personally. But I think that's another piece to put into this, that especially from the over-the-counter side of this, it may be more of a dangerous problem in that people are taking longer to be diagnosed and treated for asthma, because they're treating with over-the-counter medicines first. Thanks.

DR. OWNBY: Dr. Gerhard, you're next.

DR. GERHARD: Tobias Gerhard. So I think addressing kind of this age question, the different age cutoffs that we're presented with, obviously the risk overall is low, and we can't really quantify it given the data sources that we have. We have pretty strong indication that it's dependent on age, that it's higher in the very young, and probably declines. But again, we can't really quantify any of this.

But there seems to be no indication that the risk, compared to alternatives, would go away because you have that increased variability in the

metabolism that might be less risky in adults or the 12 to 18-year-olds than in young children. But certainly that increased risk due to the variability in the metabolism remains, even if it's small.

So trying to quantify this and have that discussion only really makes sense if we weigh that risk at different levels against a benefit. And as far as I can tell from this discussion, in either of the indications, there seems to be no strong evidence that there is a benefit that codeine has that alternatives don't have, that don't share the metabolic concerns of more variable metabolism that these other drugs don't share. So I think it's, in a sense, a moot point.

If we think that these risks are real and that there are no benefits, then the age question becomes pretty clear. So if anybody has clear opinions about the benefit, then I think we can talk about kind of a tradeoff at risks at different levels versus that benefit. But if we can't identify a quantifiable benefit, then even a small

risk is enough to be of concern.

DR. OWNBY: Dr. Dracker?

DR. DRACKER: In my mind, based upon what the AAP has said in the past, the use of codeine in 12 years and below is really a moot point. As we've discussed, there's no indication for it, there's no benefit for it. The other issue that I am concerned with, though, is the over-the-counter availability of the drug. If we're discussing the inappropriate need for using a codeine product under 12 years of age, there shouldn't even be a consideration of being able to get it over the counter in any way.

DR. OWNBY: Dr. Besco?

DR. BESCO: Yes. Just to add, also, we talked a lot about age,, but I don't think we've talked enough about risk stratification. I think there needs to be stronger warnings about using more conservative doses in patients with pre-existing risk factors for respiratory depression. I just think it's concerning.

I'm not aware that any labeling for any

opioid talks about risk stratification other than use less aggressive doses in someone that might be opiate naïve. So it might be time to open up the door to talk about how do we embed addressing risk stratification for patients with existing OSA, renal impairment, people that are taking concomitant sedating medications, and adjusting warnings to include those statements for consideration.

DR. OWNBY: Dr. Walco?

DR. WALCO: I'd like to follow up on Dr. Gerhard's comments because I think they were extremely well put. And just indulge me for a moment and take a step back. If I go to sleep when I'm 11 years, 11 months, and 29 days old, when I wake up the next morning, am I a different person? Am I in a different risk category? And the answer is obviously, no.

I think the issue of why younger people are at greater risk has to do with what we know about opioids, which is the way they behave, the younger the patient is, the more variability there is in

terms of response, which is why one is so exquisitely careful with neonates and children under 6 months, for example.

So if we're going to go with the idea that there's unneeded risk associated with codeine, I have no idea why we would stipulate a specific age cutoff, except for the fact that the data that we have from reports make clear that there's greater risk in younger patients, but that doesn't mean the risk goes away.

So if the question that we're trying to discuss here focuses on safety, I don't see why we would cut it off at 6 or 12, or 18 for that matter, but we're not being asked that question.

DR. OWNBY: Dr. Georas?

DR. GEORAS: Yes, I guess I was going to maybe bring up the question I brought up before the break a little ahead of time, and this is getting at following up very clearly on what was just stated. I mean I haven't heard a compelling reason why I would vote yes for children under 18, and I'm wondering if somebody around the panel could

articulate that for me just to help me understand.

DR. OWNBY: I think one of our problems is there's a tradition that's been embedded for a long time. To me, it's very clear. I have no doubt that under age 12, there's no reason that this should be available for cough. My equivocation is 12 to 18. And I think some of you have articulated, if it's dangerous under 12, or unacceptably risky, why should we continue it up to 18.

Does anyone else have that problem besides me?

(No response).

DR. OWNBY: Is there any more discussion, or would we like to proceed to the second question? Were there any other issues that the FDA wanted discussed on this that we haven't touched on? Drs. Seymour or Racoosin?

DR. SEYMOUR: No, but it looked like Dr. Parker wanted to say something.

DR. PARKER: It's just for the record, that I totally agree with you, but I would like to add

to the record that I have the same question for 18 and above. This seems, for how this gets interpreted and for the reality, to be incredibly confusing. So I know that we're restricted to 18 and under, but for the record I would say, why?

DR. BESCO: If I could add -- oh, sorry -- I think that's part of the issue in adults, that we do have these same risks. And I think part of it is we don't take into consideration is risk factors for respiratory depression.

So again, adults are probably more at risk, too, if we're using the one-size-fits-all dosing without taking any consideration into the risk.

DR. OWNBY: Okay. Dr. Leeder, I believe you're first, and then Dr. Alexander.

DR. LEEDER: Steve Leeder. I think one of the issues, the difference between adults and kids, is that adults can assess the risk and make a decision as to whether they want to take codeine or not. And children, somebody else is making that decision, and they want to have, I guess, as much information available, useful information as they

can to make that decision.

DR. OWNBY: Dr. Alexander?

DR. ALEXANDER: I mean I think that the arguments in favor of not changing the labeling to be more restrictive would fall into a few categories. So one is the potential for unintended effects of a labeling change.

I think you could make a second case that economists would call revealed preferences. The argument there is people wouldn't be using it if there wasn't some value to them and there wasn't some benefit. So rather than looking at what people say, look at what people are doing.

Then the third is heterogeneative [ph] treatment effects and the fact that it may not work for you, or you may not think it works, or it may not work in an RCT doesn't mean it doesn't work for me. So these are the flavors of arguments that I think would be used in conjunction with the fact that although we can't precisely estimate the magnitude of the risk, and although I wouldn't rely on FAERS to get population level estimates, it is

true that there are 24 deaths in 50 years of FAERS, which does feel kind of small relative to the number of uses that we know have taken place over that time period.

With all of that said, I am in favor of more restrictive labeling that would discourage or provide a contraindication for use, at least for children under the age of 12.

DR. OWNBY: Dr. Gudas?

DR. GUDAS: After listening to all the discussion and the thoughtful comments of the panelists, it seems to me that, again we're not being asked exactly this question, but I favor the European Medicine Agency's recommendations. They seem to me the most reasonable where they limit below the age of 12 and then they limit below 18 in certain conditions. So this seems quite like a reasonable template to me. Thank you.

DR. OWNBY: Dr. Flick?

DR. FLICK: I just wanted to respond to the comment about risk-stratified dosing, I think was the comment. That kind of dosing based on

perceived risk, let's say in a patient who was obese, for example, would make sense for a drug that didn't have such enormous variability in its effect.

So you may reduce the dose in an obese child, who is a poor metabolizer, and get no effect. So it really doesn't -- it doesn't work for codeine, which is the fundamental problem that we have here.

The European requirements for age 12 don't seem to be based in any science, and they don't support that age with any science. They simply -- they say that there's maturity to the metabolic pathways there, but that flies in the face of data that would suggest that those metabolic pathways are long matured.

If I had to guess why the age 12 would seem to be a cutoff, it was referred to by one of my colleagues across the room here, is that at about that age, children begin to take their own medicines as opposed to being given medicines.

So when children are getting to the age

where they take the medicine themselves, or communicate more clearly whether they want it or don't want it rather than being given by their parent, they're less likely to get in trouble, just like adults are less likely to get in trouble in this situation because they dose themselves rather than being dosed.

So if there is a rationale for having an age younger than 18, which I don't support by the way, it would probably be that rationale, at least in my view.

DR. OWNBY: Dr. Leeder, do you want to --

DR. LEEDER: Just going back to those EMA -- and I'll defer to my colleagues in the Office of Clinical Pharmacology. I can only find two studies of codeine metabolism in vivo in children.

One of them is actually cited in the EMA document. It's from the British Journal of Clinical Pharmacology in 1992. And they studied, I don't know, 8 or 10 infants and I think 4, 3 to 4-year-olds.

The other paper is from Williams in 2002, and the oldest child that was studied in that study, which actually compared 1 and a half milligrams per kilo of codeine in about 46 kids with about a tenth lower dose of morphine, both IM, and the oldest child in either of those arms was 12 years of age.

So I think there's only data up to 12 years of age, and so maybe that was -- I mean, I can't speak for the Europeans, but those are the codeine data, to the best of my knowledge, and there's nothing above age 12.

DR. OWNBY: Okay, thank you. Cindy, can we move on to question 2? It should look very familiar. Discuss the available data on the safety of codeine use for pain in pediatric patients. Please address the following age groups in your discussion.

So we've moved from cough to pain. Any further comments? I mean we've covered a fair amount of this it seems already in the previous discussion, but I'll be willing to entertain

additional comments now. Dr. Connett?

DR. CONNETT: Well, I don't have expertise in this, but as a grandparent or a parent, these are really very different situations. Before my child is going to have tonsillectomy, the doctor says, would you be okay with my using codeine for pain afterwards? And I would say, well, I'm not so wild about that, and I think there's good alternatives for pain.

On the other hand, in the situation of cough, I have a child that's been coughing and unable to sleep and feeling horrible, and croup and everything else, and I'm more desperate. And I'm not sure there are alternatives that -- I think Dr. Grayson said something about this earlier. So I would view these two things as quite different.

DR. OWNBY: Dr. Perrone and then Dr. Roumie.

DR. PERRONE: Jeanmarie Perrone. Just to reiterate the difference between the cough discussion and the pain discussion is that there needs to be something for pain in pediatric patients. And maybe we can emphasize the

opportunity, like I think the otolaryngologist mentioned that non-steroidals worked very well post-operatively for tonsillectomy.

So if we're looking at this discussion for pain, I'm terrified about the unintended consequences of using other opioids. But in any of those age groups for various reasons, in the younger age group because of these adverse effects, and then the older age groups because of misuse and abuse in the presence of these.

If you look at the FAERS data or the NEISS data, most of the adverse events were really related to unintended exposures and unintentional ingestion. So when you get a 5 times more potent opioid in the home of millions of patients, we're going to face even more significant consequences. So all of that I think wraps into our discussion about safety.

DR. OWNBY: Dr. Roumie?

DR. ROUMIE: I'd just like to respond to the no good alternatives for cough. I think the data in the appendix that the FDA provided, which showed

the prescribing, and the providers that prescribed codeine for certain indications, show that there are probably alternatives, given that 2 percent of pediatricians prescribe codeine, whereas most of the prescribing was from kind of family practitioners, general practice.

If you looked at some of the indications, they were really not what most pediatricians would prescribe for. I mean, it was otitis media, which is an ear infection, which yes, that's painful, but typically can be covered with over-the-counter NSAIDS and acetaminophen.

So I think 'there may not be an acceptable alternative for cough' is not really a valid argument because many other practitioners do not prescribe these drugs.

DR. OWNBY: Dr. Walco and then Dr. Brown.

DR. WALCO: I just want to take on the issue for a moment of other opioids for pain and the concern, because I think one of the reasons codeine has been as popular as it has been in the past is that somehow it's seen as being more benign. And

if you listen to what we're saying here, codeine is metabolized into morphine, and it's done so in an unpredictable way. So if you really wanted to be on top of your game, what you would do is just prescribe morphine at the get-go and take the question out of it. And it's no more risky than codeine.

So across the country, drugs like oxycodone, like morphine, et cetera, are used with regularity, with safety, and there's no greater risk. So I think that if one of the justifications for hanging onto codeine is somehow it makes us feel better, please rethink.

DR. OWNBY: Okay. Dr. Brown?

DR. BROWN: To amplify that, I think that folks have been using -- just to mention one particular drug, people have been using oxycodone in children safely for some years. Many people will have to learn to use that, and it might be a welcome addition to have the FDA behind an educational process for those people that are going to have to relearn a lifetime of giving codeine.

But Gary is absolutely right. When you have an unpredictable drug, and you administer an unpredictable drug, it's much worse for the child than administering a drug which has a predictable metabolism.

DR. OWNBY: Dr. Flick?

DR. FLICK: So the question of the different potency of various opiates is a separate conversation from how the drug is supplied. So if the drug were supplied in equal potent, you know, 1 tablespoon equals X versus, then there would be a risk. But oxycodone is supplied in a way that the volume of a liquid dose, for example, is similar to the volume of a liquid dose of codeine. Same thing for a tablet of oxycodone.

So they're supplied in a way that accounts for the differing potency. So the risk is not 10 times because the potency is 10 times. Those are a little bit different considerations.

DR. OWNBY: Dr. Parker?

DR. PARKER: So the only other thought I had was relating specifically to prescriber habits for

codeine. And I'm going to compare it to hydrocodone and the role the agency took and the DEA classification schedule, ease of access for a prescriber for a 3 versus a 2 in terms of e-prescribing, in terms of hard copy, refills, you know whatever it is.

I guess one of my thoughts was, if indeed the feeling is that it should not be used, because of safety concerns, or potential limitations of not recommended or contraindicated, that does not dictate behavior.

Making it harder to do it might have a greater impact. And I don't know if there have been deliberations in the past about a reclassification of its schedule, but it comes to mind. Because I know as a prescriber, my behavior is different when I approach prescribing a 3 versus a 2. And I see that, and I just wanted to bring that up as a comment.

DR. OWNBY: Dr. Besco?

DR. BESCO: Yeah, just an additional comment about the alternative discussion. My own

experience within our health system, when we tried to limit use in pediatric patients when the initial alert came out from FDA, the response we were met with from our physician staff, mainly in the emergency department, was, well what do I use?

So I think if we do provide a recommendation, we do need to provide a list of those alternative products and what the equianalgesic doses are compared to the standard doses of codeine that are used in pediatric patients.

DR. OWNBY: Dr. Yu?

DR. YU: Yes. I just have a question for the colleague that just made some statement about the alternative use for codeine, for oxycodone.

You use the word "children." To me, I'm a little confused. As children, do you have an age group? Do you mean children under 18 or children under 12 years old? So yes, sure, if you could answer. Thank you.

DR. FLICK: So I think we kind of addressed that question earlier, and that was the same

question I had, is what does the agency define child as? But we're being asked specific ages here, and I think that you folks can comment on that better than I can. But in my view, and I think the American Academy of Pediatrics would define a child as prior to their 18th birthday. Although differing agencies view children -- I think the World Health Organization is 21, but I may be wrong.

DR. OWNBY: Dr. White?

DR. WHITE: The agency uses different ages for different uses as well. It's under 21 for PREA. It's under 18 for some things. And a lot of the drug companies will go down to 14 I think, and will sometimes consider that children as well. It's all very -- will consider them in the adult group.

So the agency doesn't have a specific definition as well. Am I correct on that?

DR. STARKE: This is Dr. Starke.

DR. WHITE: For PREA, it's 21.

DR. STARKE: PREA is 17.

DR. SEYMOUR: I think for the purposes of this discussion, we're considering children less than 18 years of age.

DR. WHITE: Okay, that's fine. Thank you.

DR. OWNBY: Okay. Ms. Nelson? Turn your microphone on.

DR. NELSON: While I am a healthcare provider, I am not a medical physician. And as a mother of a patient with acute pain, frequent, been hospitalized over 60 times, I will tell you that physicians will not prescribe -- send you home with morphine if they're not familiar with you.

I'm from Michigan. I've been hospitalized in Washington, and I had to prove that I was not going to take my child's drugs. I had to have my doctors call from Michigan to prove that I was an okay patient, an okay mother.

So how would I ever get out of the hospital with my child without something other than morphine or oxycodone? They won't send you home with that unless they know you.

So my perspective is, if we're sick, we're

going to my doctors in Michigan so we can get out of the hospital. I don't know if that means anything to you all that prescribe, but they will not give you take-home morphine on a regular basis, so how does a kid wean down and be able to resume a normal life?

DR. OWNBY: Dr. White.

DR. WHITE: I just want to clarify. It's the FDA for devices that they use the age of 21. I apologize for saying PREA.

DR. OWNBY: Does anyone want to comment on Dr. Nelson's question about physicians are so afraid of certain drugs going home, and yet for children with chronic pain conditions, like sickle cell, that's a big issue.

DR. FINNEGAN: I totally agree with her, and that's one of the things we do. And that's one of our patient populations that's a very large problem. I think the other thing that you need to consider is price. I think there's a really good reason the sponsors aren't here because codeine has been off patent for a really long time and it's

fairly inexpensive. The others are not so inexpensive. And I think some of them are still on patent.

So as far as healthcare resources are concerned, and also for a family that has to buy something for a kid for years, this is also a consideration.

DR. OWNBY: Dr. Brown?

DR. BROWN: I appreciate your comment, and having treated children with sickle cell disease for 25 years, I know that what you're saying is absolutely true. We don't want to be in a circumstance where there are no available analgesics for children who have chronic painful conditions such as your child does.

That said, and especially for children with multiple comorbidities, such as a child who might have renal disorder, secondary to sickle cell disease or hepatic disease, secondary to sickle cell disease or pulmonary disease, one would want to provide them with the most predictable pharmacology that one could in order that they

might get reproducible results rather than something that is not going to be reproducible on a regular basis.

I will say that the three of us here are on the committee, an advisory committee, that deals with the issues of addiction and analgesia, and we are trying to deal with the issues of patients getting the drugs that they require without being forced to go through what you have.

But we live in a very difficult time, and that is a very difficult problem. Not to say that we're not working on it. I want to make sure that your child gets the best treatment that they can get, and I think that's from a medication that provides your child with reproducible pharmacology.

DR. OWNBY: Dr. Walco?

DR. WALCO: Just to punctuate a critical point, what I heard you allude to was the cost of these medications, especially when they're being used in chronic conditions. And I think the idea of using any opioid for chronic pain in pediatrics is extremely questionable and would be done only

under very, very select circumstances. And I would argue that any child who does have a condition that warrants the chronic use of opioids to treat it, if you're choosing codeine, you really missed the boat.

DR. OWNBY: Dr. Flick and then Dr. Finnegan.

DR. FLICK: So just to follow on that, the problem with codeine in the setting that you describe in your child is that it's a combination product. So you're not using codeine, you're using Tylenol with codeine or acetaminophen and codeine, which those who care for children with sickle cell typically would not do because you're tied then to the dosing of acetaminophen. And those medications should be separated in a setting of pain crisis in sickle cell. So you should be using a separate -- typically, it would be oxycodone, separately from acetaminophen so you can vary your dose of oxycodone.

So Tylenol with acetaminophen is not a drug that any one of us I think would recommend for a child with sickle cell pain crisis. And by the

way, oxycodone is off patent long ago.

DR. OWNBY: Dr. Finnegan?

DR. FINNEGAN: So what I was going to say is she's not getting Tylenol on a chronic basis, she's getting it intermittently is what we're talking --

DR. OWNBY: Okay. Dr. Nelson?

DR. NELSON: I fully agree with you, but what I'm saying, it's not that it's not recommended, I think that physicians, such as yourselves, or let's say not as yourselves, but other physicians, may, in the ER or such, have difficulty prescribing the appropriate drug because they think that the parents are drug users, or they think that the children are drug users. And that's just inherent in sickle cell disease, which is just one example.

So while I agree with you that that's probably true -- now, we get very good treatment -- physicians have a difficult time prescribing it to patients as needed for those social reasons.

DR. OWNBY: We've had a lot of discussion

here about this, and I haven't heard anyone argue for one age break versus another. I get hung up on the same thing that I did with cough, if you're saying that this really isn't indicated for pain under 18. Dr. Gerhard and then Dr. Morrato.

DR. GERHARD: Well, just very briefly let me kind of repeat the argument for having the cutoff be 18 rather than any of the intermediate cutoffs. If there is a risk, even if it declines with age, if there is no benefit to offset that risk, there is no rationale for picking 12 versus 18. That's where I'm at, at the moment.

DR. OWNBY: Dr. Morrato, you had a comment?

DR. MORRATO: Yes. I'm reading this question to talk about the safety. Looking at the benefit and risk relates to, in my mind, do we contraindicate or not? Do we have it OTC or not? And I do think that while the evidence is sparse, there can be a biological basis to say that, while it's not a sharp demarcation between 12 and 12 years and 1 day, there is a biological plausibility that the maturation of the metabolism

is occurring in a child, and by the time you get to the age 12, you may have a more mature.

So in my mind, I kind of look at that biologically as that's kind of defining for this mechanism what might be a child metabolism versus an adult. And I would agree, then there's not much difference between a 17.99 year old child and an 18.01. So that's how I'm seeing this.

Now, that may relate differently to how you weigh the benefit and risk in terms of alternatives and whether it's prudent for society to be using it if you have a 13-year-old. But I think just looking at safety data, there could be a plausible argument that there could be a cutoff.

DR. OWNBY: Any final comments? Yes?

DR. SUAREZ-ALMAZOR: Just to follow up about your question about why aren't we discussing more about the age cuts, I was not discussing them because when you say discuss the available data, I don't think we have data.

So we can discuss more and more, and what we discuss becomes data; almost like what other groups

discussed before has been used as a reference for the discussing today, but it's not that they had data.

So I think the discussing is useful because of experience, but we don't have specific data to discuss the cutoff point. There is no strong data, I think, no matter how much we talk about it.

DR. OWNBY: Dr. Georas?

DR. GEORAS: I guess in response to Dr. Morrato, I guess what I would say is that what I heard from the other side of the room was that we don't have the pharmacokinetic data for 12 to 18 and that the reference that the EMA relied on was a very small number of subjects. So that sounds like an arbitrary cutoff to me.

DR. MORRATO: Maybe Dr. Leeder would like to -- I mean, what I understood from what you said earlier was more of the biological basis in terms of how the drug is cleared, eliminated, et cetera. And that didn't seem to be referenced in those references that you gave.

So do we have the full data that the

Europeans were looking at? So maybe I'm putting more weight on that they did a careful review on that, and that may be inappropriate, or not.

DR. LEEDER: I don't think there are any data that establish when any of these pathways is fully mature. And in any event, the disposition of the compound involves more than just CYP2D6 or CYP3A4, or these UDTs. The way that the problem is framed in some way, occasionally the problem is framed in the way of, if we think there is differential risk between young children and adults, at what point does the risk of somebody under the age of 18 become equivalent to that of an adult.

In the absence of any hard data, certainly, we don't have any what I would call full PK data where you give a dose of codeine to a child and measure the concentrations of not just codeine, but also morphine, morphine 3-glucuronide, morphine 6-glucuronide, codeine 6-glucuronide over time.

In the absence of knowing what the relationship is between the dose that's

administered and the systemic exposure of the pharmacologically active compound, which is morphine and morphine 6-glucuronide, we just can't know what dose is going to produce an exposure to the pharmacologically active compound that's equivalent to a 30-milligram or 60-milligram dose in adults. We just don't know that.

The only information we have we stitched together from in vitro studies and from a couple of studies with -- the first study that I mentioned, the one from 1992, only drew 3 plasma concentrations, 3, 4 and 5 hours after the dose was given. The larger study by Williams only took a single blood sample 1 hour after an intramuscular dose. That's the data that we have to go on.

So we have to use some of these other studies to -- none of which include both pediatric patients of any age and adults, so that you can reference the pediatric level of expression or activity to an adult population using the same analytical methods and the same experimental protocols. We don't have that information.

So the best guess is that somewhere around the onset of adolescence is when we might expect to see dose exposure relationships that approach those of adults. But it's based on an inadequate set of data.

DR. OWNBY: Now you know why the FDA is asking a panel to discuss this. Dr. Hudak?

DR. HUDAK: I did have one question of clarification on the data on the adverse events. Do we have any information as to whether these were first exposures, subsequent exposures? Because my thought is the patient is his or her own crucible. And if this is a safety issue, it's really a situation of using the drug the first time in a patient if that's going to be safe.

Someone who has had codeine multiple times at a particular dose, I wouldn't have any expectation that there would be any safety concern in that case. But I don't know that we have data on first versus subsequent use.

CDR MOENY: We don't have that information in DAWN and NEISS-CADES. I believe there was at

least one FAERS report, which reported problems with an initial dose. Could DPV speak to that?

DR. HUDAK: It's not the first dose, it's the first course of treatment. So there was that one case where after one dose the patient died.

CDR MOENY: Completely naïve patient.

DR. HUDAK: I'm talking about completely naïve patients to codeine. They might have toxicity after 1 dose, or they may not have it until 3 or 4 doses when the levels accumulate. but I'm just curious in terms of first exposure of any sort.

MS. NGUYEN: Annie Nguyen. We did not receive any data that tells us whether they were codeine naïve or not. The data is limited based on what was reported. So unfortunately, most cases don't report this is the first time ever my child's ever had codeine. They just said my child received a dose of codeine without any additional information.

DR. OWNBY: Dr. Seymour, were there any other concerns from the FDA, or should we move to

question 3?

DR. SEYMOUR: You can move forward.

DR. OWNBY: The chance you've all been waiting for. We've got a voting question. Based on the discussion of the available data, with codeine, should the current contraindication for codeine for pain management in the post-tonsillectomy and adenoidectomy setting be expanded to a contraindication for codeine use for any pain management in children?

As per CFR 201.57c(5), a drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit. Only known hazards and not theoretical possibilities can be the basis for a contraindication.

You're going to get to vote (a) yes, contraindicated for pain management in children younger than 6 years of age; (b) yes, contraindicated for pain management in children younger than 12 years of age; (c) yes, contraindicated for pain management in children

younger than 18 years of age; or (d) no change to current contraindications. And you may provide the rationale for your recommendation and any recommendations you have.

Are there any clarifications or questions that we need clarified before we vote on the question?

(No response.)

DR. OWNBY: Okay. We'll be using an electronic voting system for this meeting. Once we have begun to vote, the buttons will start flashing and will continue to flash even after you have entered your vote. This is at the base of your microphone.

Please press the button firmly that corresponds to your vote. If you are unsure of your vote, or you wish to change your vote, you may press the corresponding button until the vote is closed. After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The designated federal official will read the vote from the screen into

the record.

Next, we will go around the room for each individual who voted and will state their name and vote into the record. You can also state the reason why you voted as you did if you want to. We will continue in the same manner until all questions have been answered or discussed. And I would remind you, there are 29 voting people.

If each of you make 2 minutes of comment, that's going to take us an hour each time we read this into the record. So if you don't have anything to add, you can pass. It's not necessary that you comment.

So cast your vote for (a), (b), (c) or (d). Pick one. You vote (a), (b), (c) or (d). This is multiple choice that you've all done a million times, I'm sure.

(Laughter.)

DR. ROUMIE: The letters are underneath, correct?

DR. OWNBY: Yes, these are the flashing letters -- or the one that corresponds to the

letter that's flashing directly above it on your microphone base.

While we're waiting, Dr. Grayson wants his Ouija fixed but --

(Laughter).

DR. OWNBY: It's a bad joke. We'll tell you it later.

(Vote taken.)

DR. HONG: Okay. For question 3 we have 2 A's, 6 B's, 20 C's, and 1 D.

DR. OWNBY: Okay. So why don't we start to my right. Dr. Finnegan, if you'd state your name and how you voted, and if you wish to make a comment.

DR. FINNEGAN: My name is Maureen Finnegan. I predictably voted D with clarification. I have no problems with the recommendations -- with the regulatory language about recommendations rather than contraindications. And I do think there should be a warning for obesity, respiratory issues, and concomitant use with sedatives or medications that do sedation or decrease

respirations.

DR. WALCO: Gary Walco. And I voted for C, for all the reasons that we've discussed, and I don't need to repeat them.

DR. FLICK: I'm Randall Flick. I voted C.

DR. BROWN: Rae Brown. I voted C.

DR. SUAREZ-ALMAZOR: Suarez-Almazor, C for all the reasons stated.

DR. CATALETTO: Mary Cataletto. I voted C.

DR. HUDAK: Mark Hudak. I voted C.

DR. HERNANDEZ-DIAZ: Sonja Hernandez-Diaz. I voted B.

DR. PRUCHNICKI: Maria Pruchnicki. I voted C.

DR. PARKER: Ruth Parker, C.

DR. GERHARD: Tobias Gerhard, C.

DR. BESCO: Kelly Besco, for the record. And I voted C.

DR. YU: Yanling Yu. I voted C for two reasons. One is there no solid evidence to exclude patient from 12 to 18. The second, from the national data, the number of children who were

prescribed codeine for both cold and pain medication, about the same comparable numbers, so the risk cannot be ignored for the age group between 12 and 18.

DR. CONNETT: John Connett. I confess. I panicked and pressed the wrong button. I meant to vote for C.

DR. MORRATO: Elaine Morrato. I voted for B.

DR. GEORAS: Steve Georas. I voted C. I didn't hear a reason why this drug should be used for pain in children.

DR. OWNBY: Dennis Ownby. I voted B.

DR. HARKINS: Michelle Harkins, C.

DR. TRACY: Jim Tracy, C.

DR. McCORMACK: Frank McCormack. I voted C in line with Dr. Gerhard's argument that unless there's a benefit, we really should be voting against this inferior drug. And the only benefit that I could see was that this has -- it's socially viewed as less dangerous, and it's more acceptable to the population than the other drugs. So that

doesn't seem to clearly outweigh the risk.

DR. GRAYSON: Mitch Grayson. I voted C for all the reasons that have been said.

DR. PERRONE: Jeanmarie Perrone. I voted B. We never saw any adverse event data in the older age group, and I think it's reserved for perhaps a lighter opioid analgesic. And I'm waiting for data about other alternatives in the age group after the limitation was set in 2012 and the data that I want to see on utilization and adverse events from the alternatives that are being used now.

DR. NELSON: I'm Dawn Nelson. I voted A because I live the reality of this. And while I believe that it's harmful in some children, and that's very tragic, I also know that my child would have gotten no pain relief. And I would not have been able to resume a normal life at any point in time -- and there are 60 hospitalizations -- had we not had some benefits from codeine.

DR. ROUMIE: Christianne Roumie. I voted B because most of the death data that I saw came in children under 12.

DR. GUDAS: Lorraine Gudas. I voted B for all the reasons, especially just what Dr. Perrone, or Dr. -- yes, Dr. Perrone just mentioned. Thank you.

DR. WHITE: Michael White. I voted C because of the unreliable metabolism of this drug and the unpredictable nature of whether it will be effective in some patients, dangerous in others, and the fact that there are suitable alternatives.

DR. DRACKER: Bob Dracker. I voted C.

DR. ALEXANDER: Caleb Alexander. I voted C.

DR. LEEDER: Steve Leeder. I voted C.

DR. OWNBY: Okay. Thank you very much. We can move on to the next question. This is again a voting question. Based on the discussion of the available data with codeine, should codeine be contraindicated in the treatment of cough in children.

As per 21 CFR 201.57c(5), a drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit. Only known hazards

and not theoretical possibilities can be the basis for a contraindication.

This is the same sequence of four choices: yes, contraindicated for cough in children younger than 6; yes, contraindicated for cough in children younger than 12; yes, contraindicated in cough for children younger than 18; or no, no change in the current contraindication.

Are there any questions of clarification before voting on this question?

(No response.)

DR. OWNBY: Hearing none, the same instructions that you had before, press the key firmly above the letter that you wish to cast your vote for.

(Vote taken.)

DR. HONG: Okay, for question 4 we have 1 A, 5 B's, 20 C's, and 3 D's.

DR. OWNBY: Okay. We'll start on the opposite side. Dr. Leeder, if you'd like to start. State your name for the record and how you voted, and we'll progress around the room.

DR. LEEDER: Steve Leeder. I voted C.

DR. ALEXANDER: Caleb Alexander. I voted B. Actually, I was pressing B and C rapid alternating movements --

(Laughter.)

DR. ALEXANDER: -- so that's a reflection of my sitting on the fence.

UNIDENTIFIED MALE SPEAKER: They have drugs that will fix that.

DR. ALEXANDER: Yes. I guess I just am a little more ambivalent -- yes, it was just mainly a gut ambivalence about it and sort of -- I don't think there's anything specifically in the data that I saw. I feel like there are -- I guess I'm more convinced about the lack of utility for pain relative to -- that there's a clearer unfavorable risk/benefit balance for pain, in my mind, it's an easier call than for some patients for cough, such that I'm comfortable I think with the idea that for 12 to 18-year-olds, it would not be contraindicated.

DR. DRACKER: Bob Dracker, C.

DR. WHITE: Michael White, D. I'm torn about the lack of evidence for how we suppress cough and the lack of alternatives. And I think if we let it stand as it is, there needs to be stronger, stronger recommendations for how to tell when it's dangerous and when it's not.

DR. GUDAS: Lorraine Gudas. I voted B, and Dr. Alexander summarized my reasons very well.

DR. ROUMIE: Christianne Roumie. I voted C mostly because I feel like cough is for the most part a self-limiting illness. And here, the potential for harm was greater than the illness.

DR. NELSON: Dawn Nelson. I voted for -- I want to vote for C. I mistakenly pressed D first, and then tried to do C, for the reasons stated before.

DR. PERRONE: Jeanmarie Perrone. I voted C.

DR. GRAYSON: Mitch Grayson. I voted C because I think that there's no real benefit to codeine in cough, and therefore the risk/benefit ratio falls on the negative side.

DR. McCORMACK: Frank McCormack. I voted C.

DR. TRACY: Jim Tracy. I voted B consistent with Dr. Alexander also. However, I probably will get more experience using non-codeine tussive therapy.

DR. HARKINS: I'm Michelle Harkins. I voted C. One, because cough is usually self-limiting. And if it's not in children, likely it's asthma. So I think that that should be evaluated and maybe more education to the generalists to not prescribe codeine for cough and to consider other alternatives.

DR. OWNBY: Dennis Ownby. I voted C.

DR. GEORAS: Steve Georas. I voted C. I didn't hear a compelling reason why we should be using this drug in children. And I think there are effective cough-suppressing medicines with more predictive metabolism that would work for the rare instances where a drug like this would be needed.

DR. MORRATO: Elaine Morrato, and I voted B, similar to the reasons previously stated. But I was also taking kind of a strict reading of the definition of a contraindication and felt it could

be left to clinical judgment in the 12 to 18-year-old.

DR. CONNETT: This is John Connett. I voted D, deliberately this time, because I don't think we had really enough specific information about the effects of the alternatives.

DR. YU: Yanling Yu. I voted C.

DR. BESCO: For the record, this is Kelly Besco, and I voted C. I know today's meeting has focused on children, but I do suspect that some of these reactions are also are occurring in adults. And I would just like to state that I would like to see FDA investigate if codeine's labeling should be augmented to also advise that codeine should be avoided in adults that have risk factors for respiratory depression, including advanced age, obstructive sleep apnea, and pulmonary disease.

DR. GERHARD: Tobias Gerhard. I voted C for the reasons I stated before. I just want to make one quick comment regarding the pain question before, that I found Dr. Nelson's concern incredibly important.

I think making sure that this action doesn't result in access issues for children with pain is really important. I still think the recommendation regarding codeine is correct and that drug has some issues, but there might have to be a strong emphasis on educational efforts and so forth to make sure that that access is guaranteed.

DR. PARKER: Ruth Parker. I voted C. I would underscore the same comment. And I appreciate the comment you made and glad it's in the record.

DR. PRUCHNICKI: Maria Pruchnicki. I voted C. I haven't said much today, although I agree with many of the comments that have been floating around.

I think at the bottom line with both this vote and the previous one, I'd be very concerned. Although I'm a practicing pharmacist in the state of Ohio and can't prescribe medications, my concern were I to be prescribing codeine in children would be that I would frankly kill them. So I voted C.

DR. HUDAK: Mark Hudak. I voted C. I

thought that to be intellectually honest, the risk is no different in the 12 to 18-year-olds, whether you've got cough or whether you've got pain. And I was persuaded by at least some of the colleagues of the committee that there are alternatives to treating cough, even if it's debilitating.

DR. CATALETTO: Mary Cataletto. I voted C. I think our mission as pediatricians is to evaluate and treat the cause of the cough rather than to rush off and suppress it. So given the information that we had today, I would vote C.

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. I voted B. And as Dr. Alexander, I was in between C and B. And I have no strong evidence to support why I voted for B, but I think in my mind between 18 and 19, there will be not a significant difference. And therefore, if we are allowing above 18, that's why I voted B rather than C. But again, again I would be fine with C as well.

DR. SUAREZ-ALMAZOR: Suarez-Almazor, C.

DR. BROWN: Rae Brown. I voted C.

DR. FLICK: Randall Flick. I voted C for

the reasons that have been previously discussed, but also for the additional reason that communicating this change is going to be the biggest task, and to have consistency is going to make that communication much easier.

DR. WALCO: Gary Walco. I voted C.

DR. FINNEGAN: Maureen Finnegan. I voted A. And the reason is that an understanding that there isn't a lot of good data available. The data that we're making these decisions on is not data that would be acceptable to the FDA if it was sent in as part of a drug study, so I think that needs to be taken into consideration. The data that is there does support, to a very small degree, the children under the age of 6.

DR. OWNBY: Okay. Thank you very much. We could take a break, but I've got the feeling most of you would prefer to press on at this point and do our last question and have a little bit more relaxed approach to getting to the airport. I see a lot of nodding of heads, so we'll go ahead to question 5.

Based upon the discussion of the available data with codeine, should codeine be removed from the FDA monograph for over-the-counter use for the treatment of cough in children: (a) yes, remove codeine from the monograph for children younger than 5; (b) yes, remove codeine from the monograph for children younger than 12; (c) yes, remove codeine from the monograph for children younger than 18 years of age; or (d), no change in the current monograph for codeine.

Any clarifications needed on the question? Remember -- yes?

DR. BROWN: Can you fully explain the impact of this decision, removing it from the monograph? I just want to be clear what I'm voting on.

DR. OWNBY: I cannot fully explain that, but I will turn to the colleagues in FDA since this is their issue.

(Laughter).

DR. ADAH: If it's removed from the monograph, depending on the age of course, it means it will no longer be available for that age range

over the counter. So it depends on what age range is voted for, if it is.

DR. OWNBY: Any further clarifications? Dr. Alexander?

DR. ALEXANDER: Yes, we haven't used this term yet, but if I understood correctly, in most states, it's actually behind the counter and not over the counter. So I'm just trying to understand what it means.

I'm clear on what it means to prescribe off-label for a product that's approved for a specific indication, but say that we recommended that it be removed from the monograph, quote/unquote, "for children less than 12," does that mean -- can you kind of describe what that means in a state that still offered it? How would that play out?

Because if it's removed from the monograph -- is it ever over the counter I guess is the first question, or is it always behind the counter? And then the second question is, if it's removed from the monograph for, say, children under

12, does that mean essentially that since it's behind the counter, the pharmacist would say, in fact, your child is 10; I can't give this to you? Is that how this would play out?

DR. ADAH: Let me see if I can break this down. So in terms of -- I've got to walk through this and think of it carefully. In terms of if we say that it's considered -- there is no official behind the counter in FDA speak. It is by DEA regulation that it is put behind the counter because you have to sign for it, kind of like pseudoephedrine. Okay.

So it's still considered over the counter in the sense that you don't need a prescription. You can walk in and say I'd like to purchase this, and they will sell it to you if you're the legal age.

In terms of how the states handle it, my understanding is, a state regulation cannot supersede federal regulation. It can be more conservative. So if we say that is no longer available for 12 and under, then you couldn't go in and say I want to buy it for my 10-year-old. But

the reality is, how would we know if you meet the legal requirements of being 18 or 21 or whatever they are that I could walk in and say I'm going to buy it and take it home and give it to my --

DR. ALEXANDER: Sure, sure. Okay.

DR. OWNBY: Dr. Harkins, you had a question?

DR. HARKINS: I think that that was really my question, is really trying to get my head around what does over the counter mean. And if I buy it and I have a 15-year-old at home and a 19-year-old at home and a 10-year-old at home -- that was my question.

So it still seemed a little nebulous. Someone can just come in, request the prescription for themselves, but yet give it to their kid; or anything. I know. But I mean, it probably just shouldn't be sold, period.

DR. OWNBY: Just a moment. Did the FDA want to respond to this particular issue? And there have been a couple of others of you.

DR. MICHELE: Yes, please. Just one further clarification. So if this were determined to be

not generally recognized as safe and effective in the monograph for a certain age range, then there would be no labeling for that. So if, say, an adult purchased this and wanted to give it to their child, it would say on the label, do not use in children aged whatever. But if they chose to give it, there would be no dosing instructions.

Just like there are no dosing instructions currently under the age of 6, but there is, quote/unquote, "professional labeling," which means that those dosing instructions are in the monograph, and physicians may instruct their patients to do so.

DR. OWNBY: Thank you. Dr. Flick, did you have another comment?

DR. FLICK: Yes. I just wanted to ask the FDA, do you have drugs that are contraindicated for prescription use but are available over the counter and generally recognized as safe? Do you have other examples of that?

DR. ADAH: I'll take a shot at this. It may be for different indications. The drug may be

over the counter but not prescription for an indication. But in terms of -- I can't think of an example to give you.

Does that make sense in the sense that the indication for prescription may be one thing that's a lot more serious or we don't want it used for that indication, but for another indication it could be used.

DR. FLICK: No, I'm just trying to understand how we could vote anything but C if we thought that, this is not -- we voted for a contraindication prescription side; I don't see how you could vote otherwise.

DR. WALCO: So you can clarify. Is that ever the case when it's a safety issue and not a defined indication issue?

DR. ADAH: I can't think of any. If there's an example where something would be unsafe in one indication but wouldn't be unsafe -- I shouldn't say that. There probably is.

Can you think of any? I'm going to ask everyone else. Can you think of an indication

where there's a safety issue for maybe an Rx use or a safety indication for one use but not for another?

DR. SEYMOUR: Well, currently the Rx prescription codeine products have a contraindication for not used post-tonsillectomy. So theoretically, a parent could go into the pharmacy and say my child had surgery, and I want to get this medication for them, even though it's for cough, and they might be able to get it.

So there's such a lag with the prescription versus monograph in terms of labeling and being able to update it, that there probably are these situations where the labeling is different. So we do have a contraindication on our codeine Rx products that aren't on the over-the-counter products.

DR. OWNBY: Okay. I have Dr. Morrato and then Dr. Besco.

DR. MORRATO: My comment was addressed. It was talking about the practical implications around dosing instructions on the label.

DR. OWNBY: Dr. Besco?

DR. BESCO: Yes. I was just confused by I think one of the statements. So if we remove codeine from the monograph for whatever age we choose, there still would be dosing instructions available or no?

DR. ADAH: No.

DR. BESCO: No. Okay. That's what I wasn't clear on.

DR. OWNBY: Okay. Any further clarifications or are we ready to vote?

(No response).

DR. OWNBY: Okay. Same instructions, but press the key above the letter you wish to cast your vote for. Press it firmly. Don't panic. No rapid alternating movements.

(Laughter).

(Vote taken.)

DR. OWNBY: I still think we need Jeopardy music. Everyone push firmly again. We're missing two votes.

(Vote retaken.)

DR. FINNEGAN: How do you abstain? This is so out of my wheelhouse, it's not fair for me to vote. So how do I abstain?

DR. OWNBY: Oh, is there a way -- there isn't?

DR. FINNEGAN: Oh, I said this is so out of my wheelhouse it's not fair for me to vote, so how do I abstain?

DR. HONG: Just don't vote at all.

DR. OWNBY: If you want to abstain, just don't press the key.

DR. HONG: Okay. Question 4. We have zero A's; 1 B, 27 C's, and zero D, and then 1 no vote.

DR. OWNBY: Okay. I forgot which side we should start on. I believe we're over on my right. Dr. Finnegan?

DR. FINNEGAN: This is totally out of my wheelhouse, so I am not voting.

DR. WALCO: Gary Walco. I voted C. And if there were an option to vote E, which would be that it should not be over the counter at all, that

would be my preference.

DR. FLICK: Randall Flick. I voted C.

DR. BROWN: Rae Brown. I voted C. But in the strongest possible terms, let me state for the record that this narcotic compound should not be present as an over-the-counter monograph for anyone. Children are going to get this drug because parents are going to walk in and get it and give it to their 2-year-old.

DR. SUAREZ-ALMAZOR: Suarez-Almazor. I voted C, but I also want it in the record that I would be in support of banning this as an over-the-counter drug.

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. I voted C because I think that to be over the counter, medications need to have evidence of safety and effectiveness and not only a lack of evidence or poor evidence like we have right now. And to avoid giving a false impression of safety, I voted C.

DR. CATALETTO: Mary Cataletto. I voted C.

DR. HUDAK: Mark Hudak. I voted C, but

again I would have voted E if possible. I think the GRASE that got this into the monogram is suspect, and I agree that there could be some really bad unanticipated consequences if the agency doesn't figure out just to remove it completely.

DR. PRUCHNICKI: Maria Pruchnicki. I voted C.

DR. PARKER: Ruth Parker, C; agree with the comments about it needs to extend beyond 18.

DR. GERHARD: Tobias Gerhard. I also voted C and echo the recommendations in considering the adult age range.

DR. BESCO: This is Kelly Besco and I voted C. I also agree with the rest of the group that perhaps this should not be available at all without a prescription due to potential for inappropriate use and abuse.

DR. YU: Yanling Yu: I voted C because that is the only consistent way I can see, because we say it's contraindicated for medical profession, then for its general people we should not let so easily get over the counter.

DR. CONNETT: This is John Connett. I voted C, although I think it's unlikely that ultra-metabolizers suddenly changes at age 18 to a normal.

DR. MORRATO: Elaine Morrato. I voted C for this one. I think it's very important to have consistency between the prescription and OTC labeling.

If the FDA has made a determination in the most recent review of the extended-release prescription product that they need more data in order to determine whether or not those new products can be used in under 18, then in my mind that doesn't meet the definition of generally regarded as safe and effective for broad use.

Moreover, as we've been talking, the contraindication and prescription, I agree with previous mention. That's inconsistent with generally regarded as safe.

Now, for my own internal consistency, I viewed the prescription side as allowing flexibility for prescribing physicians and their

clinical judgment for the 12 to 18-year-old labeling, and my thought was that that dosing instructions might be carried over in the professional OTC labeling.

DR. GEORAS: Yes, Steve Georas. I voted C. I would second the idea that I can't see an indication where this would be available OTC.

DR. OWNBY: Dennis Ownby. I also question the need for it to be available OTC at all.

DR. HARKINS: Michelle Harkins, voting C. Again, I don't think it should be available to any age range, and it should be consistent across the states.

DR. TRACY: Jim Tracy. I voted C, and I also agree with the sentiment about not available at all over the counter.

DR. McCORMACK: My name is Frank McCormick. I voted C, and I wonder if we should add a question and take out the "with children" at the end of this question just to have it formally on the record that everyone's in agreement with regard to taking it out of the monograph for all ages.

DR. GRAYSON: Mitch Grayson. I voted C. And just in case we don't have that vote, I strongly echo all the other comments that the agency should very seriously consider removing codeine from the monograph entirely for all ages.

DR. PERRONE: Jeanmarie Perrone. I voted C for all those reasons. And I was actually shocked at this meeting and reading the background information to find that it was available over the counter in the setting of a worse prescription drug epidemic in our country.

DR. NELSON: Dawn Nelson. I voted C. And I think it should be removed from over-the-counter access.

DR. ROUMIE: Christianne Roumie. I voted C, and I agree it should be removed from the monograph.

DR. GUDAS: Lorraine Gudas. I voted B for a couple of reasons. One is that I think between age 12 and 18, the children are old enough to discuss their feelings and the way they feel on the medication. And I also think that the evidence

that was presented here, the adverse event reports, 60 over 50 years with millions and millions of people using it, as Dr. Finnegan said earlier, that type of data would not be appropriate for the FDA to consider if they were considering a new drug application.

So I don't think that these adverse event reports are reasonable to consider, so I think it still should be available over the counter.

DR. WHITE: Michael White, voted C.

DR. DRACKER: I'm Bob Dracker. I voted C. I feel no controlled substance should be available as an over-the-counter medication. I think the strongest aspect of this committee's vote is the fact that we all are basically in agreement.

DR. ALEXANDER: Caleb Alexander. I voted C.

DR. LEEDER: Steve Leeder. I voted C. If one views the codeine as a formulation for the delivery of morphine, I think it's fair to say that the delivery of the morphine is very unreliable in the absence of knowledge of a CYP2D6 genotype. It might graduate up to just simply a variable and

unreliable, even if you do know the genotype.

To me, just from that perspective alone, that seems inconsistent with generally regarded as safe and effective. And I would, again, agree with everybody else, that doesn't end at age 18 and should consider removal for all age groups.

DR. OWNBY: Okay. Thank you very much. Are there any closing comments from the FDA, or do you really want another vote?

DR. MICHELE: If I could just ask for the folks who articulated that they would like to remove this all together from the monograph, including in adults, could you please just comment on your rationale? That will be very helpful for us moving forward.

DR. OWNBY: Dr. Grayson?

DR. GRAYSON: Sure. Mitch Grayson. I don't -- when we talk about cough and the use of codeine for cough, I don't believe -- as I said earlier, I don't believe that there's actually any data to support efficacy whatsoever.

So there's clearly a risk of -- if you want

to call it this way, an unknown delivery of morphine. I like that kind of approach. With people using this drug, we don't know what's actually going to happen to them. So there's clearly a risk with essentially no benefit. And the more recent studies have shown actually that placebo is just as effective. So I see no reason why this should be available for anybody as an over-the-counter drug.

DR. OWNBY: Does anyone else wish to comment? Dr. Brown and then Dr. Roumie.

DR. BROWN: This is a narcotic-based compound, and I fail to see how this ever -- perhaps it was a different time when we allowed narcotic-based compounds to be placed over the counter. But at this point, I don't understand in any way how a narcotic-based compound can be an over-the-counter drug. It boggles my mind.

The second thing is that this gives an opportunity for parents to give 2-year-olds doses of drug that are absolutely unregulated by anyone.

The worst possible thing we can do is not put the directions for dosing on the bottles of it, leave it on the market, and expect that parents are not going to use it. Parents will use it. Parents will use it every single day.

DR. OWNBY: Dr. Roumie?

DR. ROUMIE: My concerns were exactly what has been articulated. The first was the potential for diversion, and the second was for the unintended consequence of basically allowing whatever the purchaser decides the dose to be, to be, and for whoever they choose to give it to.

DR. OWNBY: Dr. Yu?

DR. YU: Yes. I'm glad this issue is brought up. And I'll just share a personal perspective. My dad had very severe emphysema. He's very elderly, and I always very careful not to give him any codeine, even morphine, because it really suppress his breathing.

Also, I like the things you brought up about not just absorption also elimination of the drug. When you get older, you really have a very slow

metabolism. You have a totally way than healthy adult. So for elderly patients, a lot of them have a lung disease, and that is particular risk for them, too, for the population.

DR. OWNBY: Dr. Harkins?

DR. HARKINS: I found the background reading for this session to be very interesting because I wasn't aware of all the difference in metabolism. I was shocked that New Mexico allows you to get it without a prescription. I didn't know. And I've only written codeine for maybe 5 or 6 times for patients with cough, and I treat adults because I don't think it works particularly well either. But the thing that we haven't really discussed, although it's just now been mentioned, we have a huge epidemic of prescription drug problem, and New Mexico is way up there at the top.

So having something sit behind a counter that anybody can get access to as a low-level or starting narcotic just seems crazy. And it seems like we need to do something to combat our prescription drug and/or much less over-the-counter

type narcotic abuse potential.

DR. OWNBY: We have Dr. Walco and then Dr. Dracker.

DR. WALCO: Just to follow up on what Dr. Harkins just said, I think the public often has a perception that if medications are sold over the counter, they're relatively benign, and we know that that's not true. So at the same time that we are putting on a full court press letting the public know about the epidemic of opioid abuse to also then have what might be perceived as a benign product available over the counter truly makes no sense.

DR. OWNBY: Dr. Dracker?

DR. DRACKER: I'm just really amazed before this meeting as well. Considering codeine is classified as a controlled substance, the definition of a controlled substance, something cannot be sold unless prescribed by a physician, I don't really understand how this came about.

DR. OWNBY: Tradition. Dr. Tracy?

(Laughter).

DR. OWNBY: Dr. Tracy, you had a comment?

DR. TRACY: Yes. I live in Omaha, so in Nebraska, you can't get it over the counter. In Iowa, you can. So it's really interesting to see the dynamics of how people manage that themselves. I can just tell you, it's probably not number one on the hit parade as far as alcohol augmentation, but if it's available it will be used. So I just can't imagine why it's there at all.

DR. OWNBY: Dr. Morrato?

DR. MORRATO: I would just add that I think one of the benefits of the request for this is that it forces this data to be critically evaluated. So right now, we're relying on generally regarded as safe and effective based on evaluations and data from a couple decades ago.

I think a part of the continual learning process, by forcing this question, it gets the data out in a public way. And if there is new data that says it's effective, then let it come forward. So I think this process triggers that scientific discourse.

DR. OWNBY: Okay. Any closing comments from the FDA?

DR. SEYMOUR: I just want to thank you all for participating in today's meeting. I realize you all have busy schedules. You've taken time out to travel here and participate in this discussion. But we really appreciate the feedback that you've given us. This is a very important topic. It has a lot of public health impact, and we take your feedback very seriously. And I really thank you for your participation and your feedback today.

Adjournment

DR. OWNBY: Okay. We're officially adjourned. Remember to take all your personal belongings from the room. Don't leave your computer behind like I did once before. All materials left on the table will be disposed of. Thankfully not. And please remember to drop off your name badge at registration so that it can be recycled, and thank you very much.

(Whereupon, at 3:12 p.m., the meeting was adjourned.)